Association of Expired Nitric Oxide With Urinary Metal Concentrations in Boilermakers Exposed to Residual Oil Fly Ash

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Background Exposure to metal-containing particulate matter has been associated with adverse pulmonary responses. Metals in particulate matter are soluble, hence are readily recovered in urine of exposed individuals. This study investigated the association between urinary metal concentrations and the fractional concentration of expired nitric oxide (FENO) in boilermakers (N = 32) exposed to residual oil fly ash (ROFA).

Methods Subjects were monitored at a boiler overhaul site located in the New England area, USA. FENO and urine samples were collected pre- and post-workshift for 5 consecutive workdays. Metals investigated included vanadium (V), chromium (Cr), manganese (Mn), nickel (Ni), copper (Cu), and lead (Pb).

Results The median FENO was 7.5 ppb (95% CI: 7.4–8.0), and the median creatinine-adjusted urinary metal concentrations (μg/g creatinine) were: vanadium, 1.37; chromium, 0.48; manganese, 0.30; nickel, 1.52; copper, 3.70; and lead, 2.32. Linear mixed-effects models indicated significant inverse exposure–response relationships between log FENO and the log-transformed urinary concentrations of vanadium, manganese, nickel, copper, and lead at several lag times, after adjusting for smoking status.

Conclusions Urine samples may be utilized as a biomarker of occupational metal exposure. The inverse association between FENO and urinary metal concentrations suggests that exposure to metals in particulate matter may have an adverse effect on respiratory health. Am. J. Ind. Med. 44:458–466, 2003. © 2003 Wiley-Liss, Inc.

KEY WORDS: biological monitoring; metals; air pollutants; occupational; nitric oxide; epidemiology
INTRODUCTION

Boilermakers are responsible for the construction, installation, maintenance, and repair of power-generating boilers that burn oil, coal, or natural gas. They are exposed occupationally to metal fume, which is generated from their work tasks of welding and burning. Depending on the composition of the base metal, the metal fume may contain iron, manganese, chromium, or various other transition metals [Burgess, 1995]. In addition, boilermakers are exposed to the ash that coats the inner walls of the boilers. Residual oil fly ash (ROFA), produced by the combustion of fuel oil, has a high content of bioavailable transition metals, including vanadium, nickel, iron, and zinc, often at concentrations that can affect health adversely [Huffman et al., 2000].

Recent studies have shown that transition metals serve as a catalyst in generating oxygen-based radical species, which in turn are capable of inducing lung injury [Pritchard et al., 1996]. In toxicologic studies, the soluble transition metals in ROFA were shown to induce acute pulmonary injury and airway hyperreactivity in rats [Costa and Dreher, 1997; Gavett et al., 1997]. Epidemiologic studies have found that boilermakers occupationally exposed to ROFA were shown to induce acute pulmonary injury and airway obstruction [Hauser et al., 1995a,b; Dreher et al., 1997; Gavett et al., 1997]. Epidemiologic studies have found that metal fume from boilers that burn oil, coal, or natural gas. They are exposed occupationally to metal fume, which is generated from their work tasks of welding and burning. Depending on the composition of the base metal, the metal fume may contain iron, manganese, chromium, or various other transition metals [Burgess, 1995]. In addition, boilermakers are exposed to the ash that coats the inner walls of the boilers. Residual oil fly ash (ROFA), produced by the combustion of fuel oil, has a high content of bioavailable transition metals, including vanadium, nickel, iron, and zinc, often at concentrations that can affect health adversely [Huffman et al., 2000].

In the present study, expired nitric oxide (FENO) was used as a marker of acute airway responses to occupational metal exposure. Expired NO has been found to be a sensitive and non-invasive marker for acute airway responses [Kharitonov and Barnes, 2000; Silkoff, 2000]. Endogenous NO is produced when the enzyme NO synthase (NOS) catalyzes the conversion of L-arginine to L-citrulline and NO [Marletta, 1993]. NO serves as a neurotransmitter of bronchodilator nerves and performs non-specific host defense in the respiratory tract [Belvisi et al., 1992; Moncada and Higgs, 1993]. Individuals with asthma have elevated levels of expired NO compared to healthy individuals [Kharitonov et al., 1994; Kharitonov and Barnes, 2000]. Although exposure to cigarette smoke also induces airway inflammation, smokers have decreased expired NO levels compared to non-smokers [Kharitonov et al., 1995]. Because of the crucial role NO plays in the airways, significant changes in endogenous NO levels may be of concern.

