Correlation of urinary nickel excretion with observed 'total' and inhalable aerosol exposures of nickel refinery workers

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An investigation of the relationship between observed nickel aerosol exposures and urinary nickel excretion was undertaken at a Scandinavian nickel refinery. The goal of the study was to assess the impact of nickel aerosol speciation, the use of particle size-selective sampling instrumentation and adjustment of urinary levels for creatinine excretion on the usefulness of urinary nickel excretion as a marker for exposure. Urinary nickel measurements and paired 'total' and inhalable aerosol exposure measurements were collected each day for one week from refinery workers in four process areas. The mean observed urinary nickel concentration was 12 μg L^{-1} (11 μg of Ni per g of creatinine). The strongest relationships between urinary excretion and aerosol exposure were found when urinary nickel levels were adjusted for creatinine excretion and when exposure to only soluble forms of nickel aerosol was considered. No significant difference was observed between measures of 'total' and inhalable aerosol in the ability to predict urinary excretion patterns. In the light of these results, it is recommended that consideration be given to the chemical species distribution of nickel aerosol in the use of urinary nickel measurements as a screening tool for cancer risk in occupationally-exposed populations.

Introduction

It is widely recognized that the usefulness of occupational aerosol exposure measurements in evaluating workplace health risks is limited by their inability to account sufficiently for the uptake, distribution and excretion of inhaled particulate matter, including both solid particles as well as liquid droplets, which deposit on the surfaces of the respiratory tract. This limitation often suggests that biological monitoring be conducted in order to more fully assess the health risks faced by exposed workers. An important source of guidance commonly used to aid in the interpretation of results from biological monitoring is the compilation of biological exposure indices (BEIs), published annually by the American Conference of Governmental Industrial Hygienists (ACGIH).[1] ACGIH assigns BEIs in order to '...represent the levels of determinants which are most likely to be observed in specimens collected from a healthy worker who has been exposed to chemicals to the same extent as a worker with inhalation exposure to the (threshold limit value) TLV'.

ACGIH has identified nickel as a substance for which it seeks to establish a BEI. This is driven by the fact that there has been increasing toxicological and epidemiological evidence in recent decades supporting the role of nickel as a causative agent in lung and nasal cancer in humans. Such findings have led to technical efforts aimed at further reductions in exposure levels in the nickel production industry. Uncertainty about the cancer risk at present levels of exposure to airborne nickel, and the possible role of distinct nickel species in nickel toxicity, stimulated a major epidemiological inquiry in the 1980s into nickel-induced carcinogenesis under the auspices of the International Committee on Nickel Carcinogenesis in Man (ICNCM).[2] This group examined the relationship between exposure to four nickel species groups and the occurrence of cancer. The species fractions in question were: (a) 'sulfidic' (including arsenides and tellurides); (b) 'oxidic' (including silicates); (c) metallic; and (d) water-soluble. The study focused primarily on historical conditions in the nickel primary production and nickel alloy production industries, where the highest occupational exposures to nickel were thought to have occurred. Among its conclusions, ICNCM found it likely that more than one form of nickel gives rise to lung and nasal cancer, and that the risk of cancer is largely limited to (a) those individuals whose mean exposures to soluble forms of nickel aerosol exceeded 1 mg m^{-3}, and (b) those whose mean exposures to less soluble and insoluble forms of nickel aerosol exceeded 10 mg m^{-3}. The authors also noted, however, the relative scarcity of reliable occupational exposure data on which to base firm recommendations for quantitative occupational exposure limits.

This paper discusses the results of a biological monitoring exercise carried out in parallel to an aerosol sampling campaign at a Scandinavian nickel refinery in September 1995. The goals of the study were threefold: firstly, to measure the urinary nickel concentrations of nickel refinery workers; secondly, to describe the distribution of airborne nickel among species groups; and thirdly, to characterize the relationship between urinary nickel concentrations and nickel aerosol exposures as measured using 'total' and inhalable aerosol sampling instrumentation. The work is complementary to an earlier paper (Thomassen *et al.*, 1999),[3] but here the industrial processes were distinctly different, nickel exposure levels were much lower, and many more samples were speciated. It is expected that the results of such work will be useful in assessing the exposure-related cancer risk faced by workers in nickel production industries, and, more widely, in identifying a role for biological monitoring.

