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Lung deposition versus inhalable sampling to estimate body burden of welding fume exposure: A pilot sampler study in stainless steel welders

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ABSTRACT

This pilot study evaluated the ability of a lung deposition sampler (LDS) to estimate body burden by comparing lung-deposited and inhalable nickel and chromium exposures to biomarkers of internal dose. A cohort of stainless steel welders (N = 18) wore side-by-side inhalable and lung deposition samplers for two Monday shifts and urine samples were collected pre- and post-shift. Samplers were analyzed for inhalable and lung-deposited nickel and chromium and urine was analyzed for the respective biomarkers of internal dose. There were statistically significant relationships between lung-deposited nickel (β_{Ni} = 0.10; 95% CI = 0.05–0.16) and chromium (β_{Cr} = 0.07; 95% CI = 0.006–0.14) and their internal dose biomarkers. No relationship was found between inhalable metals and internal dose biomarkers. In moving towards a more physiologically relevant exposure metric, the LDS can provide better estimates for the total body burden of exposure than traditional penetration-based samplers.

1. Introduction

The size-dependent ability of particles to penetrate the lung is well known and traditional occupational samplers have been engineered to simulate this penetration curve. However, not all inhaled particles remain in the lungs after exhalation and it is the lung-deposited fraction of particles that contribute to the overall body burden (Esmen, Johnson, & Agron, 2002; Gehr & Heyder, 2000). The deposition of particles within the lung is strongly associated with particle size, indicating that the use of penetration-based samplers can introduce variable exposure misclassification, dependent on the size distribution of the measured particles (Hodgkins et al., 1991; Koehler, Clark, & Volckens, 2009). Supporting this, animal studies have shown that total mass deposition in the lung is more strongly associated with inhalation toxicity than the ambient concentration levels (Cassee et al., 2002). The potential exposure misclassification between penetration and deposition metrics is likely particularly strong at sub-micrometer particle sizes where the penetrating and deposited fractions have the greatest disparity (Johnson & Esmen, 2004).

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Calculating the lung deposited dose from penetrative exposure estimates requires simultaneously assessing the full aerosol size distribution; however, the instrumentation necessary to do that is expensive and often bench-scale in size. Addressing this challenge, a polyurethane foam-based sampler was engineered to collect the lung-deposited aerosol fraction for the total human respiratory tract (head airways, tracheobronchial region, and alveolar region) by Koehler et al. in 2009. This foam-based sampler is referred to in this manuscript as the Lung Deposition Sampler (LDS). By using the foam as the collection substrate instead of as a size-selective sampling pre-separator, this design uses a novel approach that minimizes the risk of removing particles of interest prior to analysis as a result of incidental loss on the pre-separating foam (Koehler et al., 2009; Kuo et al., 2005). The LDS demonstrated by Koehler et al. (2009) showed good experimental agreement with the International Commission on Radiological Protection (ICRP) Deposition Model for average adult males and females under light exercise and nose breathing conditions.

A shift towards utilizing deposition-based metrics to decrease possible exposure bias is likely to be particularly relevant in settings where the primary exposure of interest is in the fine or ultra-fine particle size range (aerodynamic diameter, $d_a < 2.5$ and 0.1 μm, respectively). Welding fume, for example, is predominately composed of fine and ultra-fine metal particles of respirable size, such as chromium, manganese, iron and nickel (Antonini, 2003), and most studies report the mass median aerodynamic diameter of sampled welding fume as less than 1 μm (Antonini, 2008; Ennan, Kiro, Oprya, & Vishnyakov, 2013; Vishnyakov, Kiro, & Ennan, 2013).

Over eleven million workers worldwide are exposed to welding fume through full-time employment as welders and an additional 110 million workers incur incidental welding-related exposures as a result of their jobs (Guha et al., 2017). Occupational exposure to welding fume has long been associated with a variety of adverse health outcomes, including lung, nasal, and kidney cancer, respiratory and cardiovascular impairment, and neurotoxic outcomes such as manganism, a Parkinson's Disease-like disorder (IARC, 2018; Santamaria, Cushing, Antonini, Finley, & Mowat, 2007; Sjogren, Fossum, Lindh, & Weiner, 2002). Importantly, welding fume was reclassified from a Group 2B (possible human carcinogen) to a Group 1 known human carcinogen by the International Agency for Research on Cancer (IARC) in 2017 (IARC, 2018). Both nickel and the hexavalent species of chromium, found at relatively high levels in stainless steel welding fumes in particular, are Group 1 carcinogens (IARC, 2012; Jeffus, 2004). Additionally, as a result of their relatively short half-lives in the body (<24 h), measurable changes in urine nickel and urine total chromium after single-day welding exposures have been shown previously in the literature (Gube et al., 2013; Nordberg, 1996; Stridsklev, Schaller, & Langård, 2007; Welinder, Littorin, Gullberg, & Skerfving, 1983).

As the LDS provides an estimate of internal dose as opposed to ambient concentration, it is anticipated that the LDS will shift the exposure assessment paradigm towards a more biologically and physiologically relevant metric than the current occupational exposure metrics. To test this, the LDS was utilized in conjunction with a traditional inhalable size fraction sampler in a cohort of stainless steel welders to evaluate whether measures of the lung-deposited particle fraction were more closely related to urinary biomarkers of metals dose than measures of the inhaled particle fraction.

