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Respirable Indium Exposures, Plasma Indium, and Respiratory Health Among Indium-Tin Oxide (ITO) Workers

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Abstract

Background—Workers manufacturing indium-tin oxide (ITO) are at risk of elevated indium concentration in blood and indium lung disease, but relationships between respirable indium exposures and biomarkers of exposure and disease are unknown.

Methods—For 87 (93%) current ITO workers, we determined correlations between respirable and plasma indium and evaluated associations between exposures and health outcomes.

Results—Current respirable indium exposure ranged from 0.4 to 108 μg/m^3 and cumulative respirable indium exposure from 0.4 to 923 μg-yr/m^3. Plasma indium better correlated with cumulative (r_s = 0.77) than current exposure (r_s = 0.54) overall and with tenure ≥1.9 years. Higher cumulative respirable indium exposures were associated with more dyspnea, lower spirometric parameters, and higher serum biomarkers of lung disease (KL-6 and SP-D), with significant effects starting at 22 μg-yr/m^3, reached by 46% of participants.

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AUTHORS' CONTRIBUTIONS

All authors made substantial contributions to the conception or design of the paper; or the acquisition, analysis, or interpretation of data for the paper. All authors drafted the paper or revised it critically for important intellectual content. All authors provided final approval of the version to be published. All authors agree be accountable for all aspects of the paper in ensuring that questions related to the accuracy or integrity of any part of the paper are appropriately investigated and resolved.

ETHICS REVIEW AND APPROVAL

The Institutional Review Board of the National Institute for Occupational Safety and Health (NIOSH) approved the study and all participants provided informed consent.

DISCLOSURE (AUTHORS)

None of the authors has a conflict of interest to disclose.

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Steven Markowitz declares that he has no competing or conflicts of interest in the review and publication decision regarding this article.

Conclusions—Plasma indium concentration reflected cumulative respirable indium exposure, which was associated with clinical, functional, and serum biomarkers of lung disease.

Keywords

indium-tin oxide; spirometry; KL-6; SP-D; cumulative exposure

INTRODUCTION

Global consumption of indium has increased several-fold in recent decades, driven by increasing demand for indium-tin oxide (ITO) for uses such as touch screens and solar cells [Omae et al., 2011; USGS, 2014]. From 2003 to 2010, 10 cases of advanced lung disease were reported in young workers exposed to indium compounds during the production, use, or reclamation of ITO [Omae et al., 2011]. Indium lung disease is now recognized as a potentially fatal condition characterized by pulmonary alveolar proteinosis (PAP) that may progress to fibrosis with or without emphysema [Cummings et al., 2012]. Multiple studies have demonstrated an excess burden of respiratory abnormalities in ITO industry workforces and associations between biological exposure markers (indium concentration in blood serum or plasma) and health outcomes including reduced diffusing capacity, changes on chest imaging, and increased levels of biomarkers of interstitial lung disease such as Krebs von den Lungen (KL)-6 and surfactant protein (SP)-D [Chonan et al., 2007; Hamaguchi et al., 2008; Nakano et al., 2009; Liu et al., 2012; Choi et al., 2013; Cummings et al., 2013]. In Japan, a serum indium concentration of 3 μg/L is now used as a threshold for consideration of work restrictions [MHLW, 2010].

Despite the use of serum or plasma indium concentration as an exposure metric in epidemiologic studies and as a clinical tool for risk stratification, little is known about the relationship between serum or plasma indium concentration and workplace exposures. Perhaps even less is known about how health effects relate to workplace exposures because few published studies have included both a medical component and an environmental assessment of the workplace. In a small study of current and former workers at an indium ingot production facility, plasma indium concentrations were not correlated with airborne indium, and plasma indium remained elevated years after employment, suggesting that plasma indium levels reflect long-term exposure [Hoet et al., 2012]. In a larger study, air sampling results from eight areas did not explain observed variations in radiographic abnormalities among workers [Chonan et al., 2007].

Effective mitigation of workplace exposures requires health-based exposure limits to target controls. If indium concentrations in blood matrices reflect historical, rather than current exposures, then use of these biological exposure metrics for workplace exposure management has practical limitations. For instance, a worker’s elevated plasma indium concentration may either reflect ongoing exposure that needs to be addressed, or the legacy of working under different conditions than currently in place. As such, to identify and prioritize exposure control measures and for proper risk assessment to develop a protective exposure limit, an understanding of the direct relationship between exposure metrics and

health outcomes is critical. However, to date, airborne exposure data to fully characterize exposure-related risk for workers in the ITO industry have been unavailable.