Materials and methods

The worksites

The nickel refinery in question has about 650 employees and is engaged in the purification of nickel, copper and cobalt from a

matte of mixed composition derived from the smelting of the original ore. Raw materials in the form of the pelletized matte are received by ship from nickel smelters in Canada and Botswana. This matte is ground into a fine powder in the matte grinding area. Ground matte is transferred to the leach tanks in the chlorine leaching plant, along with recycled solution and chlorine gas from subsequent processes. During the leaching step, the bulk of the nickel in the feed is dissolved with copper. The copper is precipitated by adding matte, whereupon the slurry is filtered to remove copper sulfide from the pregnant solution. The pregnant nickel solution is then neutralized and oxidized with chlorine to precipitate iron and arsenic. The filtrate is cooled, re-filtered for gypsum removal, and pumped to the cobalt refining area for extraction with a 15% solution of tri-isooctylamine in an aromatic solvent to remove the cobalt. The raffinate from the cobalt extraction is diluted so that lead and other metals can be precipitated by treatment with nickel carbonate and chlorine. The pure nickel solution is then passed to the tank house for electrowinning, with chlorine being generated at the anode and recycled to the chlorine leaching process. Cobalt cathodes are produced from an all-chloride electrolyte in a tankhouse similar to that for nickel. The sulfide residue is filtered off after chlorine leaching and cementation, and is transferred to the roasting/smelting plant where it is re-pulped with water and slurry-fed to fluidized bed roasters. Sulfur dioxide in the roaster off-gases is recovered as sulfuric acid. The calcine is leached in spent copper anolyte and copper is produced by electrowinning from the purified solution. The residue from the copper leaching is treated further to extract precious metals. All plant workers are provided with respiratory protection equipment, which is required to be worn at all areas where atmospheric nickel exceeds the occupational exposure limit.

Biological monitoring

Urine samples were collected from workers at the four nickel refining processes outlined above, matte grinding, chlorine leaching, electrowinning and roasting/smelting, as part of a surveillance programme being conducted by the occupational health staff at the plant in cooperation with the Norwegian National Institute of Occupational Health. The 20 subjects were selected from a pool of workers who volunteered to participate in a separate aerosol exposure study carried out by other researchers. Each subject was followed for a five-day period, with ten subjects followed per week. Four subjects were selected from matte grinding areas, five from chlorine leaching, five from roasting/smelting and six from electrowinning. Subjects were asked to submit two urine samples per day for each day of the workweek, one in the morning and one in the afternoon. Morning samples were collected by workers at home before leaving for work and delivered directly to researchers at the plant upon arriving at the plant. Afternoon samples were taken at the plant immediately before workers left for the day and after removing their work clothes. Workers were directed to wash their hands before sampling to reduce the potential for contamination.

Methods employed in this investigation for the collection and analysis of urine samples have been previously described.[3] Urine samples were collected in disposable plastic cups from which sub-samples were poured into a screw-capped vial (Universal Container 25 ml, NUNC, Denmark). Control cups and vials were tested for nickel content to assure the absence of nickel contamination from these sources (*i.e.*, less than the detection limit for the method employed of 0.5 $\mu g\ L^{-1}$). Samples were kept frozen at $-20\ ^{\circ}C$ prior to analysis. Thawed samples were heated at $95\ ^{\circ}C$ for one hour to re-dissolve urine precipitates and to prevent the risk of laboratory-acquired infection. Urinary nickel concentration was measured by direct injection of undiluted urine without the use of a chemical modifier with electrothermal atomic absorption spectrometry employing a Zeeman-based Perkin Elmer Model 5100 PC/HGA-600 and a Perkin Elmer SIMAA 6000/THGA graphite atomizer calibrated with urine-matched standard solutions (calibration range 0–50 $\mu g\ L^{-1}$). The accuracy and precision of measurements were assessed continuously with human urine quality control materials produced by Sero Ltd. (Asker, Norway; Seronorm STE 101021 and 403125). Day-to-day variability of nickel measurements in reference materials was typically of the order of 10%. The average measured nickel concentrations of STE 101021 and 403125 were within $\pm 10\%$ of the values given by the manufacturer. The creatinine content of urine samples was measured using a Beckman creatinine analyzer (which operated on the basis of the Jaffe reaction).

