

Pulmonary effects in workers exposed to indium metal: A cross-sectional study

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Abstract: Pulmonary effects in workers exposed to indium metal: A cross-sectional study: Makiko NAKANO, et al. Department of Preventive Medicine and Public Health, Keio University School of Medicine—Objectives: Indium was added to the list of substances regulated by the Ordinance on Prevention of Hazards due to Specified Chemical Substances (OPHSCS) in 2013. Indium metal (IM), however, is not regulated by the OPHSCS due to insufficient information on pulmonary effects following exposure. **Methods:** From 2011 to 2013, a cross-sectional study was conducted on 141 IM-exposed workers at 11 factories. Subjective symptoms were assessed, including levels of serum biomarkers, spirometry readings and total and diffuse lung capacity. Krebs von den Lungen-6 (KL-6) and surfactant protein D (SP-D) were selected as biomarkers of interstitial pneumonia. Indium serum concentration (In-S) and personal air sampling data were used to estimate exposure. Subjects were categorized into 5 groups based on occupation and type of exposure: smelting, soldering, dental technician, bonding and other. **Results:** The highest level of In-S was 25.4 $\mu\text{g/l}$, and the mean In-S level was significantly higher in the smelting group than in other groups. In the smelting group, the prevalence of increased In-S levels was 9.1%, while that of abnormal KL-6 was 15.2%. A significant dose-effect relationship was observed between the In-S and KL-6 levels. No marked differences were observed between any of the groups in SP-D values, pulmonary symptoms, or pulmonary func-

tion test results. A total of 31% of the subjects worked in an environment with IM levels exceeding 0.3 $\mu\text{g}/\text{m}^3$, which requires a protective mask to be worn. **Conclusions:** For workers exposed to IM, work environments should be monitored, appropriate protective masks should be worn, and medical monitoring should be conducted according to the OPHSCS. (J Occup Health 2015; 57: 346–352)

Key words: Cross-sectional study, Indium metal, Indium concentration, Interstitial pneumonia, Krebs von den Lungen-6 (KL-6), Surfactant protein D (SP-D)

Indium lung disease is a newly described occupational lung disease that affects workers exposed to indium compounds, such as indium tin oxide (ITO), which is used to manufacture electrodes to produce flat-panel displays, and indium oxide, indium hydroxide, and indium chloride, which are involved in the production or reclamation of ITO. The Japanese Society of Occupational Health recommended an exposure limit for indium and indium compounds of 3.0 $\mu\text{g}/\text{l}$ ⁽¹⁾ based on monitoring of the dose-effect relationship between the level of serum indium (In-S; exposure index) and the serum biomarker of interstitial pneumonia (Krebs von den Lungen, KL-6) associated with adverse pulmonary effects^(2–4) in 2007. An inhalation experiment conducted in rats over 2 years identified ITO with an indium concentration of 0.01 mg/m^3 as a lung carcinogen⁽⁵⁾. Based on these findings, the Japanese Ministry of Health, Labour and Welfare established prevention guidelines for workers exposed to ITO and other indium compounds in 2010⁽⁶⁾. In addition, indium compounds were added to the list of substances regulated by the Ordinance on Prevention of Hazards due to Specified Chemical Substances (OPHSCS) in 2013^(7,8). Under the OPHSCS, employers at indium-processing factories are required to measure indium concentrations in the respirable dust fraction at their sites and to

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Abbreviations: IM, indium metal. In-S, serum indium concentration. ITO, indium-tin oxide. In-A, 8-hour time-weighted average personal indium concentration in respirable dust fractions. KL-6, Krebs von den Lungen-6. SP-D, surfactant protein D. OPHSCS, Ordinance on Prevention of Hazards due to Specified Chemical Substances.

conduct health checks twice a year. These health checks consisted of a review of job career and working conditions; a review of past medical history, including pulmonary symptoms of coughing, sputum, dyspnea, cyanosis and clubbed fingers; evaluation of current pulmonary symptoms, including coughing, sputum, dyspnea, cyanosis, and clubbed fingers; and measurement of In-S and KL-6 values of workers. In addition, X-Ray or computed tomography of the chest was conducted at the start and end of employment. However, due to insufficient information on the pulmonary effects of indium metal (IM) exposure, IM and indium alloys are not listed in the OPHSCS. To our knowledge, no studies have been conducted in IM-processing factories.