2. Methods

2.1. Site and participant information

This pilot study was carried out in October and November of 2017 in a stainless steel fabrication facility near Boise, Idaho. Briefly, eighteen of twenty-four employees at the site fit the inclusion criteria of being employed as either a full-time welder/fabricator or a laser operator and were enrolled to participate. All participants were administered informed consent and the Colorado Multiple Institutional Review Board (COMIRB) approved this study.

The fabrication facility was comprised of three shops with separated areas for welding, machining, and laser cutting. Shops 1 and 3 had functioning general ventilation systems, but Shop 2 did not have an operable general ventilation system for the duration of the study period. Gas Tungsten Arc Welding (GTAW) on stainless steel accounted for more than 85% of the total reported welding hours of the participants, followed by Gas Metal Arc Welding (GMAW) on mild steel.

Sampling was conducted on four Mondays during the study period with participants being monitored for the duration of their work-shift on two non-consecutive Mondays for personal exposure to inhalable and lung-deposited metals. Participant urine samples were collected before and after each shift. Pre-shift surveys were administered to collect demographic and health information, including alcohol, medication and nicotine usage and asthma history. Cigarette smoke is known to contain high levels of toxic metals, including chromium, nickel, and manganese (Bernhard, Rossmann, & Wick, 2005). Alcohol and nicotine use have also been shown to have effects on metabolism in the general population (Harris, Zopey & Friedman, 2016) and in welders (Wang et al., 2012), and have been correlated with increases in oxidative stress (Sakano et al., 2009). Post-shift surveys were administered to collect information on daily activities, including time-task logs for the different metal working tasks performed at that facility (e.g., welding, grinding, or cutting), during-shift exposure to nicotine-containing products, and the use of any personal protective equipment. Additionally, each participant was observed by study personnel at least twice per monitored shift to collect additional information on work conditions and any other determinants that could affect exposure, such as use of respiratory protection or the number of welders in close proximity.

2.2. Personal air sampling

Study participants wore two side-by-side samplers to collect the inhalable and lung-deposited size fractions of particles. An IOM sampler (SKC Inc., Eighty Four, PA) was used to measure the inhalable size fraction and the polyurethane foam sampler (LDS) described in Koehler et al. (2009) was used to measure the lung-deposited fraction. The LDS is comprised of commercially manufactured foam (fiber diameter = 49.6 μm; length = 8 cm) in a sample holder engineered from heat-resistant polyetherimide (PEI)

thermoplastic rods (McMaster-Carr, Elmhurst, IL). The LDS substrate was identical to the samplers used by Koehler *et* al in 2009 and did not include a size-selective sampling inlet. Samplers were located at the center of the collar, just below the welding hood (Fig. 1) in order to minimize left shoulder/right shoulder inter-sampler exposure differences relating to handedness and welding position. IOM samplers were operated at a flow rate of 2 L per minute (LPM) and LDS samplers were operated at a flow rate of 4 LPM.

2.3. Gravimetric analysis

IOM filters with their cassettes were pre- and post-weighed in a temperature and humidity-controlled weighing room at Johns Hopkins School of Public Health using a Mettler Toledo microbalance (Columbus, OH; ±0.001 mg accuracy).

2.4. Chemicals and materials

All chemicals were analytical grade or higher and used as received without further purification. Single and multi-element standards were purchased from Inorganic Ventures (Christiansburg, VA, USA) and certified reference materials (CRMs) for stainless steel welding fume and trace metals in urine were purchased from Health and Safety Laboratory (Harpur Hill, Buxton, UK) and Sero AS (Billingstad, Norway), respectively. Concentrated nitric and hydrofluoric acid (TraceMetal grade) were purchased from Fisher Scientific (Waltham, MA, USA) and hydrogen peroxide (Suprapur grade) was purchased from Millipore Sigma (Burlington, MA, USA). IOM samplers, cassettes, and mixed cellulose ester (MCE) filters (25 mm, 0.8 μm) were purchased from SKC Inc. (Eighty Four, PA, USA). Foam LDS substrates are commercially available through custom order and were purchased from UFP Technologies (Denver, CO).

2.5. Filter and foam metals analysis

All IOM filters and LDS substrates were digested using a strong acid microwave-assisted digestion method developed in-house to ensure total dissolution of LDS substrate. As particulate matter also deposits on the inside of the IOM cassette inlet, 2 cm × 2 cm squares of KimWipe (Thomas Scientific, Swedesboro, NJ) were used to wipe the interior of the IOM. LDS substrates were cut in half using metal-free scissors to better facilitate dissolution of the foam in the acid. Polyetherimide sampler walls were not wiped to account for any possible electrostatic losses as the electrical properties of PEI do not suggest that this would be a significant source of sample loss. Briefly, IOM filters, IOM inlet wipes, and both halves of the LDS substrate were placed in separate 50 mL Teflon microwave vessels with 4 mL 70% HNO_3, 2 mL 35% H_2O_2, and 0.35 mL 49% HF. The vessels were then digested in a Mars Express Scientific Microwave (CEM Corporation, Matthews, NC) with a temperature-controlled program reaching a final temperature of 180 °C.