Aerosol sampling

Measurements were made of two indices of worker aerosol exposure as determined using two different personal aerosol samplers. The first involved the measurement of inhalable aerosol, defined as the fraction of aerosol that is inhaled through the nose and/or mouth during breathing, reflecting the effect of particle size on what enters. This index is consistent with the criterion for nickel exposure as specified by ACGIH in relation to its TLVs. This was achieved using a sampler developed specifically for this purpose at the Institute of Occupational Medicine (IOM), Edinburgh, UK.[4] This instrument, known as the 'IOM personal inhalable aerosol sampler', is widely thought to be currently the best reference sampler for the inhalable fraction. The second approach involved the measurement of so-called 'total' aerosol, the concept upon which aerosol exposure assessment and occupational exposure standards are largely based in most countries. This was performed using the 37 mm closed-face plastic cassette, which is widely used in the United States and in many other countries. Recent wind tunnel experiments have shown that whereas the IOM sampler provides a good measure of inhalable aerosol exposure, matching closely the particle size-selective inhalability criterion specified by ACGIH, the 37 mm sampler undersamples significantly with respect to that fraction.[5]

For each volunteer, two personal aerosol samples were taken simultaneously, one for each sampler type mounted in the worker's breathing zone. Such samples were taken for a full workshift whenever possible, with all samples taken for at least four hours. All samplers were operated at a flow rate of 2 $L\ min^{-1}$. At the conclusion of the sampling campaign, the samples were divided into two groups for analysis. The first set, comprising 43 sample pairs, was assayed for 30 elements by inductively coupled plasma absorption emission spectrophotometry (ICP-AES). A smaller set of 20 sample pairs was submitted for the analysis of nickel species content by the method described by Zatka *et al.*[6] Division of samples between the two groups was done so that the subset of samples for speciation was equally representative of the various processes at the facility and so that the speciation subset included samples from as many individual workers as possible.

The Zatka method involves the sequential leaching of aerosol samples with three reagents, each of which extracts a distinct group of chemical species from the sample. In the laboratory, filters from the 37 mm cassette were laid out on support membranes upon which the sequence of reagents was applied. Filters from the IOM sampler were arranged similarly, with the addition of a cotton pad containing material wiped from the inside of the IOM sampling capsule from each sample (as is prescribed in the use of this instrument). The sample was leached first with a 0.1 M ammonium citrate solution to extract the soluble nickel component from the sample. A second leach was conducted with a solution containing ammonium citrate and hydrogen peroxide to extract the 'sulfidic' group of nickel

species. A solution containing methanol and bromine was added to the remaining sample, extracting the elemental nickel component. The residual material contained the 'oxidic' group of nickel species. This residual material and the three leachate solutions were dried, treated with nitric and perchloric acids, and analyzed separately for nickel content by atomic absorption spectrophotometry.

Data analysis

Correlation and linear regression methods were employed to characterize the relationships between urinary nickel (NiU) measurements and aerosol sampling results. A common problem in biological monitoring is the observation of a high variability in urinary output volume from sample to sample. For this reason, urinary monitoring results are often expressed as the ratio of observed urinary nickel concentration (μg Ni per L urine) and creatinine concentration (g creatinine per L urine). This is referred to hereafter as the 'adjusted NiU' concentration. Creatinine serves as an index of kidney function, and its use in the denominator in this context allows for urinary nickel concentrations to be expressed in a manner that is largely independent of the volume of urine excreted.

Linear regression procedures were employed to describe the relationship between average NiU concentrations from the sampling week (adjusted and unadjusted) and the mean weekly nickel aerosol exposure levels as measured with both 'total' and inhalable aerosol sampling methods, respectively. Estimates of soluble nickel exposure for all samples were obtained by multiplying nickel exposure estimates by a factor reflecting the prevalence of soluble nickel for 'total' and inhalable aerosol in each of the four workplaces in the refinery. These were performed using the results of the speciation analyses of the 20 sample pairs set aside specifically for this purpose. Estimates of insoluble nickel exposure were likewise calculated, using the sum of observed concentrations for the three remaining species groups (sulfidic, metallic and oxidic). In sum, estimates were obtained for exposures to elemental, soluble and insoluble nickel as measured with both 'total' and inhalable sampling methods, yielding a total of six sets of aerosol exposure estimates.