We sought to better understand the relationships among indium exposure, plasma indium, and respiratory health at an ITO production and reclamation facility where two workers previously developed PAP, including one fatal case [Cummings et al., 2010]. Subsequent review of corporate medical surveillance data collected through 2010 revealed that pulmonary function abnormalities were in excess, but associations between adverse respiratory effects and average airborne indium concentrations were not evident using the facility's available air sampling data [Cummings et al., 2013]. More recently, we found that plasma indium concentrations as low as 1 μg/L were associated with chest symptoms, decreased spirometric parameters, and increased serum biomarkers of lung disease among current workers [Cummings et al., 2014].

Indium lung disease primarily involves the alveolar or deep region of the lung [Nagano et al., 2011a,b; Cummings et al., 2012]. Thus, we hypothesized that particles with a mass median aerodynamic diameter less than 4 μm, which can penetrate into the alveolar region when inhaled, would be most biologically relevant. We therefore focused our exposure characterization on the respirable fraction of airborne particles.

MATERIALS AND METHODS

Study Design and Data Collection

The study population consisted of 87 (94%) current ITO facility workers, with median age of 44 years, median facility tenure of 1.9 years, and median plasma indium of 1.0 μg/L in July 2012. Approximately three-quarters worked in production areas (production or production support positions) and the remainder worked in laboratories or offices. The participants' respiratory health has been described previously and was notable for few clinically significant abnormalities [Cummings et al., 2014]. An additional three workers contributed to the exposure assessment (described below) but did not participate in the study's health component.

Exposure assessment was conducted at the facility over 2 weeks in June and September 2012. We collected full- or multi-shift (range: 6–22 hr duration) personal samples to assess exposures to respirable indium. Respirable samples were collected at 4.2 Lpm using the GK2.69 cyclone (BGI, Inc., Waltham, MA) mounted onto two-piece, 37-mm cassette samplers loaded with 37-mm, 5-μm pore size polyvinyl chloride filters. Where personal sampling was not feasible, general area (GA) multi-shift air respirable cyclone samples were collected instead. A total of 110 personal respirable samples were collected from 49 workers (46 of whom participated in the study's health component) for all jobs except for administrative (office) workers; one GA respirable sample was collected from the administrative office area.

Air samples were analyzed for indium by inductively coupled plasma atomic emission spectrometry (ICP-AES) using NIOSH Method 7303 [NIOSH, 2003], with a limit of detection (LOD) of 0.375 μg/sample and limit of quantification (LOQ) of 1.25 μg/sample.

Statistical Analyses

A substitution method was used to replace measurements below the LOD with a value of LOD/2, as the number of LOD measurements was small [Lubin et al., 2004]. Specifically, none of the respirable indium samples and four of the plasma indium samples had measurements below the LOD.

All personal samples for respirable indium were summarized for each job and department using the arithmetic mean (specifically, the minimum variance unbiased estimator [MVUE]). The arithmetic mean was used in this calculation as it is the desired measure of central tendency for estimating cumulative exposure [Smith, 1992], and the MVUE is the preferred estimator of the arithmetic mean when the data are lognormally distributed [Mulhausen and Damiano, 1998]. The job-specific mean was then assigned to each participant with that current job to obtain a metric of current respirable indium exposure (hereafter, "current exposure"). Administrative (office) workers were assigned the GA sample concentration. To calculate a metric of cumulative respirable indium exposure (hereafter, "cumulative exposure"), the current exposures were assigned to jobs in each worker's work history regardless of calendar time, as detailed historical information on workplace conditions, processes, and representative historical exposure estimates were not available to assess or account for differences in exposure over time. The exposure associated with each job in the work history was then multiplied by the duration (in years) that the job was performed and summed across all jobs held to obtain cumulative exposure for each worker.

We examined correlations among the exposure variables and plasma indium using Spearman's rank correlation coefficient. In addition, we used logistic, linear, and restricted cubic spline [Desquilbet and Mariotti, 2010] regression models to assess the relationship between exposure variables and plasma indium and health outcomes. In the logistic and linear regression models, we used the natural log of exposure variables to account for non-linear relationships. Health outcomes consisted of respiratory symptoms as reported on the questionnaire, lung function test results, and KL-6 and SP-D results [Cummings et al., 2014].

For spline regression models with cumulative exposure as the predictor variable, we used the study participants' lowest cumulative exposures (≤0.44 μg-yr/m^3; n =5 [6%]) as the reference; all were administrative (office) workers. We predicted health outcomes associated with specific values of cumulative exposure of interest, for example, the cumulative exposure value of 12 μg-yr/m^3 associated with working lifetime exposure (40 years) at the Japanese respirable exposure limit of 0.3 μg/m^3 [MHLW, 2010], the median cumulative exposure value, and the lowest cumulative exposure values to have statistically significant relationships with the outcome variables.