Here, we determined whether or not IM exposure induces adverse pulmonary effects similar to the effects of non-IM indium compounds. We measured In-S and pulmonary effects of IM exposure and evaluated the relationship between IM exposure and markers of pulmonary effects at IM-processing factories.

Methods

This study was approved by the Ethics Committee of the School of Medicine at Keio University (approval number 20110268). Written informed consent was obtained from all subjects.

Study design and subjects

This multicenter study was conducted at 11 IM-processing factories, including 2 dental technician shops, 1 electric contact plant, 1 indium alloy target manufacturing plant, 3 lead-free solder manufacturing plants using an alloy containing less than 10% indium, 3 dental manufacturing plants using an alloy containing less than 25% indium, and 1 indium-free target plate bonding plant using 100% indium as an adhesive material. This study was conducted from 2011 to 2013. There were 142 subjects, and the proportions of subjects enrolled were dependent on the size of each factory and ranged from 2 to 41. One of the subjects was excluded from the statistical analysis due to a history of exposure to non-IM indium compounds.

Study subjects were categorized into five groups, as follows: high-temperature ($\geq 1,000^{\circ}\text{C}$) alloy smelting workers (smelting workers), soldering workers, dental technicians, bonding workers and other workers.

All subjects underwent a health check, which consisted of a medical interview, questionnaire, blood test, spirometry examination and evaluation of total lung capacity (TLC) and diffuse lung capacity for carbon monoxide (DLCO). To investigate the relationship between the levels of In-S and serum biomarkers of interstitial pneumonia (KL-6 or surfactant protein

D [SP-D]), subjects were divided into currently and formerly exposed workers according to their exposure status. Job history was based on records at the plants or, if unavailable, on findings from the interview regarding occupational history.

Exposure indices

In-S ($\mu\text{g/l}$) was measured by inductively coupled plasma mass spectrometry (ICP-MS) at the Center of Advanced Instrumental Analysis, Kyushu University^{3,6} or the Japan Industrial Safety and Health Association⁶. In-S below the detection limit ($0.1\mu\text{g/l}$) was ascribed an arbitrary value of $0.05\mu\text{g/l}$ for statistical analysis.

Effect indices and confounding factors

KL-6 (EIDIA Co., Ltd., Tokyo, Japan)^{9,10} and SP-D (Yamasa Corporation, Tokyo, Japan)¹¹ were used as biomarkers for assessing interstitial changes in the lungs and were evaluated at a major commercial clinical laboratory (Special Reference Laboratory, Tokyo, Japan). SP-D levels were not measured in 26 subjects due to logistics.

Spirometry was performed using an electronic spirometer (HI-801; Chest MI, Tokyo, Japan) based on the standards of the Japanese Respiratory Society¹². TLC was determined by helium dilution lung volume tests, and DLCO was determined by single breath diffusing capacity tests performed using a portable compact machine (EasyOne Pro[®], nnd Medical Technologies, Zurich, Switzerland) based on the standards of the American Thoracic Society/European Respiratory Society¹³. TLC and DLCO were not measured in 12 workers due to rib fractures ($n=1$) or lack of measurement at the factory due to logistics ($n=11$). Spirometry was not evaluated in 5 workers due to rib fracture ($n=1$) or lack of measurement at the factory due to logistics ($n=4$). Age- and height-adjusted predicted values of vital capacity (VC), forced vital capacity (FVC), and forced expiratory volume in one second ($\text{FEV}_{1.0}$) were determined by sex, using the regression formula recommended by the Japanese Respiratory Society¹⁴. TLC was determined by sex, using reference values generated from the third National Health and Nutrition Examination Survey (NHANES III)¹⁵. DLCO and DLCO/VA were determined by sex, using the regression formula of Nishida for Japanese subjects¹⁶. Predictions were calculated for VC, FVC, $\text{FEV}_{1.0}$, TLC, DLCO and DLCO/VA.