Regression procedures were first carried out using each of the six measures of aerosol exposure individually as predictor variables. In addition, two multiple regression procedures were executed employing as predictor variables the soluble and overall insoluble exposure levels for each sampler type. It was expected from previous experience of ourselves and others that the distributions of both urinary nickel excretion values and nickel aerosol exposure measurements would be approximately lognormal. So the NiU and aerosol exposure measurements and estimates were log-transformed prior to analysis in order to normalize them. This enabled them to satisfy the assumptions required for such regression analysis procedures.[7] This expectation of lognormality was subsequently confirmed upon analysis of the urinary excretion and aerosol exposure data.

Results

Nickel aerosol species measurements

The results of the aerosol exposure assessment exercise are summarized in Table 1. They reflect a wide range of mean inhalable exposure values for the three less-soluble species across the range of plant processes, with mean exposures by process ranging over more than two orders of magnitude. The exception is soluble nickel, where observed mean exposure-values differ by a factor no greater than four across the four process areas. This pattern is seen for both samplers.

Fig. 1 displays the distribution of inhalable nickel exposures in refining operations among the 'sulfidic', 'oxidic', metallic and water-soluble species groups. It is clear that marked differences exist in the distribution of airborne nickel among the species groups for the four process areas. For example, in three of the four process areas, a single species comprises more than 60% of all collected inhalable nickel aerosol, the 'sulfidic' group in matte grinding, the 'oxidic' group in roasting and smelting, and the soluble component in electrowinning. In the chlorine leach plant, the 'sulfidic' group is the most prevalent, followed closely by soluble nickel.

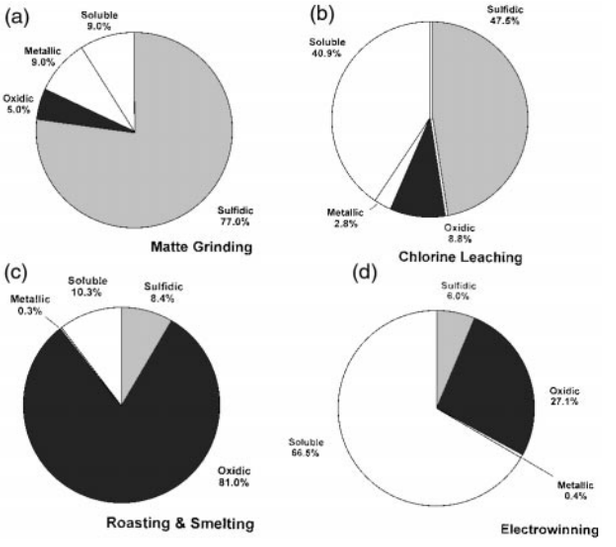

Fig. 1 Distribution of nickel species among refining processes: prevalence of four nickel species groups in workplace aerosol among nickel refinery process areas. The percentage values shown are from measurements of inhalable nickel (with the IOM personal inhalable aerosol sampler).

Table 1 Exposure to nickel species groups in nickel refining processes: mean exposure estimates from measurements of observed (a) inhalable and (b) 'total' aerosol exposures to nickel species in nickel refining (species identified by process)

(a) Process	Soluble/mg m^{-3}	'Sulfidic'/mg m^{-3}	Metallic/mg m^{-3}	'Oxidic'/mg m^{-3}
Matte grinding	0.0348	0.3914	0.0339	0.0182
Chlorine leaching	0.0304	0.0367	0.0028	0.0047
Roasting/smelting	0.0114	0.0094	0.0004	0.1010
Electrowinning	0.0531	0.0013	0.0001	0.0054

(b) Process	Soluble/mg m^{-3}	'Sulfidic'/mg m^{-3}	Metallic/mg m^{-3}	'Oxidic'/mg m^{-3}
Matte grinding	0.0286	0.2022	0.0374	0.0104
Chlorine leaching	0.0133	0.0207	0.0031	0.0030
Roasting/smelting	0.0081	0.0049	0.0008	0.0826
Electrowinning	0.0176	0.0010	0.0012	0.0070