Final models were adjusted for cigarette smoking status (current/former/never) and age (years). Age was not included as a covariate in models of percent predicted values of lung function parameters, as the percent predicted values already account for age. We included facility tenure (dichotomized at the median value) as a covariate in models of current exposure. Past work with asbestos, silica, or other lung hazards was not associated with

health outcomes or plasma indium in simple analyses, and thus was not included as a covariate [Cummings et al., 2014].

Statistical analyses were conducted using SAS software version 9.3 and JMP software version 10.0.1 (SAS Institute, Inc., Cary, NC). We considered two-sided *P* values ≤0.05 to be statistically significant.

RESULTS

A summary of the air samples collected are presented in Table I, stratified by department. The mean exposures were highest in the reclaim, ITO, refinery, and rotary grinding departments, and lowest in the administrative, shipping and receiving, and the quality control laboratory areas. Within departments, exposures were highly variable, often ranging by one to two orders of magnitude because of the differences in jobs and tasks performed within the departments. All measurements were greater than 0.3 μg/m^3, which is the Japanese respirable indium standard. A large fraction (50/69; 72%) of the measurements collected in the production departments exceeded 10 μg/m^3, which represents the Japanese target concentration requiring immediate actions to be taken to reduce exposures.

The current and cumulative exposures for the study participants ranged from 0.4 to 108 μg/m^3 and 0.4 to 923 μg-yr/m^3, respectively. Correlations between plasma indium and current (r_s = 0.54) and cumulative (r_s = 0.78) exposure variables were evident when plotted on a log scale (Fig. 1). This pattern also was seen for participants with tenure ≥1.9 years (r_s = 0.53 for current exposure and r_s = 0.72 for cumulative exposure). For participants with tenure <1.9 years, the correlation between plasma indium and respirable indium was similar for current (r_s = 0.74) and cumulative (r_s = 0.72) exposure. For all participants, a significant relationship was observed between log-transformed plasma indium and log-transformed cumulative indium exposure using a simple regression model, which explained 60% of the variation in plasma indium (equation: Ln [Plasma Indium] =−2.35 +0.662*Ln [Cumulative Indium]).

In adjusted logistic and linear regression models, associations were observed between health outcomes and the exposure variables. KL-6 (U/ml) was associated with logged current exposure (β coefficient =118; 95%CI =64.9–172). Dyspnea, spirometric abnormality, low alveolar volume, percent predicted forced expiratory volume in 1 s (FEV_1), percent predicted forced vital capacity (FVC), KL-6, and SP-D (ng/ml) were each associated with logged cumulative exposure (Table II). Associations between sputum production, chest tightness, low diffusing capacity, FEV1/FVC ratio, and logged cumulative exposure did not reach statistical significance (Table II).

Adjusted spline regression demonstrated statistically significant overall associations between all continuous health outcomes shown in Figure 2 and unlogged cumulative exposure. The relationships were significantly non-linear by the Wald test for percent predicted FEV_1, FEV_1/FVC ratio, and KL-6, but not for percent predicted FVC, and SP-D (Fig. 2). The shapes of the exposure-response curves for all of these continuous health outcomes showed steeper slopes at lower values of cumulative exposure and flatter slopes at higher cumulative

exposure values. Log-transformation of cumulative exposure resulted in some linearization of the associations for percent predicted FEV_1, FEV_1/FVC ratio, and KL-6, but upon graphical inspection, the curves looked non-linear, albeit not statistically significant (data not shown). The estimated percent predicted FEV_1, percent predicted FVC, and FEV_1/FVC ratio decreased, and the estimated KL-6 and SP-D increased relative to the corresponding values for the reference group's cumulative exposure value of ≤0.44 μg-yr/m^3. Significant differences were seen for percent predicted FEV_1 starting at a cumulative exposure of 22 μg-yr/m^3, for FEV_1/FVC ratio at 30 μg-yr/m^3, for KL-6 at 63 μg-yr/m^3, for percent predicted FVC at 240 μg-yr/m^3, and for SP-D at 232 μg-yr/m^3 (Table III).

Nearly half (46%) of participants had cumulative exposure levels greater than 22 μg-yr/m^3 (Fig. 3). If divided evenly over a 40-year working lifetime, these cumulative exposure values correspond to current exposures as low as 0.6 μg/m^3 (for percent predicted FEV_1) to 6.0 μg/m^3 (for SP-D). The majority (82%) of participants had current exposure levels greater than 0.6 μg/m^3, and 41% had current exposure levels greater than 6.0 μg/m^3 (Fig. 3).

The last three columns in Table I show the number of years it would to take to reach a cumulative exposure of 22 μg-yr/m^3 at the mean exposure levels in each department. Without respiratory protection, administrative (office) workers were the only participants who would not reach a cumulative exposure of 22 μg-yr/m^3 during a 40-year working lifetime. Without respiratory protection, workers in the reclaim, ITO, rotary grind, planar grind, and research and development departments would reach 22 μg-yr/m^3 in less than 1 year of employment. With a disposable N95 filtering-facepiece respirator (assigned protection factor [APF] of 10), this time period would be extended to 2.0–8.1 years. With a powered air-purifying respirator (APF of 25), this time period would be extended to 5.1–20.2 years.