Respiratory symptoms, smoking history and confounding factors of sex, age, medical history and history of exposure to indium metal and other materials were investigated using the Japanese version¹⁷ of the American Thoracic Society Division of Lung Disease questionnaire¹⁸ and supplementary questions.

Personal indium exposure concentration in respirable dust fraction

Eight-hour time-weighted average personal indium concentrations in respirable dust fractions (In-A) were measured in 35 study subjects using respirable dust samplers (GS-3 Respirable Dust Cyclone; SKC Inc., Eighty Four, PA, USA) and ICP-MS (Agilent 7500i; Agilent Technologies, Santa Clara, CA, USA) by the Japan Industrial Safety and Health Association according to guidelines⁶⁾ at approximately the same time as the health checks. An In-A level below the detection limit ($0.006 \mu\text{g}/\text{m}^3$) was ascribed an arbitrary value of $0.006 \mu\text{g}/\text{m}^3$ for statistical analysis.

Statistical analysis

Non-normally distributed data for KL-6 and SP-D were log-transformed to an approximately normal distribution before analysis. In-S and values of lung function were not log-transformed before analysis. Differences between occupational groups were assessed using one-way analysis of variance (ANOVA) for KL-6, SP-D, and values of lung function or the Kruskal-Wallis test (non-normal distribution) for age, exposure duration, time since last exposure and In-S. The Chi-square test was used to compare the proportion and prevalence of sex, smoking habits, exposure status, pulmonary symptoms, increased In-S levels and abnormal KL-6 and SP-D levels. A single regression model was used to evaluate the dose-effect relationship between In-S and KL-6 or SP-D levels by exposure status and between In-A and KL-6 or S-D levels.

Based on the adopted reference value of In-S⁴⁾, subjects were classified as either In-S < $3.0 \mu\text{g}/\text{l}$ or

$\geq 3.0 \mu\text{g}/\text{l}$. In-S $\geq 3.0 \mu\text{g}/\text{l}$ was used to assess the risk of indium exposure on the effect variables. The prevalence of abnormalities for biomarkers and lung function was analyzed using the following cutoffs for abnormal values: KL-6 $\geq 500 \text{ U}/\text{ml}$, SP-D $\geq 110 \text{ ng}/\text{ml}$, $\text{FEV}_{1.0}/\text{FVC} < 70\%$, $\% \text{VC} < 80\%$, $\% \text{FVC} < 80\%$, $\% \text{FEV}_{1.0} < 80\%$, $\% \text{TLC} < 80\%$, $\% \text{DLCO} < 70\%$ and $\% \text{DLCO}/\text{VA} < 70\%$.

The reference value of In-A was set as $10 \mu\text{g}/\text{m}^3$ based on the target indium concentration in respirable dust for immediately improved workplace environments or as $\geq 0.3 \mu\text{g}/\text{m}^3$ based on the acceptable exposure limits calculated according to the exposure concentration found to be potentially carcinogenic in rats, as established in the technical guidelines of the Japanese Ministry of Health, Labour and Welfare⁶⁾.

Statistical significance was assessed by two-tailed analysis, with $p < 0.05$. All statistical analyses were performed using SPSS version 19 (IBM Corp., Armonk, NY, USA).