An Agilent 7500 Series Octopole Inductively Coupled Plasma Mass Spectrometer (ICP-MS; Agilent Technologies, Santa Clara, CA) was used to analyze diluted digestant fluid. Percent recovery for all elements of interest was verified as 95 ± 5% using the welding fume CRM. Blanks, spikes, and duplicates were carried out at a rate of one in every ten samples.

2.6. Urine analysis

Urine was analyzed for creatinine, cotinine, and urine metals. Pre-shift and post-shift urine samples were collected from participants in 100 mL sample containers and stored on ice. Immediately upon leaving the fabrication facility each sample day, the urine was transported to Boise State University (BSU) and each sample was aliquoted into two metal-free vials (VWR International, Radnor, PA). Samples were subsequently stored at −80 °C in the BSU Biorepository. After the field study ended, aliquots of each urine sample were shipped overnight on dry ice to the Koehler lab at the Johns Hopkins School of Public Health and to the Bioanalytical Resource and

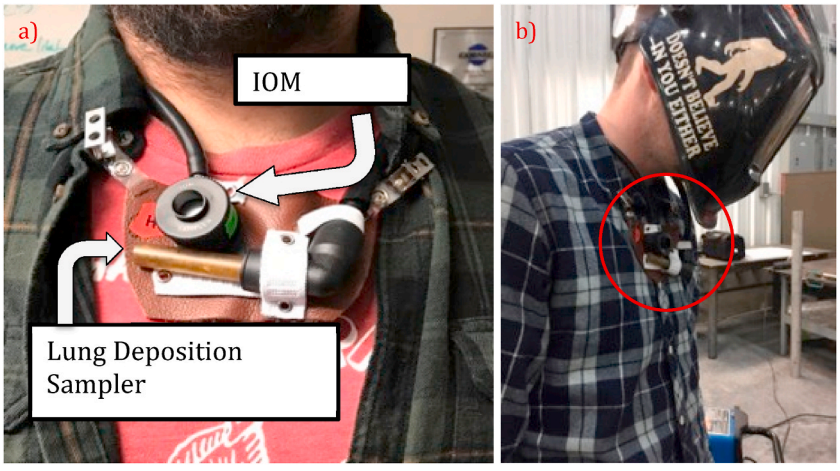

Fig. 1. a) Close up of collar sampler holder with IOM and LDS samplers attached; b) Collar sampler holder position in relation to welding hood.

Service Center at the University of Colorado. Urine creatinine was analyzed colorimetrically with a Beckman Coulter AU analyzer (Brea, CA) at the University of Colorado Hospitals Clinical Laboratory and cotinine and urine metals were measured using ELISA (Biquant Inc, San Diego, CA) and ICP-MS, respectively, at the Johns Hopkins School of Public Health.

Prior to ICP-MS metals analysis, the urine was centrifuged for 10 min at 1000 G (JS4.0 motor, Beckman Coulter, Brea, CA) and the supernatant was immediately decanted into a metal-free vial. The supernatant was subsequently diluted 1:5 with a dilution standard for a final sample concentration of 2% v/v HNO_3 and 10 ppb internal standard. All aliquots were analyzed in duplicate and blanks and spikes were run at a rate of one in every fifteen samples. Urine metal results are reported as the mean of the duplicate sample aliquots.

2.7. Statistical analysis

Summary statistics and geometric means were tabulated for each airborne metals exposure and urine biomarker. Repeated measures general linear mixed models (GLMM) with random participant intercepts were used to examine associations between airborne metals exposure and urine metals biomarkers. Separate models were created for each of the four sampler-biomarker pairs (LDS Cr & urine Cr; IOM Cr & urine Cr; LDS Ni & urine Ni; IOM Ni & urine Ni). All airborne metals and urine metals were approximately lognormally distributed and were log-transformed prior to analysis; the log-transformed post-shift urine metal was the dependent variable in each model. It was decided *a priori* to adjust for log-transformed urine cotinine and whether the participant had welded in the previous 24 h before beginning work (i.e., on Sunday) based on their known relationship with urine metals, and urine creatinine in order to account for urine dilution as spot urine samples were used for analysis. Age, self-reported ethnicity (as white or other than white), self-reported number of alcoholic drinks consumed in previous 24 h, and self-reported medication use (yes or no) were also screened for significance as covariates ($\alpha < 0.05$). For current medication use, survey responses were used to determine if a participant used any medication on the day of the study, including multivitamins that may contain chromium picolinate. However, multivitamin use was reported inconsistently between individual participants on different sampling days and participant responses did not include sufficient detail to determine if chromium picolinate was present. In favor of a more parsimonious final model, age, current medication use, and alcohol use were not included in the final analyses based on non-significance in full models. The final models are described below:

$$\begin{aligned}&\log(post-shift\ \ urine\ \ chromium)_{ij}\\&\quad=\beta_0+\beta_1[log(lung-deposited\ \ chromium)]+\beta_2(urine\ \ creatinine)\\&\quad+\beta_3[log(urine\ \ cotinine)]+\beta_4(24-hr\ \ welding)+\upsilon_j+\varepsilon_{ij}\end{aligned}$$