This study used a biological marker to determine the occupational exposure to metals. The use of a biomarker may provide a better estimate of dose than ambient measurements. Urine samples were used for biological monitoring primarily due to the ease of collection and analysis. Due to the highly soluble nature of metals in ROFA [Dreher et al., 1997], urinary metal excretion should serve as an appropriate measure of dose. Many other studies have analyzed urinary levels of vanadium, chromium, nickel, and other metals to determine occupational exposure levels [White et al., 1987; Hauser et al., 1998; Lucchini et al., 1999; Domingo et al., 2001].

In this study, we investigated the association between the fractional concentration of nitric oxide in mixed expired gas (FENO) and urinary metal concentrations in a group of boilermakers exposed to ROFA and metal fume. Urine samples were analyzed for the following six metals: vanadium, chromium, manganese, nickel, copper, and lead. Expired air and urine samples were collected twice daily at approximately 12-hr intervals during a 5-day work period using a repeated-measures study design. Our previous study found that ambient exposure to metals in fine particulate matter was significantly associated with decreased FENO levels in the boilermakers [Kim et al., 2003]. Therefore, in this study we hypothesized that FENO levels would be inversely associated with urinary concentrations of these six metals following occupational particulate metal exposure.

MATERIALS AND METHODS

Study Population

The study population consisted of 32 boilermakers working at a power plant during the overhaul of oil-fired boilers in New England, USA. The overhaul entailed removal and replacement of several large panels of the interior wall and the water circulating tubing of the boiler. In addition, repair of the ash pit was performed. The various work tasks of the boilermakers included welding, burning, and grinding. Twenty boilermakers were studied in June 1999 and 12 additional boilermakers were studied in October 2000. Two subjects from 1999 participated again in 2000. A self-administered questionnaire was used to obtain information on medical history, including respiratory symptoms and diseases, smoking history, and occupational history. The study was approved by the Institutional Review Board of the Harvard School of Public Health. Written informed consent was obtained from each subject prior to participation in the study.

FENO Collection

The collection of FENO has been described previously [Kim et al., 2003]. Briefly, FENO samples were collected pre- and post-workshift each day during a 5-day sampling period. Baseline FENO samples were collected pre-workshift on the first day of the workweek, after 1–2 days away from work. The offline collection and measurement of FENO was in accordance with American Thoracic Society (ATS) recommendations [Anonymous, 1999]. Subjects wore nose clips and tidal breathed through an apparatus with two one-way
vals. Subjects then inhaled to total lung capacity and expired their entire vital capacity into a Mylar balloon attached to the expiratory limb while maintaining an oropharyngeal pressure of 12.5 cm H2O. NO levels in the balloons were measured using a calibrated Sievers NOA 280 chemiluminescence analyzer (Boulder, CO).

**Urine Sample Collection**

Urine samples were collected pre- and post-workshift each day during a 5-day sampling period. After samples were collected in sterile 120-ml urine collection cups, they were aliquoted into 15-ml polypropylene tubes. Specimens were frozen and stored at −20°C until analyzed.

**Urine Analysis for Metals**

Calibration solutions were prepared from single-element stock solutions (1,000 mg/L, Clärítas PPT, SPEX CertiPrep, Metuchen, NJ) and diluted using 5% high-purity nitric acid. A blank solution of 5% nitric acid was also prepared. A 1 ml aliquot of each urine sample was mixed with equal volumes of concentrated nitric acid and a stock solution containing 100 ppb scandium (Sc) as an internal standard. The resulting mixture was then diluted to 20 ml using distilled, deionized water.

A Finnigan MAT Element 1 magnetic sector inductively coupled plasma–mass spectrometer (ICP–MS) was used for this analysis [Feldmann et al., 1994; Moens and Jakubowski, 1998; Houk, 2002]. The element was operated in medium resolution mode (R = m/Δm = 4,000) for all elements, which was necessary to remove polyatomic ion interferences on certain isotopes. The sensitivity in medium resolution is lower than that in low resolution by a factor of 10. A “shielded” load coil (CD-1 torch, Finnigan MAT) improved sensitivity by a factor of 3–20 (depending upon m/z) while still maintaining the extremely low background and high precision of the double-focusing instrument [Appelblad et al., 2000].