Results

Tables 1 and 2 show the characteristics of study subjects and the pulmonary effects for each group. The mean age of the subjects was 40.9 years, and 88.7% were male. The mean duration from the start to end of indium exposure for all workers was 7.5 years. For currently exposed workers, the duration of indium exposure was calculated from the start to the time of the health check. The proportion of formerly exposed workers who were no longer experiencing indium exposure at the time of the health check was 24.2% in the smelting group, 31.3% in the bond-

Table 1. Study subjects by occupational group

Occupational group	Smelting (n=33)	Soldering (n=37)	Dental technician (n=5)	Bonding (n=16)	Other (n=50)	<i>P</i>
Age (yr), mean (SD)	39.5 (14.5)	38.7 (11.3)	41.6 (15.7)	39.5 (13.1)	43.9 (11.5)	0.334
Male, n (%)	33 (100.0)	29 (78.4)	2 (40.0)	16 (100.0)	45 (90.0)	<0.001
Exposure duration (yr), mean (range)	7.9 (0.08–33.2)	10.2 (0.83–34.8)	16.1 (0.75–32.7)	5.4 (0.25–17.8)	4.9 (0.33–36.2)	0.001
Time since last exposure (yr), mean (range)	6.6 (0.83–29.6)	—	—	9.7 (4.67–22.7)	6.4 (1.17–12.6)	0.122
In-S ($\mu\text{g}/\text{l}$), mean (range)	2.2 (0.1>–25.4)	0.1 (0.1>–0.4)	0.1 (0.1>–0.5)	0.1 (0.1>–0.5)	0.1 (0.1>–0.9)	<0.001
Smoking habit, n (%)						0.438
Nonsmokers	10 (30.3)	16 (43.2)	2 (40.0)	3 (18.8)	15 (30.0)	
Ex-smokers	10 (30.3)	6 (16.2)	2 (40.0)	8 (50.0)	15 (30.0)	
Current smokers	13 (39.4)	15 (40.5)	1 (20.0)	5 (31.3)	20 (40.0)	
Exposure status, n (%)						<0.001
Currently exposed	25 (75.8)	37 (100.0)	5 (100.0)	11 (68.8)	30 (60.0)	
Formerly exposed	8 (24.2)	0 (0.0)	0 (0.0)	5 (31.3)	20 (40.0)	

Prev, prevalence; SD, standard deviation; In-S, serum indium; yr, year; exposure duration, duration from start to end of indium exposure or to time of health check. *p*-value by one-way analysis of variance, Kruskal-Wallis test, or chi-square test among all groups.

Table 2. Effective markers by occupational group

Occupational group	Smelting (n=33)	Soldering (n=37)	Dental technician (n=5)	Bonding (n=16)	Other (n=50)	<i>P</i>
In-S $\geq 3.0 \mu\text{g/l}$, n (%)	3/33 (9.1)	0/37 (0.0)	0/5 (0.0)	0/16 (0.0)	0/50 (0.0)	0.040
Cough or sputum, n (%)	2/33 (6.1)	3/37 (8.1)	0/5 (0.0)	0/15 (0.0)	3/50 (6.0)	0.805
Biomarkers						
KL-6 (U/ml), GM (GSD)	322.0 (1.7)	216.5 (1.3)	181.0 (1.2)	237.6 (1.4)	261.8 (1.4)	<0.001
KL-6 ≥ 500 U/ml, n (%)	5/33 (15.2)	0/37 (0.0)	0/5 (0.0)	0/16 (0.0)	2/50 (4.0)	0.034
SP-D (ng/ml), GM (GSD)	55.7 (2.2)	38.1 (1.8)	28.4 (1.5)	43.0 (2.0)	41.5 (1.7)	0.105
SP-D ≥ 110 ng/ml, n (%)	7/33 (21.2)	0/14 (0.0)	0/5 (0.0)	1/15 (6.7)	3/48 (6.3)	0.094
Lung function, mean (SD)						
%VC	104.8 (12.5)	109.7 (11.3)	105.8 (13.0)	111.1 (12.7)	105.1 (12.2)	0.224
%FVC	101.8 (11.5)	108.3 (11.8)	103.4 (12.0)	107.9 (9.9)	103.0 (11.9)	0.112
%FEV _{1.0}	97.0 (12.8)	103.0 (12.6)	99.5 (19.0)	103.0 (10.4)	99.7 (11.6)	0.314
FEV _{1.0} /FVC	82.7 (5.8)	82.4 (5.4)	82.4 (11.3)	82.8 (4.6)	83.5 (7.0)	0.951
%TLC	94.8 (8.8)	94.2 (8.6)	94.3 (7.9)	98.6 (9.7)	94.2 (10.1)	0.743
%DLCO	96.9 (13.4)	89.9 (12.8)	95.8 (11.6)	94.9 (11.4)	91.5 (15.2)	0.260
%DLCO/VA	93.6 (9.5)	87.0 (14.1)	91.2 (13.5)	87.3 (12.0)	90.6 (14.2)	0.294