Measurements of urinary nickel concentrations

A total of 214 urine samples were collected and analyzed for nickel and creatinine content. This number includes 79 pairs which represent morning and afternoon samples from workers for whom 'total' and/or inhalable aerosol sampling results are also available. Table 2 summarizes the results of the urinary nickel concentration measurements. Individual mean weekly NiU concentrations were in the range from 2.7 to 52 μg L^{-1} of urine (unadjusted) and from 1.8 to 44 μg per mmol of creatinine (adjusted). The results indicate that observed urinary concentrations were markedly lower for the roasting/smelting workers than for workers in the remaining three process areas. The observed standard deviation values show considerably greater variability in urinary nickel excretion among matte grinding workers than for workers in other process areas. This may be attributed to the presence in the matte grinding cohort of a single worker, represented by the uppermost point in Figs. 2 and 3, whose urinary nickel output was markedly elevated.

While the composite mean of all afternoon samples was higher than the corresponding mean for morning samples, no significant trends were observed between concentrations measured in the morning *versus* afternoon measurements. Similarly, no trend in urinary nickel excretion was observed across the work week.

Relationship between urinary and air measurements

Figs. 2 and 3 display the data for mean weekly NiU concentration as a function of the mean weekly nickel exposures of the participating workers. Table 3 shows the results of linear regression analyses in greater detail, where the strengths of the assumed linear associations are now best represented by R^2. These results show that, for both unadjusted and adjusted NiU and for regression procedures employing a single aerosol exposure variable, R^2 values are appreciably larger when soluble nickel aerosol exposure is employed as the independent variable. Further, in those cases estimated R^2 values are greater for the NiU concentrations adjusted for creatinine content. In the multiple regression analyses, the addition of insoluble aerosol exposure as a predictor variable resulted in a negligible improvement in the observed relationship, with R^2-values increasing by less than 0.05. In all cases, coefficients for insoluble exposure were found not to be significantly different from zero.

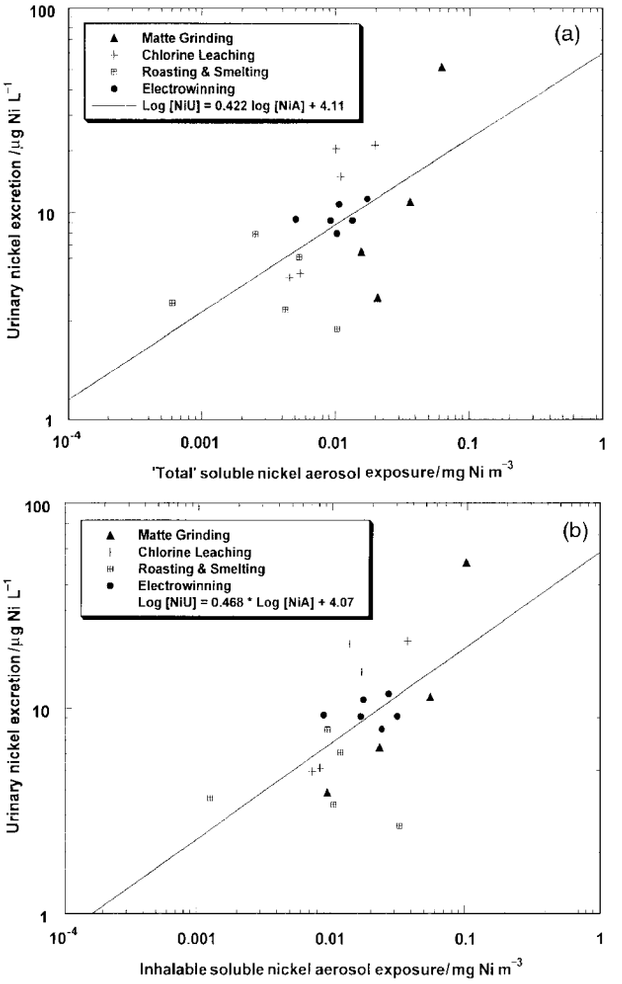

Fig. 2 Nickel aerosol exposures and raw urinary nickel concentrations: plot of unadjusted urinary nickel concentrations *versus* (a) 'total' and (b) inhalable measures of soluble nickel aerosol exposure. Lines representing the results from regression analysis are also displayed (see legend).