A Teflon spray chamber and micro-concentric nebulizer (Model PFA-20, Elemental Scientific, Omaha, NE) were used. The sample was drawn up at approximately 100 μl/min by natural suction. The Teflon nebulizer was cleaned on-line by aspirating 2% aqueous hydrofluoric acid for 15 s before the analysis of each urine sample.

Each urine sample was vortexed prior to analysis to insure sample homogeneity. Six metal analytes—vanadium (V), chromium (Cr), manganese (Mn), nickel (Ni), copper (Cu), and lead (Pb)—were determined in each urine sample. The spectrometer measured 20 lines/peak using 50 ms/line for the following seven isotopes: 45Sc, 51V, 52Cr, 55Mn, 60Ni, 63Cu, and 208Pb. Ten spectra were measured and averaged for each urine sample. The spectroscopic peaks measured for each analyte were integrated and then corrected for blank levels and isotopic abundance. The metal concentrations were calculated after adjusting for the internal standard and dilution factor. The following percentage of urine samples had metal concentrations that were below the limit of detection: 3% of all samples for chromium; 17% for manganese; 7% for nickel; 1% for copper; and 9% for lead. The samples with metal concentrations below the limit of detection were assigned half the limit of detection value.

**Urine Analysis for Creatinine**

A polypropylene tube containing a minimum of 5 ml of frozen urine was sent to ESA Laboratories, Incorporated (Chelmsford, MA) for creatinine analysis. The creatinine level in the urine sample was measured with the Shimadzu Model UV-1601 spectrophotometer using the Jaffé reaction [Jaffé, 1886]. The creatinine levels were used to correct for the variability in urine dilution.

**Statistical Analysis**

Statistical analyses were performed using SAS version 6.12 (SAS Institute Incorporated, Cary, NC) and S-Plus2000 for Windows (MathSoft Incorporated, Cambridge, MA). Creatinine-adjusted urinary metal concentrations were used in all analyzes. The Spearman rank correlation coefficient was used to determine the correlation amongst the creatinine-adjusted urinary concentrations for the six metals. Mixed models were used to compare the baseline and non-baseline FeNO measurements, and to compare the pre- and post-workshift median creatinine-adjusted urinary metal concentrations. In addition, Wilcoxon signed rank tests were performed to compare the median creatinine-adjusted urinary metal concentrations at each collection time.

Linear mixed regression models were constructed to study the association between FeNO and creatinine-adjusted urinary metal concentrations. Effect modification and confounding of the association by self-reported current cigarette smoking status (yes/no), sampling year, and chronic obstructive pulmonary disease (COPD) status also was investigated in the models. A first-order autoregressive covariance structure was used because it resulted in the best Akaike’s Information Criterion compared to models with other covariance structures. A first-order autoregressive structure assumes that the correlation function decays exponentially as the interval between the measurements increases [Verbeke and Molenberghs, 1997]. Restricted maximum likelihood was used to estimate the covariance parameters. FeNO and creatinine-adjusted urinary metal concentration were log-transformed to improve normality.

To account for the kinetics of metal elimination through urine, lag models were constructed. Urine samples were collected pre- and post-workshift, approximately 12 hr apart, during a 5-day sampling period. The lag time of urine
sampling was defined as the number of hours following the corresponding FENO sample collection. For instance, in a 12-hr lag model, the relationship between FENO from day 1 pre-work and the creatinine-adjusted urinary metal concentration from day 1 post-work was examined. For each additional 12-hr lag model, the day 1 pre-work FENO was associated with a creatinine-adjusted urinary metal concentration shifted an additional 12 hr back. Ten different lag models, from 0-hr lag to 108-hr lag, were investigated for each metal.

RESULTS

Description of Study Population

The demographic data are summarized in Table I. The study population consisted of 32 men, 31 of whom were white (97%). Twenty subjects were monitored in 1999 and 14 subjects, including 2 that were monitored in 1999, were monitored in 2000. Thirteen of the 32 subjects (41%) were current cigarette smokers. Six of the 32 subjects (19%) had COPD. Five subjects were chronic bronchitics, as diagnosed by a physician or with symptoms as defined by ATS [Anonymous, 1995]. One subject had emphysema diagnosed by a physician. Their ages ranged from 18 to 59 years, with 2 weeks to 40 years of boilermaking experience.