DISCUSSION

At an ITO production and reclamation facility where health risks were previously demonstrated [Cummings et al., 2010, 2013, 2014], we found that plasma indium correlated well with measures of airborne respirable indium, particularly when we accounted for the time that workers spent in different jobs at the facility. Furthermore, associations that we previously reported between health outcomes and plasma indium [Cummings et al., 2014] were also evident between health outcomes and a cumulative indium exposure metric developed on the basis of air measurements. Indeed, workers with higher cumulative exposures had more dyspnea, lower lung function, and increased serum concentrations of the interstitial lung disease biomarkers KL-6 and SP-D that were not explained by age or smoking status. The demonstration of relationships between respirable indium exposure metrics and health is particularly important from a practical viewpoint because airborne metrics of exposure, rather than biomarkers of exposure, are measured by industrial hygienists in the workplace to guide controls.

To our knowledge, ours is the first study to demonstrate a relationship between concentrations of indium in plasma and air. Hoet et al. [2012] found no such association, but with only nine current workers, their study may not have had adequate power for this

outcome. Variations in the chemical forms of indium present in the air and the air sampling methods employed in the two studies may also have contributed to the different findings. Hoet et al. [2012] conducted their study in a facility with indium but not ITO and collected the inhalable fraction, while we conducted our study in an ITO production facility and used the respirable fraction. We found that cumulative exposure had a stronger relationship with plasma indium than did current exposure, which was driven by participants with longer tenure. This finding is consistent with prior evidence of indium compounds' slow dissolution and clearance from the body. In one study, current and former workers had similar mean serum indium concentration (8.4 vs. 9.6 μg/L), though former workers' indium exposure had ended an average of nearly 5 years before the study [Nakano et al., 2009]. Urine indium concentrations did not vary over the workweek or after a weekend in the study by Hoet et al. [2012], which is consistent with the slow dissolution of indium, and suggests the presence of a body burden of indium. Furthermore, in hamsters exposed to ITO or indium oxide by intratracheal instillation, serum indium concentration increased consistently during the follow-up period, up to 78 weeks after the final exposure [Tanaka et al., 2010].

Our demonstration of associations between health outcomes and airborne exposure metrics is also, to our knowledge, unique. We found one association with current exposure and more numerous associations with cumulative exposure. Notably, cumulative exposure variables performed quite comparably to plasma indium, identifying the same health outcomes and similar relational patterns [Cummings et al., 2014]. Associations with health outcomes were evident at cumulative exposures as low as 22 μg-yr/m^3 for this short-tenure workforce. In calculating exposures, we did not account for participants' use of respiratory protection, which was primarily task-based and thus intermittent. Use of respiratory protection likely reduced the actual exposures compared to the measured concentrations of indium in the air for some participants. Overestimation of exposure leads to underestimation of risk. Thus, had we been able to accurately account for the effects of respiratory protection, we expect that we would have found health effects at even lower levels of cumulative exposure.

We found that many production workers would reach a cumulative exposure of 22 μg-yr/m^3 in less than 1 year of employment without respiratory protection, and within a few years even with the use respiratory protection. The calculated times while using respiratory protection relied on the APF, which could overestimates the actual protective capacity of the respirator if it is not fitted and worn properly. Hence, it is possible that we overestimated the time a worker wearing respiratory protection would reach a cumulative exposure of 22 μg-yr/m^3. It is important to note that respiratory protection is the intervention choice of last resort and should be instituted as a temporary solution while more permanent engineering and administrative controls are evaluated and implemented.

Despite the relatively short tenure of the workers we studied, the associations we found are likely to be due to the effect of indium compounds on the lung for several reasons. First, they are biologically plausible, given the lung toxicity of indium oxide and ITO observed in animal studies [Leach et al., 1961; Lison et al., 2009; Tanaka et al., 2010; Nagano et al., 2011a,b; Badding et al., 2015]. Second, they are consistent with the lung disease reported in ITO industry workers, which was notable for short latency from first exposure to diagnosis [Cummings et al., 2012]. Indeed, the two cases of PAP in this facility occurred within 12

months of hire [Cummings et al., 2010]. Third, they reflect subclinical or undiagnosed lung disease experienced by ITO industry workers in many other facilities worldwide [Chonan et al., 2007; Hamaguchi et al., 2008; Nakano et al., 2009; Liu et al., 2012; Choi et al., 2013]. Fourth, they were not accounted for by potential confounders such as age or smoking, which are known risk factors for decreased lung function. In addition, we previously showed that there were no associations between health outcomes and self-reported prior occupational exposure to asbestos, silica, or other lung hazards [Cummings et al., 2014]. Finally, although we could not address temporality in a cross-sectional study, a recently reported 5-year follow-up of indium workers found that serum indium, KL-6, and SP-D all declined to similar degrees with cessation or reduction of exposure [Nakano et al., 2014].