Discussion

Previous studies have sought to describe the relationship between observed 'total' and inhalable aerosol exposures during primary metals production and to examine the impact

Table 2 Urinary nickel excretion in nickel refining processes: summary of mean weekly (a) unadjusted and (b) adjusted urinary nickel concentrations observed in nickel refinery workers

(a)

Process	Number of workers	Number of worker-days[a]	Mean (range) (μg Ni per L of urine)	Standard deviation (μg Ni per L of urine)	Median (μg Ni per L of urine)
Matte grinding	4	16	18.3 (3.9–51.5)	22.4	8.9
Chlorine leaching	5	18	13.4 (4.9–21.3)	8.0	15.0
Roasting/smelting	5	19	4.8 (2.7–7.9)	2.2	3.7
Electrowinning	6	25	9.7 (7.9–11.7)	1.4	9.2
Plant-wide	20	78	11.1 (2.7–51.5)	10.8	8.5

(b)

Process	Number of workers	Number of worker-days[a]	Mean(range) (μg Ni per L of urine)	Standard deviation (μg Ni per L of urine)	Median (μg Ni per L of urine)
Matte grinding	4	16	17.1 (3.8–44.5)	18.7	10.2
Chlorine leaching	5	18	10.9 (2.9–22.1)	8.0	10.4
Roasting/smelting	5	19	3.1 (1.8–4.6)	1.1	4.4
Electrowinning	6	25	9.7 (5.4–17.5)	4.4	8.0
Plant-wide	20	78	9.8 (1.8–44.5)	9.8	7.2

[a]Two urine samples collected per day.

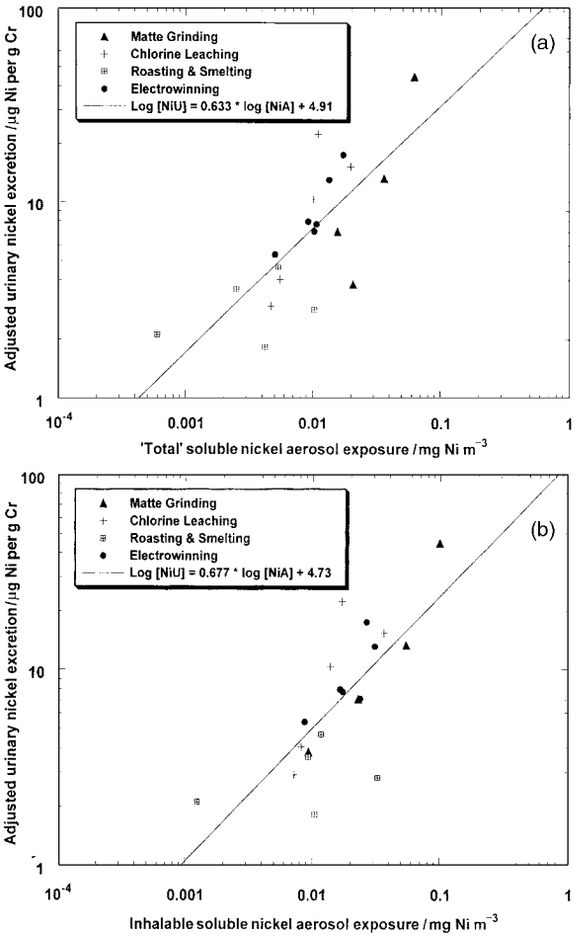

Fig. 3 Nickel aerosol exposures and creatinine-adjusted urinary nickel concentration: plot of adjusted urinary nickel concentrations *versus* (a) 'total' and (b) inhalable measures of soluble nickel aerosol exposure. Lines representing results from regression analysis are also displayed (see key).

of the differences on occupational exposures and standards.[8–10] The principal finding was that inhalable aerosol exposures were roughly twice as great as the corresponding 'total' aerosol exposures. A summary of the corresponding intersampler comparison results from the current data set at the nickel refinery studied, for nickel and several other metallic elements, are shown in Table 4.[11] They are broadly consistent with trends observed in the earlier studies.