Prev, prevalence; SD, standard deviation; KL-6, Krebs von den Lungen-6; SP-D, surfactant protein D; VC, vital capacity; FVC, forced vital capacity; FEV_{1.0}, forced expiratory volume in one second; TLC, total lung capacity; DLCO, diffusing lung capacity for carbon monoxide; VA, alveolar volume. *p*-value by one-way analysis of variance, Kruskal-Wallis test, or chi-square test among all groups. %VC, %FVC, %FEV_{1.0} and FEV_{1.0}/FVC measured in the smelting (n=32), soldering (n=37), dental technician (n=5), bonding (n=14) and other groups (n=48) (total, n=136). %TLC, %DLCO and %DLCO/VA measured in the smelting (n=32), soldering (n=37), dental technician (n=5), bonding (n=10) and other groups (n=45) (total, n=129).

ing group, 40.0% in the “other” group and 0% in the remaining two groups. No marked differences in smoking history or age were observed among groups. The highest level of In-S in the smelting group was 25.4 $\mu\text{g/l}$, and the highest level of In-S among all other groups, excluding the smelting group, was less than 1.0 $\mu\text{g/l}$, with In-S levels below the detection limit being found in 82% of workers (89/108). The In-S level in the smelting group was significantly higher than that in all other groups ($p < 0.001$). The KL-6 level in the smelting group was also significantly higher than that in the other groups ($p < 0.001$). However, no marked differences were observed in the SP-D level, pulmonary symptoms or pulmonary function test results among all groups.

For each group, the respective proportions of subjects with abnormal levels of In-S, KL-6 and SP-D stratified by occupation type were as follows: 9.1, 15.2 and 21.2% (smelting); 0.0, 0.0, and 0.0% (soldering); 0.0, 0.0, and 0.0% (dental technicians); 0.0, 0.0, and 6.7% (bonding); and 0.0, 4.0, and 6.3% (other). The proportion of increased In-S and abnormal KL-6 levels were significantly higher in the smelting group than in the other groups ($p = 0.040$ and $p = 0.034$, respectively).

Figure 1 shows a scattergram comparing the levels of In-S and KL-6 or SP-D by exposure status (currently and formerly exposed workers). In currently exposed workers, significant increases in KL-6 levels were

observed with increasing In-S levels ($p < 0.001$). Dose-effect relationships between In-S and SP-D levels in currently and formerly exposed workers ($p = 0.018$ and 0.014, respectively) were also observed. However, in formerly exposed workers, no significant dose-effect relationship between In-S and KL-6 levels was observed ($p = 0.192$).

The Mean In-A level (n=35) was 15.93 $\mu\text{g/m}^3$, with values ranging from <0.006 (undetectable) to 510.28 $\mu\text{g/m}^3$ and differing significantly between groups ($p = 0.006$). In-A in the smelting group (mean, 68.36 $\mu\text{g/m}^3$; standard deviation, 178.75 $\mu\text{g/m}^3$; range, 0.12–510.28 $\mu\text{g/m}^3$) represented the highest level of exposure to respirable indium dust among groups. The proportions of workers with In-A levels exceeding 10 $\mu\text{g/m}^3$ (target indium concentration criteria requiring immediate improvement of work environments) in each group were as follows: 25% (smelting), 0% (soldering), 0% (dental technicians), 0% (bonding) and 0% (other). The proportions of workers with In-A levels exceeding 0.3 $\mu\text{g/m}^3$ (acceptable exposure concentration limit not requiring an appropriate mask) in each group were as follows: 63% (smelting), 14% (soldering), 20% (dental technicians), 17% (bonding), and 33% (other).