Indium and dust exposure metrics were highly correlated ($r_s \geq 0.89$), and results were similar between models of health outcomes that used respirable indium exposure and those that used respirable dust exposure (data not shown). These findings are not unexpected, given that most processes in the facility involved some form of indium. The agreement between indium and dust exposure metrics suggests that respirable dust concentration is a reasonable surrogate for respirable indium exposure in this facility. This observation has practical consequence, as real-time dust monitors can be used to identify high exposure tasks that warrant intervention. High exposure tasks may not only increase personal exposures of workers performing the task, but also act as a source for general area contamination and increase exposures for nearby tasks. Dust measurement also can be used as a surveillance tool to quickly, simply, and cost-efficiently identify new and developing problem situations that can be targeted for measurement of indium concentrations in air.

Since acquiring the facility in 2002, the owner made multiple changes intended to reduce workers' exposures to indium compounds. These included ventilation improvements, process enclosures, and the introduction of a respiratory protection program [Cummings et al., 2013]. Systematic longitudinal exposure assessment was not conducted, but it is likely that workplace improvements that occurred over the 10 years preceding the study resulted in lower exposures over time, although reductions may not have been uniform throughout the facility. Yet without accurate representative historical exposure data, we were unable to account for possible secular trends in exposure when developing the cumulative exposure variable. Rather, this variable was based on exposures measured in 2012, adjusted only for time spent in a job and jobs held at the facility. To the extent that exposures in 2012 were lower than in years prior, the cumulative exposure that we used likely underestimated true cumulative exposures to some degree. While underestimation of exposure will lead to overestimation of risk, half of the participants had been hired in the previous 2 years and 75% in the previous 5 years, so most participants' experiences reflected the more recent conditions.

Potential indium exposures at this facility were not limited to ITO, but also included indium metal, indium hydroxide, indium salts, and indium oxide. The toxicity profiles of these compounds, though not fully elucidated, are unlikely to be the same. Available information indicates differential toxicity between indium oxide and ITO [Lison et al., 2009; Nagano et al., 2011a,b]. In an in vitro studies using eight process materials from this facility, we recently showed differences among the materials in terms of cell survival and viability

[Badding et al., 2014]. In this context, it is important to note that neither plasma indium nor respirable indium differentiates between the various indium compounds used at the facility. Rather, these are non-specific metrics that integrate information on all chemical forms of indium exposures, regardless of relative toxicity; thus, their use may have led to some exposure misclassification.

Understanding the relationship between indium exposures and respiratory health has critical implications for prevention of indium lung disease in current and future ITO industry workers. Although in estimating time to a cumulative exposure of 22 μg-yr/m^3 we assumed risk over time was linear, follow-up will be needed to determine the long-term effects of exposures at the observed levels in this short-tenure workforce. Furthermore, the generalizability of our findings should be confirmed through study of other worker cohorts, such as those with longer tenure and different exposure profiles. The risks to workers encountering indium compounds outside of the primary ITO industry are largely unknown. One case of indium lung disease was reported in a Chinese mobile telephone worker who cleaned components of ITO thin-film production machinery by sandblasting [Xiao et al., 2010; Cummings et al., 2012], and a recent investigation found associations between serum indium and KL-6 in dental technicians, solder workers, and others with indium metal exposure [Nakano et al., 2015], suggesting broader investigation is warranted.

CONCLUSIONS

Among ITO production and reclamation workers, we found good correlation between plasma indium concentrations and respirable indium exposures. Current and cumulative indium exposure variables had similar correlations with plasma indium for workers with facility tenure <1.9 years, while cumulative indium exposure variables were better correlated with plasma indium for those with tenure ≥1.9 years and for the group as a whole. Cumulative respirable indium exposures were associated with more dyspnea, lower spirometric parameters, and higher serum biomarkers of interstitial lung disease, reflecting previously reported associations between plasma indium concentration and health outcomes. These findings indicate adverse health effects with relatively low respirable exposure to indium compounds and support efforts aimed at further exposure reduction in the ITO industry.