This paper represents results from the first attempt to correlate urinary nickel excretion with nickel aerosol exposures as measured with sampling instrumentation corresponding to the ACGIH particle size-selective criterion for inhalable aerosol [also widely adopted by other bodies, including the International Standards Organisation (ISO) and the Comité Européen Normalisation (CEN)]. In this study, correlation coefficients for the relationship between urinary nickel excretion and aerosol exposure levels were quite similar for the two sampling methods (see Table 3). This suggests that there is no substantial difference in the ability to accurately predict urinary nickel levels on the basis of either 'total' or inhalable aerosol sampling results. It should be kept in mind, however, that the similarity of these correlation coefficients should not be interpreted as suggesting that the two sampling methods are equally suited to the assessment of exposure-related health risks for nickel. Nickel has been shown to be a likely nasal carcinogen and, as such, exposures to nickel-containing aerosol should be assessed on a basis which accounts for all airborne particulate matter which may enter the respiratory tract, including the nose. This, therefore, is part of the rationale

Table 3 Relationship between nickel aerosol exposure and urinary nickel excretion: results of regression analysis for (a) unadjusted and (b) adjusted NiU concentrations and various measures of nickel aerosol exposure according to the model $\ln[\mathrm{NiU}] = K \times \ln[\mathrm{NiA}] + b$, in which [NiU] represents the urinary nickel concentration and [NiA] the nickel aerosol concentration. The K values in parentheses are for those regression procedures where K was found not to be significantly different from zero ($\alpha = 0.05$)

(a) Sampler	Analyte	K	b	$P: K>0$	R^2
'Total'	Elemental Ni	(0.108)	2.49	0.35	0.05
Inhalable	Elemental Ni	(0.104)	2.42	0.39	0.04
'Total'	Soluble Ni	0.422	4.11	0.006	0.35
Inhalable	Soluble Ni	0.468	4.07	0.005	0.36
'Total'	Insoluble Ni	(0.024)	2.23	0.76	0.005
Inhalable	Insoluble Ni	(0.019)	2.20	0.82	0.003

(b) Sampler	Analyte	K	b	$P: K>0$	R^2
'Total'	Elemental Ni	(0.185)	2.55	0.17	0.10
Inhalable	Elemental Ni	(0.168)	2.40	0.23	0.08
'Total'	Soluble Ni	0.633	4.91	<0.001	0.56
Inhalable	Soluble Ni	0.677	4.73	<0.001	0.54
'Total'	Insoluble Ni	(0.043)	2.11	0.65	0.01
Inhalable	Insoluble Ni	(0.030)	2.04	0.75	0.006

behind the adoption of the inhalable fraction as the criterion for nickel aerosol exposure.

Furthermore, a number of insoluble nickel species have been implicated as likely carcinogens. However, the results presented in this paper suggest that observed urinary nickel levels are not highly responsive to insoluble nickel. It follows that NiU should not be regarded as a reliable marker for exposure to insoluble forms of nickel. Conversely, however, strong correlations were found between observed exposures to soluble nickel aerosol and NiU concentrations. This is, of course, consistent with expectations based on the relatively high efficiency with which water-soluble materials may pass from the respiratory tract into the blood and thence into the urine, as has been found by other researchers for occupational situations where appreciable amounts of soluble nickel aerosol were likely to have been present.[12–14]

Two important factors to consider in interpreting these results are the use of respiratory protection by plant workers and non-occupational exposure to nickel. In the plant, the use of respiratory protection was required, and observed, in areas where nickel aerosol exposures were above applicable occupational exposure limits. So it is likely that there may have been some interferences in the relationships studied. More specifically, it is likely that, for a given measured nickel aerosol exposure level, a more significant contribution to urinary nickel excretion would be observed for workers in areas with low observed dust exposures, such as electrowinning, than for workers in areas with high dust exposures, such as matte grinding. Differences in the prevalence of use of respiratory protection across work areas may, therefore, have a significant impact on urinary excretion, and must be considered in drawing conclusions on the basis of this research. In addition, nickel is a natural constituent of many foods and of tobacco. These may represent important non-occupational sources of nickel that may influence observed urinary nickel excretion patterns.