Measurements of FENO

A summary of the FENO measurements is shown in Table II. Wilcoxon confidence intervals and corresponding medians are presented because of the positively skewed distribution of FENO. Baseline measurements of FENO were taken on average after 1–2 days away from work. The median baseline FENO for all subjects was 9.1 ppb (95% CI: 7.9–10.3). The non-baseline samples included all pre- and post-workshift FENO samples except the ones collected on pre-workshift day 1. The FENO levels for the non-baseline samples were significantly lower than the FENO levels from the baseline samples ($P < 0.001$). The median FENO by collection time is shown in Figure 1.

Urinary Metal Assessment

The Wilcoxon median creatinine level was 1.90 g/L (95% CI: 1.86–2.12). The Wilcoxon confidence interval and corresponding median was calculated because of the positively skewed distribution of creatinine levels. The urinary metal concentrations, adjusted for creatinine levels, are shown in Table III. Of the six metals, copper had the highest creatinine-adjusted urinary concentrations, with a Wilcoxon median value of 3.70 $\mu$g/g creatinine (95% CI: 3.47–3.95). Manganese had the lowest creatinine-adjusted urinary concentrations, with a median of 0.30 $\mu$g/g creatinine (95% CI: 0.26–0.34). Correlation analyzes indicated that the creatinine-adjusted urinary concentrations of each metal were moderately correlated with each other, with R values ranging from 0.43 ($P < 0.001$) for vanadium and chromium to 0.14 ($P < 0.02$) for manganese and lead.
TABLE III. Summary of Creatinine-Adjusted Urinary Metal Concentrations (μg/g Creatinine)* in New England Boilermakers, USA

<table>
<thead>
<tr>
<th></th>
<th>Pre-workshift samples (N = 156)</th>
<th>Post-workshift samples (N = 154)</th>
<th>All samples (N = 310)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median a 95% CI</td>
<td>Median a 95% CI</td>
<td>Median a 95% CI</td>
</tr>
<tr>
<td>Vanadium</td>
<td>129 1.12–148</td>
<td>149 1.24–182</td>
<td>137 1.23–154</td>
</tr>
<tr>
<td>Chromium</td>
<td>0.47 0.40–0.55</td>
<td>0.48 0.41–0.57</td>
<td>0.48 0.42–0.53</td>
</tr>
<tr>
<td>Manganese</td>
<td>0.31 0.26–0.38</td>
<td>0.28 0.24–0.35</td>
<td>0.30 0.26–0.34</td>
</tr>
<tr>
<td>Nickel</td>
<td>1.34 1.17–1.50</td>
<td>1.70 1.53–1.89</td>
<td>1.52 1.40–1.65</td>
</tr>
<tr>
<td>Copper</td>
<td>3.77 3.44–4.12</td>
<td>3.62 3.30–4.00</td>
<td>3.70 3.47–3.95</td>
</tr>
<tr>
<td>Lead</td>
<td>2.35 1.95–2.78</td>
<td>2.32 2.04–2.64</td>
<td>2.32 2.08–2.58</td>
</tr>
</tbody>
</table>

*aUrinary metal data are adjusted for creatinine levels to correct for urine dilution.

The median creatinine-adjusted urinary metal concentrations by collection time are shown in Figure 2. Statistically significant differences in pre- and post-workshift creatinine-adjusted urinary metal concentrations were observed only for vanadium, nickel, and lead. The post-workshift creatinine-adjusted urinary vanadium, nickel, and lead concentrations were significantly higher than pre-workshift levels (P values < 0.01).

The median creatinine-adjusted urinary metal concentrations were found to differ significantly at varying collection times for vanadium, manganese, nickel, copper, and lead (P values < 0.05). For chromium, the median creatinine-adjusted urinary metal concentrations at each of the 10 collection times were not significantly different.

**Association Between FE\textsubscript{NO} and Urinary Metal Concentrations**

The linear mixed-effects regression models indicated significant exposure–response relationships between F\textsubscript{E}NO and several individual creatinine-adjusted urinary metal concentrations. The results of the regression analyses are summarized in Table IV. While the exposure–response relationship was not statistically significant at all lag times, all the regression coefficients were negative for vanadium, nickel, copper, and lead, suggesting a consistent inverse association between F\textsubscript{E}NO and urinary metal concentrations. The regression coefficients were mostly negative for manganese also, with the exception of the models using a lag of 24 hr (β = 0.007, 95% CI: −0.02 to 0.03) and 48 hr (β = 0.003, 95% CI: −0.03 to 0.03). Likewise, most of the regression coefficients were negative for chromium, although none of the regression coefficients were statistically significant. Cigarette smoking status was significantly associated with a decrease that ranged from −0.20 to −0.31 in log F\textsubscript{E}NO in the presented urinary metal models (P values < 0.02). However, smoking status was not found to modify the association between F\textsubscript{E}NO and urinary metal concentrations.