$$\begin{aligned}&\log(post-shift\ \ urine\ \ chromium)_{ij}\\&\quad=\beta_0+\beta_1[log(inhalable\ \ chromium)]+\beta_2(urine\ \ creatinine)\\&\quad+\beta_3[log(urine\ \ cotinine)]+\beta_4(24-hr\ \ welding)+\upsilon_j+\varepsilon_{ij}\end{aligned}$$

$$\begin{aligned}&\log(post-shift\ \ urine\ \ nickel)_{ij}\\&\quad=\beta_0+\beta_1[log(lung-deposited\ \ nickel)]+\beta_2(urine\ \ creatinine)\\&\quad+\beta_3[log(urine\ \ cotinine)]+\beta_4(24-hr\ \ welding)+\upsilon_j+\varepsilon_{ij}\end{aligned}$$

$$\begin{aligned}&\log(post-shift\ \ urine\ \ nickel)_{ij}\\&\quad=\beta_0+\beta_1[log(inhalable\ \ nickel)]+\beta_2(urine\ \ creatinine)\\&\quad+\beta_3[log(urine\ \ cotinine)]+\beta_4(24-hr\ \ welding)+\upsilon_j+\varepsilon_{ij}\end{aligned}$$

for i = 1-2 study days and j = 1–18 participants, where υ_j represents the random intercept by participant and ε_{ij} is the error term.

One participant with the highest level of creatinine-adjusted urine nickel was identified as a potential outlier with post-shift creatinine-adjusted urine nickel over two standard deviations above the geometric group mean. This participant's pattern of nickel excretion emulates a differential systemic absorption of nickel as similarly observed in an outlier participant in a study by Roels, Van de Voorde, Vargas, and Lauwerys (1993). Pre-shift urinary nickel values were similar to other participants, but post-shift levels increased by an order of magnitude despite comparable metals exposure to other participants (Roels et al., 1993). A sensitivity analysis was conducted excluding this individual to determine potential influence on the model.

In order to calculate the amount of variance explained by the airborne exposure in each model, a modified R^2 value was calculated as described by Selya et al. (Selya, Rose, Dierker, Hedeker, & Mermelstein, 2012). Briefly, the proportion of variance explained for each full model, in relation to a null model with no regressors, was determined and labeled as the modified R^2 for the full model, or R_F^2. This calculation was repeated for each restricted model in which all fixed effects from the full model were present except for the airborne metal exposure and the random effects were constrained to be the same as those from the full model. The modified R^2 values for the restricted models are labeled as R_R^2. The proportion of variance in the urine biomarker explained solely by the airborne metal exposure (R_{air}^2) was obtained by subtracting R_R^2 from R_F^2.

In order to better determine the practical significance of the effect estimate magnitudes, Cohen's f^2 was determined using the formula below:

$$f^2=\frac{R_F^2-R_R^2}{1-R_F^2}$$

This variation of Cohen's f^2 measures the local effect size and is considered appropriate for multiple linear mixed models where

both the dependent variable (the urine metal biomarker) and the independent variable of interest (the airborne metal exposure) are continuous. According to Cohen's guidelines (1988), f^2 values greater than 0.15 signify moderate effect sizes and f^2 values greater than 0.35 signify large effect sizes.

Stata 14 was used for all statistical analysis (StataCorp, College Station, TX).

3. Results

3.1. Characteristics of study population

The study population was predominately composed of Caucasian males, and fourteen of the eighteen participants enrolled identified as either current or former users of nicotine containing products (e.g., traditional cigarettes, e-cigarettes, or chewing tobacco). Five of the eighteen participants consumed between one and three alcoholic beverages in the 24 h preceding their first measured shift, while three participants consumed between one and three alcoholic beverages in the 24 h preceding their second measured shift. None of the participants reported or were observed using any form of respiratory personal protective equipment during welding activities. Welding helmets were worn during welding operations, but they did not include respiratory protection features. Demographic, health, work history, and exposure characteristics of the cohort are shown in Table 1. Additionally, the mean gravimetric inhalable particulate matter (PM) exposure was calculated for each of the 18 workers across their two measured shifts. The median of the participant cross-shift means was 1.95 mg/m^3 and workers were stratified into a high and low exposure group based on whether their mean exposure fell above or below the group median. Demographic characteristics were similar between groups and mean metal-specific exposures (both inhalable and lung-deposited) were higher in the group with the highest inhalable PM exposures. There were also more Shop 2 workers in the high exposure group than in the low exposure group. (Shop 2 did not have a general ventilation system for the duration of the study period.)

3.2. Airborne metals

The median personal inhalable chromium concentration across all measured shifts (n = 35) was 52 (range: 12–256) μg/m^3 and the median inhalable nickel concentration was 22 (range: 5–111) μg/m^3. The median lung-deposited chromium concentration was 58 (range: 0.5–454) μg/m^3 and the median lung-deposited nickel concentration was 28 (range:0.3–206) μg/m^3.

There were high levels of exposure variability for nickel and total chromium both between and within participants. While some workers had similar nickel and chromium exposures between their two shifts, others exhibited as high as three-fold difference between days. Previous work calculated the intraclass correlation coefficients ($\widehat{\rho}$) for each metal in order to better partition the observed variance into between and within worker fractions. For both chromium and nickel, the majority of variance was seen between workers ($\widehat{\rho}_{Cr} = 0.67; \widehat{\rho}_{Ni} = 0.70$). The exposure range between each participant's two measured shifts is shown in Fig. 2. One worker was called

Table 1
Population demographic, work history, health, and exposure characteristics (shown on next page).