The findings in this study are in interesting contrast to the findings of Culver *et al.*[15] in their study of the relationship between observed 'total' and inhalable boron exposures and levels of boron in urine and blood for workers in the borate production industry. In that study, regression of blood and urine boron levels on observed inhalable aerosol exposures yielded substantially higher R^2 values (0.85 for urine, 0.77 for

Table 4 Intersampler ratios for inhalable and 'total' nickel aerosol exposures in nickel refining: summary of results from analysis of intersampler comparison data from nickel refining as reported by Werner *et al.*[11] The *S*-values listed are coefficients from the model $E_{IOM} = S \times E_{37}$, where E_{IOM} represents inhalable nickel aerosol exposure (as measured using the IOM personal inhalable aerosol sampler) and E_{37} represents 'total' nickel aerosol exposure (as measured using the 37 mm sampler in closed-face mode). Results in italics are for analyses with designated outliers included in the dataset; LCL is the lower bound of the 95% confidence interval and UCL is the upper bound of 95% confidence interval

Worksite	*S*	Standard error	R^2	*n*	LCL 95%	UCL 95%
Matte grinding	1.80	0.29	0.79	11	1.14	2.46
	2.29	*0.56*	*0.61*	*12*	*1.04*	*3.54*
Chlorine leaching	1.65	0.13	0.93	14	1.37	1.93
Roasting/smelting	2.29	0.33	0.82	12	1.55	3.03
Electrowinning	1.54	0.12	0.94	13	1.28	1.80
Plant-wide	1.81	0.12	0.83	50	1.57	2.05
	1.92	*0.16*	*0.74*	*51*	*1.60*	*2.24*

blood) than those from regression of the same biological indices on corresponding observed 'total' aerosol exposures (0.49 for both urine and blood). This contrast is likely to be attributable to the relative complexity of the toxicokinetics of nickel in comparison with boron, which is excreted from the body largely unmetabolized.

The results from the speciation of nickel aerosol in the workers' exposures show the presence of a wide variation in the prevalence of individual nickel species groups in the various nickel refining processes of this plant. Given the observation that only soluble nickel aerosol was found to significantly affect observed urinary nickel levels, the results suggest that the measurement of individual nickel species groups in aerosol samples may provide useful information in the interpretation of urinary nickel measurements. The observation that more than one nickel species group may be abundantly present in an industrial process has been noted elsewhere.[16,17] Taken as a whole, these findings suggest that the characterization of the exposures of nickel industry workers can be greatly enhanced by the consideration of the species distribution of nickel in workplace aerosol. With this in mind, we are currently conducting research to 'fingerprint' nickel production industry workplaces in this way.

An interesting methodological issue is raised in the comparison between the exposures to airborne nickel and NiU, as reflected in the two separate indices, that is, 'raw' urinary nickel concentration and values adjusted with respect to urinary creatinine concentrations, respectively. A recent review of urinary nickel concentrations for occupationally exposed populations has shown that urinary nickel concentrations have been commonly reported as either raw concentrations or as creatinine-adjusted levels,[18] that is, one or the other. In our study, as shown in Table 3, adjustment of urinary nickel measurements for creatinine resulted in correlation coefficients and R^2 values that were consistently higher. This suggests that, where available, the use of urinary creatinine concentrations as a standardization tool may reduce the amount of random variability in urinary nickel measurements and allow for urinary excretion to be better explained on the basis of measurements of nickel aerosol exposure.

Conclusions

This work was stimulated primarily by the recognition of the need to characterize workplace nickel aerosol exposures in terms of the inhalable fraction. The findings, however, are particularly interesting in the light of the recent proposal by the ACGIH to express its threshold limit value (TLV) for nickel in terms of a number of speciation groups, as well as continuing interest in identifying the degree to which biological levels of nickel may be indicative of exposure-related health risk. An important consideration in light of these results is the role that biological monitoring might play in the assessment of health risks posed by nickel exposures in the primary nickel production industries. Given that a primary health risk of concern for nickel-exposed workers is the development of cancers of the respiratory tract, presumably near sites at which nickel-containing particulate is deposited, it appears that assessments of workplace exposure to inhalable aerosol are likely to better reflect health risk for nickel than consideration of nickel levels in urine or plasma. This should be considered in future deliberations, by ACGIH or other bodies, about the development of reference urinary concentrations for nickel. It should also emphasize the need for caution in using the results of biological monitoring to make inferences about the health status of nickel industry workers.

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