Figure 2 shows a scattergram comparing In-A and KL-6 or SP-D levels by occupation groups in currently exposed workers. Although increasing In-A levels were associated with increasing KL-6 and SP-D

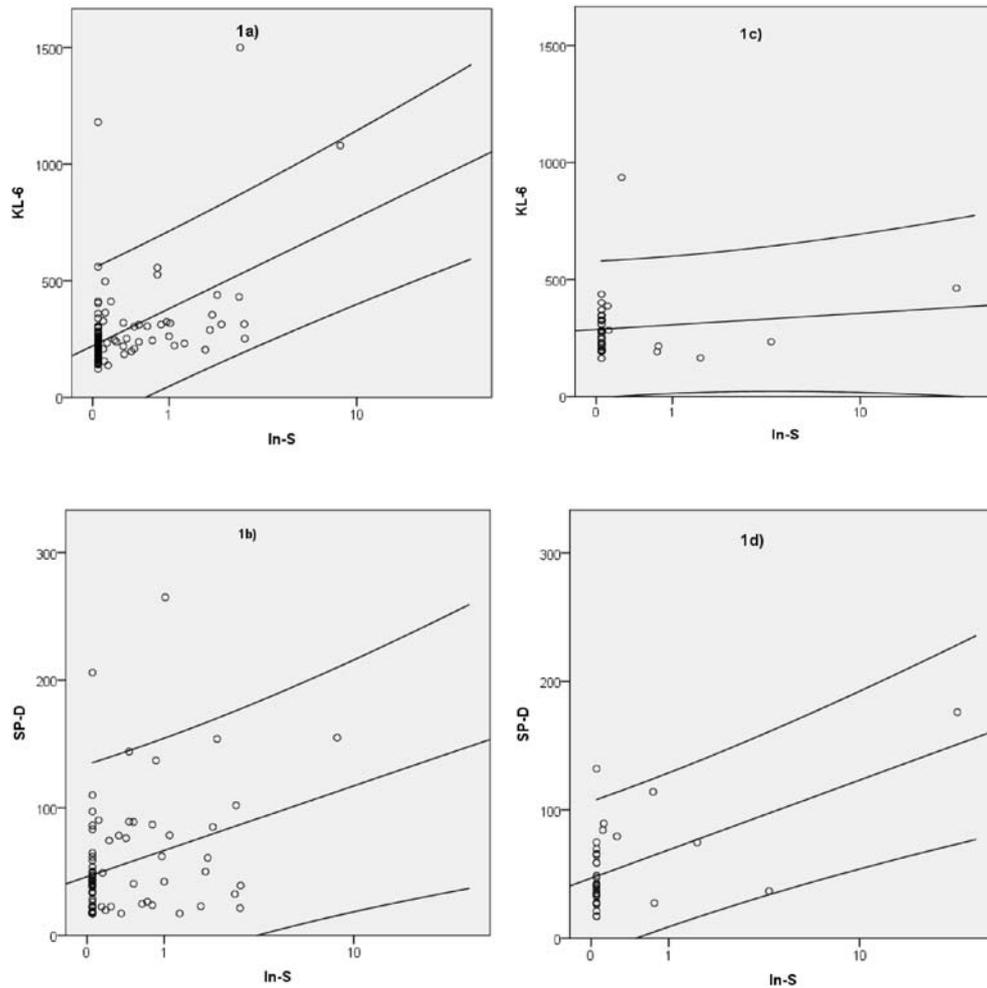


Fig. 1. Dose-effect relationships between In-S and biomarkers by exposure status
 1a) and 1b) Scattergrams between In-S and KL-6 or SP-D in currently exposed workers. 1c) and 1d) Scattergrams between In-S and KL-6 or SP-D in formerly exposed workers. Cut-off values: KL-6, 500 U/ml, and SP-D, 110 U/ml. A single regression model was used to evaluate the dose-effect relationship between In-S and KL-6 or SP-D levels.

levels, the relationships between these parameters were not significant ($p=0.687$ and $p=0.657$, respectively).