Characteristic	N = 18	Mean Inhalable PM Exposure (Median = 1.95 mg/m^3)	
		Below Median	Above Median
Age, median (range)	30 (20–49)	29 (23–49)	31 (20–47)
Male, n	17	8	9
Race/Ethnicity, n	–	–	–
White	14	8	7
Other	3	1	1
Choose Not to Respond	1	–	1
BMI, median (range)	25 (18–48)	25 (20–48)	26 (18–34)
Nicotine Use, n	–	–	–
Current	6	2	4
Former	8	4	4
Mean PM Urine Cotinine (range, μg/mL)	1.5 (0.001–15)	2.1 (0.001–15)	1.0 (0.001–5.2)
Asthma, n	3	1	2
Other Medication, n	5	1	4
Welded in Past 24 Hours	2	1	1
Participant Shop Location	–	–	–
Shop 1	5	5	–
Shop 2	10	3	7
Shop 3	3	1	2
Mean Welding Hours	3.9	3.4	4.5
Mean Chromium Exposure (μg/m^3, range)	–	–	–
Inhalable	65 (12–255)	43 (12–81)	85 (23–255)
Lung-Deposited	79 (0.5–454)	61 (0.5–192)	97 (18–454)
Mean Nickel Exposure (μg/m^3, range)	–	–	–
Inhalable	28 (5–111)	18 (5–35)	36 (10–111)
Lung-Deposited	36 (0.31–206)	28 (0.31–87)	45 (8–206)
Median Inhalable PM (8-hr TWA, mg/m^3)	1.9 (.79–5.2)	1.2 (.79–2.6)	2.5 (1.1–5.2)

off-site before measurements began for his second shift and therefore only seventeen paired samples are shown.

The lung-deposited metals exposure for each participant is shown plotted against that participant's corresponding inhalable metals concentration on the same sample day in Fig. 3. The non-parametric Spearman correlation coefficient (ρ) between inhalable and lung-deposited metals was 0.39 for both nickel and chromium, indicating a moderate correlation between the two measured size fractions. There are several examples, particularly evident for chromium, in which the LDS measured much higher concentrations than the inhalable sampler.

3.3. Urine biomarkers

Median pre-shift urine chromium, adjusted for creatinine excretion, was 0.83 (range: 0.11–8.9) μg/g creatinine and median post-shift urine chromium was 0.97 (range: 0.08–4.4) μg/g creatinine. Median pre-shift urine nickel, adjusted for creatinine, was 0.85 (range: 0.5–7.7) μg/g creatinine and median post-shift urinary nickel was 1.1 (range 0.15–11) μg/g creatinine. Values for mean urine biomarkers of cotinine, creatinine, and urine metals are listed in Table 2. As in Table 1, the results are stratified into a high and low exposure group based on each participant's mean inhalable PM mass.

The inhalable and lung-deposited metals concentrations plotted against the creatinine-adjusted urine metals are shown in Fig. 4. One participant was an outlier with a post-shift urine nickel concentration of 10.7 μg/g creatinine (more than two geometric standard deviations above the geometric mean).

3.4. Model results

Results for the four linear mixed models are listed in Table 3 and statistically significant covariates are indicated in bold. There are statistically significant positive correlations between lung-deposited chromium and post-shift urine chromium ($p = 0.03$) as well as between lung-deposited nickel and post-shift urine nickel ($p < 0.001$). However, there is no relationship between inhalable metals and post-shift creatinine-adjusted metals concentrations.

R^2 values and Cohen's f^2 estimates for each model are listed in Table 4. R_F^2 describes the variance explained by each of the full models and R_R^2 describes the variance explained in a restricted model that included all fixed effects except the airborne exposure covariate. R_{air}^2 describes the proportion of variance in the model explained solely by the airborne metals exposure. While the amounts of variance described by lung-deposited and inhalable chromium are very similar, 14% and 11%, respectively, lung-deposited nickel explains 37% of the variance in post-shift urine nickel, whereas the restricted inhalable nickel model actually explains more of the variance than the full model ($R_F^2 = -0.02$). The negative value of the modified R^2 is most probably an artifact resulting from the negligible effect size of inhalable nickel on post-shift urine nickel ($\beta_{Ni} = 0.008$; 95% CI = −0.07-0.29; $p = 0.92$). By artificially restraining the random effects in the restricted models to match that of the full model, there was likely a slight increase in explained variance in the null model. As negative R^2 values cannot be interpreted, the modified R_F^2 for inhalable nickel was replaced with zero in Table 4.