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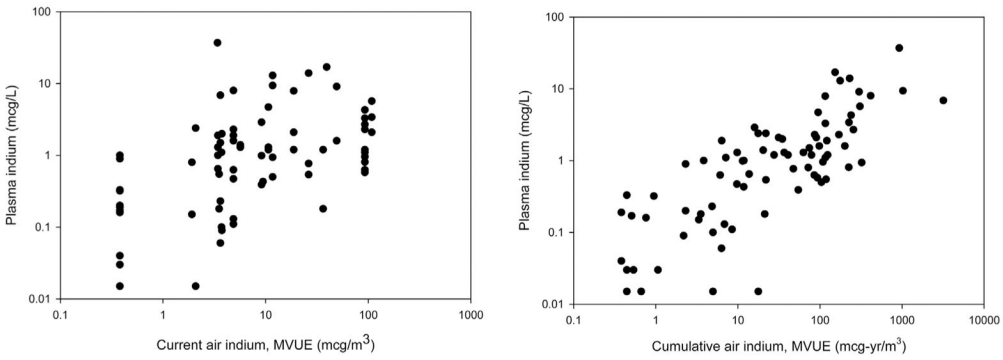

FIGURE 1.

Correlation between current (left) and cumulative (right) indium exposure and plasma indium concentration among workers at an indium-tin oxide facility. Current exposure values were assigned on the basis of indium concentrations measured for a participant's current job; cumulative exposure values account for the time a participant spent in each job during employment at the facility. Both air and plasma values plotted using a log scale. The relationship between log transformed plasma indium and log transformed cumulative indium was given by the following equation: Ln (Plasma Indium) =−2.35 +0.662*Ln (Cumulative Indium), R^2 =0.60, P <0.05. r_s = Spearman's rank correlation coefficient.

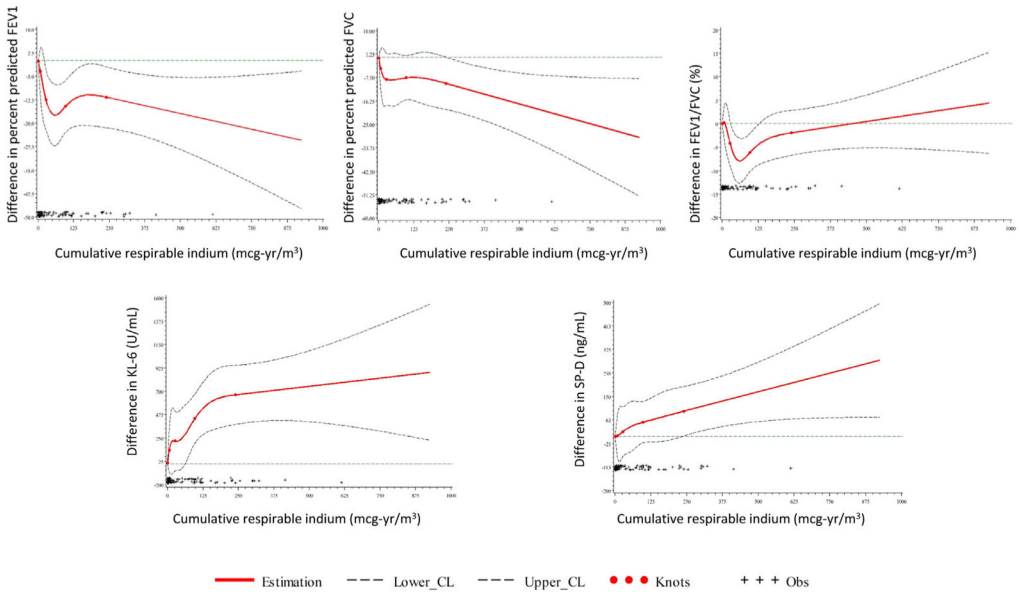

FIGURE 2.

Restricted cubic splines show non-linear relationships between spirometric parameters (top) and serum biomarkers of interstitial lung disease (bottom) on the vertical axis and cumulative indium exposure on the horizontal axis, adjusted for smoking status (current/former/never). Splines for FEV_1/FVC ratio, KL-6, and SP-D are also adjusted for age (years). Cumulative indium exposure values account for the time a participant spent in each job during employment at the facility. The splines model the difference in the value of the health outcome at any given value of cumulative exposure compared to a cumulative indium exposure value of 0.44 μg/L. Individual cumulative indium exposure values (observations) are indicated by the crosses above the x-axis. FEV_1, forced expiratory volume in 1s; FVC, forced vital capacity; KL, Krebs von den Lungen; SP-D, surfactant protein-D; CL, confidence limit; Obs, observation.