Discussion

In currently exposed workers, a dose-effect relationship between the levels of In-S and KL-6 was observed. In particular, in the smelting group, the level of In-S increased to over $20 \mu\text{g/l}$, which is a risk factor for interstitial pneumonia and progression of emphysematous changes^{2-4, 19}. Workers in the smelting group were involved in constructing indium alloys with palladium, gold, silver and other metals. Although the melting point of indium is 157°C , the dissolution temperature in the melting process is dependent on the other mixed metals in the alloy and exceeds $1,000^\circ\text{C}$. Although exposure to indium metal at room temperature is generally not harmful

to workers, indium melts at 157°C , and indium vapor is generated at higher temperature²⁰. The vapor is cooled down in air and ultimately becomes airborne respirable particles. These respirable particles might contribute to increases in In-A and In-S levels.

In the smelting group, 25% of workers required immediate improvement to their work environment according to prevention guidelines⁶. In addition, regardless of occupational group, approximately 31% of workers exposed to IM exceeding $0.3 \mu\text{g}/\text{m}^3$ were required to wear a protective mask according to prevention guidelines⁶. Based on these results, for workers exposed to IM, periodical monitoring of the work environment including monitoring of whether or not they wear an appropriate protective mask and medical monitoring is required.

In this study, IM-exposed workers who were work-

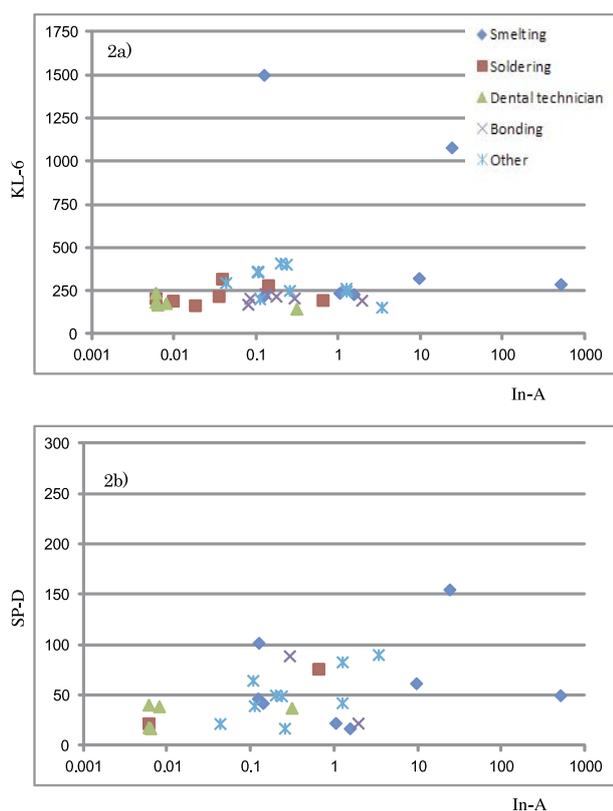


Fig. 2. Dose-effect relationships between In-A and biomarkers by occupational group

2a) Scattergram between In-A and KL-6 levels in currently exposed workers. 2b) Scattergram between In-A and SP-D levels in currently exposed workers. Target concentration for indium according to prevention guidelines: $10 \mu\text{g}/\text{m}^3$. Acceptable exposure limit for concentration of indium according to prevention guidelines: $0.3 \mu\text{g}/\text{m}^3$. A single regression model was used to evaluate the dose-effect relationship between In-A and KL-6 or S-D levels.

ing without improvement of the workplace environment or use of a protective mask were investigated. The level of exposure to respirable indium dust might be directly reflected in the amount of dust inhaled in the lungs. Although an increase in In-A levels resulted in an increase in KL-6 and SP-D levels, this change was not significant. The In-A levels were considered to be low, with only a small proportion of subjects having levels in excess of $10 \mu\text{g}/\text{m}^3$. A metric of cumulative exposure might have a preference for In-S levels over In-A levels.