Additionally, the Cohen's local f^2 values for lung-deposited and inhalable chromium are 0.18 and 0.15, respectively, signifying small to moderate effect sizes. However, the Cohen's f^2 for lung-deposited nickel is 0.70, indicating a large local effect size by Cohen's

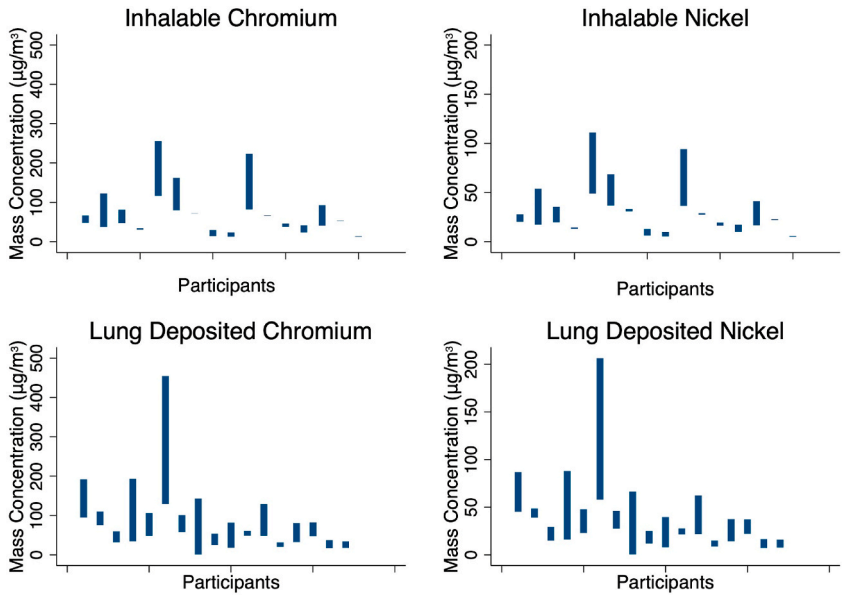

Fig. 2. Range in between-day nickel and total chromium exposures by participant.

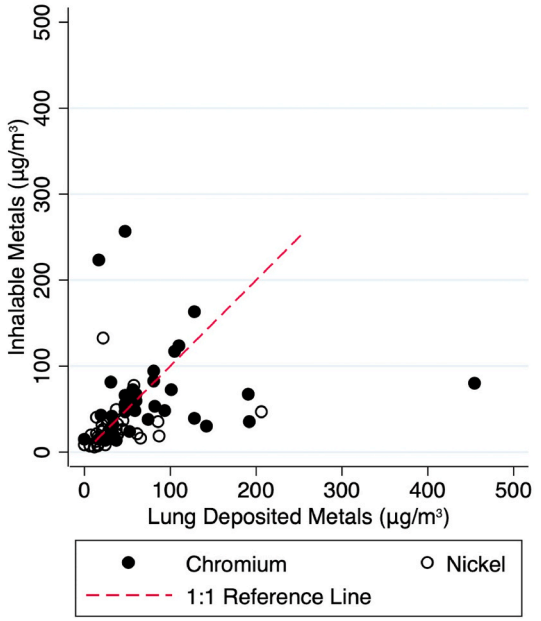

Fig. 3. Side-by-side measurements of inhalable versus lung-deposited metals. Red dashed line is 1:1 reference line. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Population urine biomarkers.

Post-Shift Biomarker, mean (range)	All (N = 18)	Mean Inhalable PM Exposure (Median = 1.95 mg/m^3)	
		Below Median	Above Median
Urine cotinine, µg/mL	1.5 (0.001–15)	2.1 (0.001–15)	1.0 (0.001–5.2)
Urine creatinine, mg/dL	114 (18–225)	103 (18–225)	123 (35–225)
Urine chromium, µg/L	1.1 (0.12–3.1)	0.90 (.13–1.9)	1.25 (.31–3.1)
Urine nickel, µg/L	1.4 (0.10–4.3)	1.5 (0.10–3.9)	1.3 (0.43–4.3)
Urine chromium, µg/g creatinine	1.3 (0.08–4.4)	1.4 (0.08–4.4)	1.2 (0.21–3.1)
Urine nickel, µg/g creatinine	1.7 (0.16–10.7)	2.3 (0.16–10.7)	1.2 (0.31–4.2)

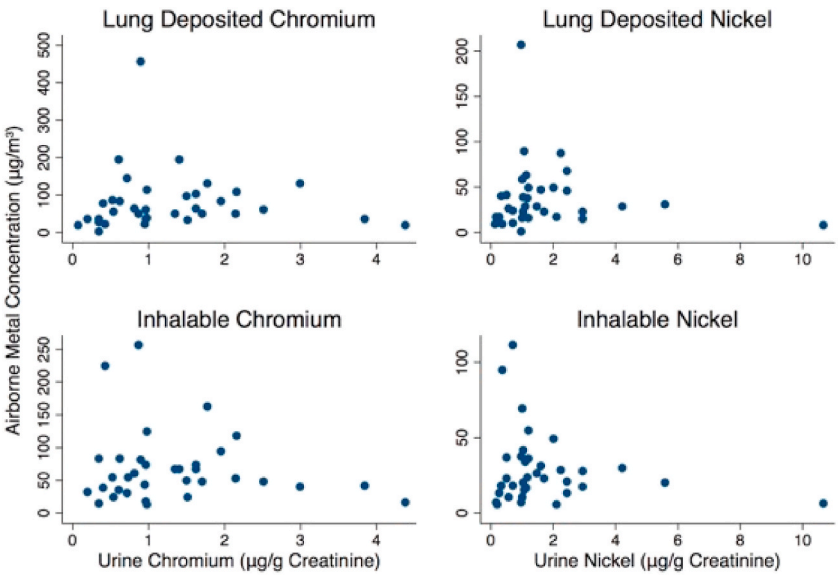

Fig. 4. Scatter plots of lung-deposited and inhalable nickel and chromium against respective urine metals.