With no lag in the urine sampling, log-transformed creatinine-adjusted urinary nickel and lead concentrations were found to be significantly associated with decreases in log F\textsubscript{E}NO, after adjusting for cigarette smoking status. The association between log F\textsubscript{E}NO and log creatinine-adjusted urinary metal concentrations was not modified by sampling year or COPD status. Log F\textsubscript{E}NO changed by −0.05 (95% CI: −0.10 to −0.004) with each one unit increase in log creatinine-adjusted urinary nickel concentration. A one unit increase in log creatinine-adjusted urinary lead concentration was associated with a change in log F\textsubscript{E}NO of −0.04 (95% CI: −0.08 to −0.002). In addition to the association observed at no lag in urine sampling, log creatinine-adjusted urinary lead concentrations were found to be associated with log F\textsubscript{E}NO with a 48-hr lag and 60-hr lag in urine sampling. A one unit increase in log creatinine-adjusted urinary nickel concentration was associated with a change in log F\textsubscript{E}NO of −0.10 (95% CI: −0.15 to −0.05) with a 48-hr lag and −0.04 (95% CI: −0.08 to −0.001) with a 60-hr lag.

Linear mixed-effects models with other metals also showed statistically significant associations between F\textsubscript{E}NO and lagged creatinine-adjusted urinary metal concentrations. Log-transformed creatinine-adjusted urinary manganese concentrations collected 12 and 36 hr after the corresponding F\textsubscript{E}NO sample collection were associated with significant decreases in log F\textsubscript{E}NO. Each one unit increase in log creatinine-adjusted urinary manganese concentration was associated with a change in log F\textsubscript{E}NO of −0.04 (95% CI: −0.10 to −0.06) with 12-hr lag and −0.03 (95% CI: −0.06 to −0.02) with a 36-hr lag.

Log-transformed creatinine-adjusted urinary copper concentration was found to be associated with a decrease in log F\textsubscript{E}NO with a 72-hr lag in urine sampling. The association with log F\textsubscript{E}NO was significant with an 84-hr lag for log-transformed creatinine-adjusted urinary vanadium concentrations. With each one unit increase in log creatinine-adjusted urinary copper concentration at a 72-hr lag and vanadium concentration at an 84-hr lag, log F\textsubscript{E}NO changed by −0.07 (95% CI: −0.15 to −0.001) and −0.11 (95% CI:
Statistically significant associations between log FENO and log creatinine-adjusted urinary metal concentrations were not found in other additional lag models.