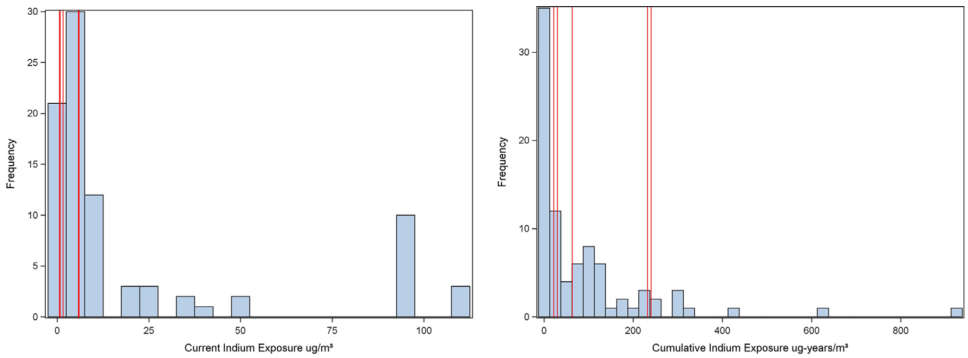

FIGURE 3.

Histograms showing the distributions of current (left) and cumulative (right) respirable indium exposures of the study participants. Reference lines show the percent of participants with exposures greater than those associated with changes in health outcomes. For cumulative exposure, reference lines indicate 46% >22 μg-years/m^3 (decline in percent predicted FEV_1); 43% >30 μg-years/m^3 (decline in FEV_1/FVC ratio); 36% >63 μg-years/m^3 (increase in KL-6); 9% >232 μg-years/m^3 (decline in percent predicted FVC); and 8% >240 μg-years/m^3 (increase in SP-D). For current exposure, reference lines indicate 82% >0.6 μg/m^3; 82% >0.8 μg/m^3; 82% >1.6 μg/m^3; 41% >5.8 μg/m^3; and 41% >6 μg/m^3. These values were chosen because they reflect the current exposures that would lead to cumulative exposures of 22, 30, 63, 232, and 240 μg-years/m^3 after 40 years.

TABLE I

Personal[a] Respirable Indium Exposure Levels by Department at an Indium-Tin Oxide (ITO) Production Facility

					Years to accumulate 22 μg-years/m^3 (range for jobs)[d]		
Department	**N**	**Mean μg/m^3[b]**	**Min–Max μg/m^3**	**% ≤10 μg/m^3[c]**	**No respirator**	**N95 FFPR**	**PAPR**
ITO	25	81.9	9.9–518.3	4	0.3 (0.2–1.9)	2.7 (2.4–18.8)	6.7 (5.9–>40)
Planar bond	5	9.1	3.2–17.6	60	2.4	24.2	>40
Planar grind	8	27.2	4.6–148.4	50	0.8 (0.6–1.2)	8.1 (6.0–11.7)	20.2 (15.1–29.3)
Reclaim	12	108.4	4.8–796.6	17	0.2 (0.1–2.5)	2.0 (0.7–24.7)	5.1 (1.8–>40)
Refinery	6	26.3	10.9–40.9	0	8.8	8.4	20.9
Rotary bond	9	3.7	0.7–6.4	100	5.9	>40	>40
Rotary grind	4	39.4	20.9–59.3	0	0.6	5.6	14.0
Engineering	9	4.9	1.7–23.2	89	4.5 (2.3–12.2)	>40 (23.4–>40)	>40 (>40)
Maintenance and facilities	8	8.6	2.2–16.0	62	2.6 (1.7–6.5)	25.6 (17.2–>40)	>40 (>40)
Forming	8	5.7	1.3–12.4	87	3.9	38.6	>40
QC lab	6	3.5	1.9–5.4	100	6.3 (6.1–6.5)	>40 (>40)	>40 (>40)
R&D	8	35.5	2.1–111.1	50	0.6 (0.4–10.5)	6.2 (4.5–>40)	15.5 (11.2–>40)
Shipping and receiving	2	1.9	1.7–2.1	100	11.6	>40	>40
Administrative[a]	1	0.4	–	100	>40	>40	>40

N, number of measurements.

[a] All results shown are from personal sampling, with the exception of those for the Administrative Department, which was evaluated with area sampling.

[b] Represents the minimum variance unbiased estimate (MVUE) of the arithmetic mean. These measurements do not reflect the actual use of respiratory protection during exposure monitoring.

[c] None of the measurements was below 0.3 μg/m^3, the Japanese exposure limit. The remainder of measurements were all greater than 10 μg/m^3, the Japanese target concentration requiring immediate actions to be taken to reduce exposures (process enclosures, ventilation, process changes, respiratory protection, etc.).

[d] Number of years it would take at the mean exposure level for the department and jobs within department to reach cumulative exposure of 22 mcg-years/m^3, the lowest cumulative exposure at which a significant effect on health outcomes was noted, with no respirator use, or using a disposable N95 filtering facepiece respirator (FFR) with an assigned protection factor (APF) of 10 or a powered air purifying respirator (PAPR) with an APF of 25. For departments with more than one job, the range of values for those jobs is shown in parentheses. For departments with one job, no range is shown.