Table 3
Associations between airborne metals and urine biomarkers from linear mixed models.

	Lung-deposited			Inhalable		
	Coefficient	p-value	95% CI	Coefficient	p-value	95% CI
Airborne Chromium	0.07	**0.03**	0.01–0.14	0.05	0.41	−0.07–0.17
Urine Creatinine	0.001	0.15	−0.003–0.002	0.001	0.10	−0.0002–0.002
Urine Cotinine	−0.01	0.56	−0.04–0.02	−0.01	0.50	−0.4–0.02
24-hr *Welding*	0.20	0.21	−0.12–0.52	0.20	0.23	−0.13–0.54
Airborne Nickel	0.10	**<0.001**	0.01–0.22	0.008	0.92	−0.07–0.29
Urine Creatinine	0.001	**0.01**	−0.06–0.03	0.001	0.11	−0.05–0.02
Urine Cotinine	−0.01	0.58	0.01–0.99	−0.007	0.76	0.05–1.15
24-hr *Welding*	0.14	0.26	−0.41–0.29	0.13	0.46	−0.42–0.30

*Italicized covariate is binary. All other covariates are continuous.
**Bold indicates statistically significant results.

Table 4
Measures of explained variance and effect significance by model.

Model	Effect Estimate	p-value	R_F^2	R_R^2	R_{air}^2	f^2
Lung-deposited Chromium	0.07	0.03	0.20	0.06	0.14	0.18
Inhalable Chromium	0.05	0.41	0.19	0.08	0.11	0.14
Lung-deposited Nickel	0.10	<0.001	0.48	0.11	0.37	0.70
Inhalable Nickel	0.01	0.92	0[a]	0[a]	0[a]	0[a]

[a] Values have been changed to zero for interpretability.

(1988) guidelines.

4. Discussion

This study found statistically significant relationships between lung-deposited and urinary chromium and nickel. Interpreting the effect estimates for the log-transformed covariates, there is a 1% change in post-shift urinary nickel for every one percentage change in exposure to lung-deposited nickel and a 0.7% change in urine chromium for every 1% change in lung-deposited chromium. No relationships were found between inhalable metals and urine biomarkers. These findings may suggest that the LDS provides a more biologically and physiologically relevant exposure metric than traditional penetration-based samplers.

Once adjusted for excreted creatinine, urine metals concentrations were similar in magnitude, although slightly lower, than levels reported in other occupational cohorts of stainless steel welders and grinders (Roels et al., 1993; Stridsklev et al., 2007). The slightly lower levels are likely a product of metals clearance over the preceding weekend as all measured shifts were on Mondays and comparative studies did not restrict sampling days. Poor or non-significant associations between inhalable metals and their respective urinary biomarkers are common across the literature (Golbabaei et al., 2012; Werner et al., 1999; Yokota, Johyama, Kunitani, Michitsuji, & Yamada, 2007), especially in studies with relatively small sample sizes or low exposure variability. Additionally, the mean creatinine-standardized urine metals biomarkers in Table 2 were higher in the low exposure group than the higher exposure group when stratified across the median for participant-averaged total inhalable PM. This further suggests that inhalable PM has a poor correlation with metals exposure in this study.

One limitation in this study is that for approximately half of the IOM and LDS sampler pairs (the side-by-side measurements for one individual during a single shift), the LDS measured a higher time-weighted average metal concentration than the paired IOM. The difference between sampler types was not significant in Wilcoxon matched-pairs signed-rank tests for either nickel or chromium ($p = 0.31$ and $p = 0.11$, respectively). As the lung-deposited size fraction is a portion of the inhalable fraction, we expected that the LDS measurements would be lower than the inhalable measurements. Higher levels of LDS-measured metal concentrations indicate that some of the measured mass was outside of the inhalable fraction. It is probable that the increased LDS masses are a result of large, supra-inhalable particles (e.g., from grinding or other mechanical processes) that could have deposited on the foam substrate at the inlet of the LDS, which was open to shop air.

Unlike particles from welding fume or ambient air, the equipment used in grinding (e.g., grinding wheels) can aerosolize particles from the surface at very high velocities, potentially causing them to be captured by a sampler's collection substrate even if their diameter is beyond the sampler's engineered particle cut-point. While most grinding wheels are designed to reduce exposure to the user, the set-up and proper use of this equipment was not a part of the post-shift survey or the brief twice-daily observations by study personnel. Additionally, the inlet of the LDS was oriented at a 90° angle compared to the IOM (ref Fig. 1), on the right-hand side of the participant. Based on positioning of study participants in relation to grinding equipment during the twice-daily observations, the LDS inlet was often in the direct path of the visible particle plume (on the right side of the welder) whereas the IOM inlet was partially shielded by the raised walls of the cassette. Although the sampling equipment is not visible due to positioning of participant's arms in Fig. 5, this orientation can be seen in Fig. 1.