**DISCUSSION**

The urinary metal concentrations observed in this occupational study were greater than that observed in the
adjusted urinary concentrations of manganese, 0.30
[54x359]m
Huang, 2001]. In the present study, the median creatinine-
[54x383][White et al., 1987; Angerer and Lehnert, 1990; Lin and
[54x442]are reported to be 0.11, 0.68, and 1.89
m
copper. In the general population, the median creatinine-
[54x478]general population with the exception of manganese and
[54x478]nickel concentration of 0.6
m
nickel, but the BEI for chromium is 30
m
g/L, a median urinary nickel concentration of 0.6 µg/L, and urinary copper levels
[305x418]were at the lower
[276x418]g/L in non-exposed individuals
[276x646]coefficient b 95% CI
  Regression
variable
Log FENO
studies performed. There is no ACGIH BEI
[305x442]case of vanadium, none of our samples exceeded the ACGIH
BEI for chromium.
In our previous study, we found a significant inverse
association between log-transformed F\textsubscript{ENO} and airborne fine particulate concentrations of vanadium, chromium, manganese, and nickel [Kim et al., 2003]. Log-transformed F\textsubscript{ENO} also was found to be marginally associated with fine particulate levels of copper and lead [Kim et al., 2003]. In the present study, there were significant inverse associations between log F\textsubscript{ENO} and log creatinine-adjusted urinary concentrations of vanadium, manganese, nickel, copper, and lead at various lag times. With an increase in creatinine-adjusted urinary vanadium concentration from the 25th centile value of 0.82 µg/g creatinine to the 75th centile value of 2.21 µg/g creatinine, F\textsubscript{ENO} decreased by 11%. Likewise, an increase from the 25th centile value to the 75th centile value in creatinine-adjusted urinary concentrations of manganese, nickel, copper, and lead resulted in a decline between 4 and 5% in F\textsubscript{ENO}.
In contrast to our previous study [Kim et al., 2003], a significant association between log F\textsubscript{ENO} and the log-transformed urinary concentration of chromium was not found. The lack of a relationship between F\textsubscript{ENO} and urinary concentrations of chromium may be due to the inability of urinary chromium concentrations to represent acute chromium exposure. The median creatinine-adjusted urinary chromium concentrations were not significantly different from each other at any of the sampling times, which may indicate a slow and constant clearance rate. In rats exposed to hexavalent chromate, which is the form of chromium produced by welding, urinary levels of chromium remained elevated compared to unexposed rats for up to 4 days post-exposure [Langård et al., 1978].
Although we performed multiple analyzes, the association between F_{ENO} and metals in urine was consistent across lag times. All regression coefficients were negative for vanadium, nickel, copper, and lead, and most were negative for manganese. The negative regression coefficients indicate a consistent inverse association between F_{ENO} and urinary metal concentrations. In addition, the lag hours used in each model agree with information available on the kinetics of the urinary excretion of these metals [Langård et al., 1978; Morgan and Holmes, 1978; Bernacki et al., 1980; Hauser et al., 1998]. Bernacki et al. [1980] found that nickel concentrations in personal air samples were correlated with post-workshift samples (R = 0.70, P < 0.05) in electroplating workers. Given the rapid clearance of nickel, it is not surprising to find an association between F_{ENO} and urinary nickel concentrations at a lag time of zero. The significant exposure–response relationship between F_{ENO} and urinary lead concentrations at 0-lag, then 48- and 60-lag hr may indicate that after an initial rapid clearance, lead may be excreted slowly. An animal study using rats found that lead excretion in the urine was initially rapid after inhalation exposure to lead in exhaust particulates, followed by a long clearance period [Morgan and Holmes, 1978]. Hauser et al. [1998] had found that vanadium has an initial rapid clearance, which might represent only a portion of the total vanadium dose, followed by a period of slow clearance. We observed a significant increase in post-workshift urinary vanadium concentrations compared to pre-workshift levels, as in the Hauser study. In addition, we found that creatinine-adjusted urinary vanadium concentrations at the beginning of the 5-day sampling period significantly differed from the concentrations near the end of the sampling period. These results suggest that complete vanadium clearance might occur over a 3–4 day period, which may explain the lag time of 84 hr for a significant association between urinary vanadium concentration and F_{ENO}.

Increased exposure to metal-containing fine particulate matter, as determined by increased urinary concentrations of metals, was found to be associated with decreased F_{ENO} in our study. Previous clinical studies have found that individuals with inflammatory lung diseases such as asthma and bronchiectasis have increased F_{ENO}, thus F_{ENO} often has been labeled as an effective biomarker for airway inflammation. However, other studies have found that airway inflammation is not always associated with increased levels of expired NO.

ROFA and cigarette smoke have been shown to induce an inflammatory response in exposed individuals. However, Huang et al. [2002] observed that exposure to ROFA resulted in decreased NO production in isolated perfused rabbit lungs. NO production also was reduced following exposure to vanadium, indicating that the metal component of ROFA may be responsible for the decreased NO production. Cigarette smoke, which also contains significant levels of various metals [Chiba and Masironi, 1992], has been shown to decrease endogenous NO levels [Kharitonov et al., 1995]. The reduction in F_{ENO} following exposure to metals may represent an important acute airway response since endogenous NO is necessary for airway function.

Urine samples may be used for biological monitoring of metal exposures. Due to the variation in metal elimination kinetics, an understanding of the relevant lag-time of sampling is important when studying acute health effects. In this study, we found a significant inverse association between log F_{ENO} and log-transformed creatinine-adjusted urinary metal concentrations of vanadium, nickel, manganese, copper, and lead at various lag times. Given the important contribution of endogenous NO to respiratory health, the significant reduction in F_{ENO} following airborne metal exposure may be of concern and should be assessed further in human studies.

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