TABLE II

Results of Adjusted Models of Relationship Between Health Outcomes and Log-Transformed Cumulative Indium Exposure for Workers at an Indium-Tin Oxide (ITO) Facility

	Value
Health outcome	**OR (95%CI)[a]**
Cough[b]	1.0 (0.7; 1.3)
Sputum production[b]	1.4 (0.9; 2.5)
Dyspnea[b]	**1.5 (1.0; 2.4)**
Wheeze[b]	1.0 (0.7; 1.3)
Chest tightness[b]	1.3 (0.9; 2.0)
Spirometric abnormality[c]	**1.5 (1.0; 2.4)**
Low DLCO[c]	1.5 (0.9; 2.7)
Low V_A[c]	**1.6 (1.0; 2.7)**
	βcoefficient (95%CI)[a]
FEV_1 % predicted [c]	**−2.7 (−4.3; −1.1)**
FVC % predicted[c]	**−1.9 (−3.5; −0.3)**
FEV_1/FVC % [b]	−0.7 (−1.5; 0.1)
DLCO % predicted[c]	−0.1 (−1.9; 1.7)
V_A % predicted [c]	−0.4 (−1.8; 1.0)
KL-6 (U/ml)[b]	**107 (61.0; 154)**
SP-D (ng/ml)[b]	**19.1 (4.2; 34.1)**

OR, odds ratio; CI, confidence interval; DLCO, diffusing capacity of the lungs for carbon monoxide; V_A, alveolar volume; FEV_1, forced expiratory volume in 1s; FVC, forced vital capacity; KL, Krebs von den Lungen; SP-D, surfactant protein-D.

[a] Odds ratios are presented for categorical outcomes and β coefficients for continuous outcomes. Significant ($P \leq 0.05$) differences are in bold.

[b] Model adjusted for age and smoking status (current/former/never).

[c] Model adjusted for smoking status (current/former/never).

TABLE III

Difference From Reference Values for Pulmonary Function Parameters and Serum Biomarkers by Cumulative Indium Exposure for Workers at an Indium-Tin Oxide (ITO) Facility[a]

	Difference (95%CI)[c]				
Cumulative indium exposure (μg-yr/m^3)[b]	**FEV_1%**	**FVC%**	**FEV_1/FVC (%)**	**KL-6 (U/ml)**	**SP-D (ng/ml)**
5.0	−2.4 (−7.7; 2.9)	−3 (−8.3; 2.3)	0.2 (−2.4; 2.8)	98.8 (−61; 259)	1.5 (−50; 53)
12.0	−5.9 (−15.8; 4.1)	−6.2 (−16.1; 3.7)	−0.4 (−5.3; 4.5)	195 (−103.7; 493)	5.3 (−91; 102)
22.0	**−10.4 (−20.7; −0.1)**	−8 (−18.3; 2.3)	−2.7 (−7.8; 2.3)	222 (−81.8; 530)	13.6 (−85.1; 11)
27.5	**−12.5 (−22.2; −2.8)**	−8.2 (−17.9; 1.5)	−4.2 (−9; 0.6)	219 (−67.3; 505)	18.5 (−73.7; 111)
30.0	**−13.3 (−22.9; −3.8)**	−8.3 (−17.8; 1.3)	**−4.8 (−9.5; −0.1)**	217 (−64.4; 498)	20.7 (−70; 111)
63.0	**−17.4 (−27; −7.7)**	−8.3 (−17.9; 1.4)	**−7.9 (−12.6; −3.1)**	**285 (2.1; 567)**	41.2 (−49.9; 132)
232.0	**−11.6 (−21.4; −1.8)**	−9.5 (−19.3; 0.3)	−2 (−6.8; 2.8)	**662 (376; 948)**	**92.3 (0.02; 185)**
240.0	**−11.7 (−21.5; −2)**	**−9.8 (−19.5; −0.02)**	−2 (−6.7; 2.8)	**665 (380; 950)**	**94.6 (2.7; 187)**
300.0	**−12.9 (−22.5; −3.4)**	**−11.5 (−21.1; −2)**	−1.4 (−6.1; 3.3)	**684 (407; 965)**	**111 (20.5; 202)**

FEV_1%, forced expiratory volume in1s, percent of predicted; FVC%, forced vital capacity, percent of predicted; KL, Krebs von den Lungen; SP-D, surfactant protein-D.

[a] Pulmonary function data are for 75 (86%) and serum biomarker data are for 80 (92%) of 87 participants in this study.

[b] The reference group comprised the 5 (6%) participants with cumulative indium exposure of −0.44 μg/L.

[c] Differences were calculated using restricted cubic spline regression, adjusted for smoking status (current/former/never). Regression models for FEV_1/FVC ratio, KL-6, and SP-D were also adjusted for age (years). Differences with 95%CI that exclude 0 (before rounding) are in bold.