Furthermore, for every instance in which the LDS concentration was reported as higher than the IOM concentration, the participant reported one or more hour of grind time during their post-shift survey (mean: 2.2 h). While the mechanical force acting on these particles may also have caused them to be inhaled by the participant even if they would be outside of the traditional inhalable size fraction, particles resulting from grinding and other mechanical process are expected to be largely insoluble (Antonini, 2008) and thus may not substantially contribute to the internal dose in the time period being measured. The LDS is designed to capture the deposited size-fraction for the total respiratory tract, including the nasopharyngeal, tracheobronchial, and alveolar regions. Dependent on particle solubility, there can be large variations in clearance time, and thus overall body burden, between these regions (Pepelko, 1987; Stuart, 1984). While particles deposited in the two upper regions are typically swallowed relatively rapidly (on the order of hours), particles that deposit in the alveolar region (beneath the ciliated epithelium) must be cleared either through dissolution or through phagocytosis by pulmonary macrophages (Stuart, 1984). For insoluble particles, half-life within the lung can dramatically increase compared to other regions of the lung. One magnetopneumography study in shipyard welders, for example, estimated that lung-retained dust particles (likely primarily insoluble) were only cleared at a rate of twenty-percent per year (Kalliomaki, Kalliomaki, Rahkonen, & Aittoniemi, 1983). A sampler has been developed that can estimate deposition to the head airways, tracheobronchial and alveolar regions (Koehler et al., 2013), but it is too large for use in personal sampling.

As this manuscript compared both inhalable and lung-deposited metals to urine metals across a single Monday shift after a non-working weekend, it seems likely that the respective urine metals biomarkers were dominated by more soluble metal or metal-oxide particles that were able to quickly enter the blood stream. Supporting this, a Scandinavian study of welders using high alloy Ni–Cr steel found a correlation between urine chromium and concomitant, same-day exposure to the water-soluble fraction of airborne chromium, but they found no correlation between urine chromium and concomitant, same-day to the water-insoluble fraction of airborne chromium (Tola, Kilpio, Virtamo, & Haapa, 1977). The largest expected difference in the inhalable and lung-deposited size fraction centers in the sub-micron particle range (~200 μm AED), whereas grinding and spatter particles are typically supra-micron (Antonini, 2003). Recent work in the pharmaceutical industry indicates that smaller particles (e.g., welding fumes) have both increased solubility and bioavailability compared to larger particles (e.g., grinding and spatter particles), which may help explain the sensitivity of the LDS in detecting statistically significant correlations between urine and lung-deposited metals (Kesisglou, 2008; Sun et al., 2012). However, as we only have measures of total metals, not soluble metals, this analysis does not take into account body-burden differences that are a function of solubility or bioavailability. While the total respiratory tract-deposition based LDS sampler does represent a more biologically-relevant exposure measurement than traditional, penetration based measurements, it may still not be fully representative of the true biological dose.

In future studies, a size-selective inlet should be used in conjunction with the LDS in order to prevent sampling of non-inhalable particles and the inlet of both samplers should be pointed in the same direction as compared to the source.

A sensitivity analyses was run including only side-by-side pairs where the LDS measured a smaller metals mass concentration than the IOM (N = 11). Because of the decrease in sample size, models were only adjusted for urine creatinine. In this analysis, the effect estimate between post-shift urine chromium and lung-deposited chromium increased slightly ($\beta_{LDS\_Cr} = 0.09$; 95% CI = −0.01-0.18), although the magnitude of effect decreased for lung-deposited nickel ($\beta_{LDS\_Ni} = 0.02$; 95% CI = −0.14-0.18). Both inhalable metals models had large decreases in effect size with no significant association.

Additional sensitivity analyses were run to check for effects of the potential outlier participant. When excluding this individual (10.7 μg Ni/g creatinine in urine), effects on both chromium models (LDS and inhalable) were negligible. However, the magnitude of the association between urine nickel and airborne nickel increased for both lung-deposited ($\beta_{LDS\_Ni} = 0.11$; 95% CI = 0.05–0.16) and inhalable ($\beta_{IOM\_Ni} = 0.05$; 95% CI = −0.12-0.21) nickel. The association between lung-deposited nickel and urine nickel remained statistically significant ($p < 0.001$).

A second limitation for this study is that both airborne samplers measured only total metals. The bioavailability of both nickel and chromium is affected by speciation and solubility (Denkhaus & Salnikow, 2002; Katz & Salem, 1993; Werner et al., 1999), and this can

Fig. 5. Participant positioning with right-hand side towards grinding wheel plume. See Fig. 1 for the directionalities of the front-facing IOM sampler inlet and the right shoulder-facing LDS sampler inlet.

change both the magnitude of the measured biomarker as well as the half-life in urine. This is particularly significant when comparing exposure to the carcinogenic and typically highly soluble hexavalent chromium, Cr(VI), with exposure to chromium's less toxic valency states, Cr(III) and Cr(IV). Additionally, the study was limited by a small sample size.

5. Conclusions

In moving towards a more biologically relevant exposure metric, the LDS can provide better estimates for the total body burden of exposure than traditional penetration-based samplers. As a measurement of the internal dose, as opposed to the external concentration, the LDS may help in reducing exposure misclassification in future epidemiological studies and thus aid in better clarifying the relationship between exposure and disease.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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