Although hamsters exposed to indium oxide²¹⁾ and workers formerly exposed to indium compounds have been found to have elevated In-S levels for a prolonged period of time^{4, 19)}, the dose-effect relationship between In-S and KL-6 levels was not significant in the formerly exposed workers in the present

study. Clearance of the indium burden on the lungs may be more rapid following the inhalation of mist containing indium oxide²²⁾ than that of dust containing ITO or indium oxide at room temperature. In addition, the amount of indium inhaled into the lungs by IM-exposed workers in this study might be lower than that by ITO-exposed workers observed in previous studies^{4, 19)}.

Full evaluation with high-resolution computed tomography (HRCT) of the chest was not conducted in the present study. However, one IM-exposed worker with high In-S levels ($\geq 20 \mu\text{g}/\text{l}$) visited a hospital and underwent chest HRCT, which showed interlobular septal thickening and a mild reticular shadow. IM-exposed workers with high In-S levels might therefore suffer adverse effects that are similar to those of workers with noted exposure to indium compounds at ITO-processing factories²⁻⁴⁾.

Due to the cross-sectional nature of our study, a longitudinal observational study is also required. We recommend that future studies monitor the lung conditions of workers following the reduction of occupational exposure to IM.

Conclusions

We observed a dose-effect relationship between In-S and KL-6 levels in workers currently exposed to IM. The results of this study indicate that workers exposed to IM require monitoring of their work environment, appropriate protective masks and ongoing medical checks according to the OPHSCS to prevent indium lung disease.

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Conflicts of interests: None of the authors have any conflicts of interest to disclose.

References

- 1) Recommendation of occupational exposure limits (2007–2008). *J Occup Health* 2007; 49: 328–44.
- 2) Chonan T, Taguchi O, Omae K. Interstitial pulmonary disorders in indium-processing workers. *Eur*

- Respir J 2007; 29: 317–24.
- 3) Hamaguchi T, Omae K, Takebayashi T, et al. Exposure to hardly soluble indium compounds in ITO production and recycling plants is a new risk for interstitial lung damage. *Occup Environ Med* 2008; 65: 51–5.
 - 4) Nakano M, Omae K, Tanaka A, et al. Causal relationship between indium compound inhalation and effects on the lungs. *J Occup Health* 2009; 51: 513–21.
 - 5) Nagano K, Nishizawa T, Umeda Y, et al. Inhalation carcinogenicity and chronic toxicity of indium-tin oxide in rats and mice. *J Occup Health* 2011; 53: 175–87.
 - 6) Ministry of Health, Labor, and Welfare. Technical guideline for preventing health impairment of workers engaged in the indium tin oxide handling processes. Tokyo, Japan: Government of Japan. [Online]. 2010 [cited 2014 Nov 17]; Available from: URL: <http://www.mhlw.go.jp/bunya/roudoukijun/anzenisei42/dl/03.pdf>
 - 7) Sakurai H. Occupational safety and health in Japan: current situations and the future. *Ind Health* 2012; 50: 253–60.
 - 8) Ministry of Health, Labor, and Welfare. Amendment to Ordinance on Industrial Safety and Health Law and to Ordinance on Prevention of Hazards due to Specified Chemical Substances. Tokyo: Government of Japan. [Online]. 2013 [cited 2014 Nov 17]; Available from: URL: <http://www.mhlw.go.jp/bunya/roudoukijun/anzenisei48/dl/anzenisei48-01.pdf> (in Japanese)
 - 9) Kobayashi J, Kitamura S. KL-6: a serum marker for interstitial pneumonia. *Chest* 1995; 108: 311–5.
 - 10) Ohnishi H, Yokoyama A, Kondo K, et al. Comparative study of KL-6, surfactant protein-A, surfactant protein-D, and monocyte chemoattractant protein-1 as serum markers for interstitial lung diseases. *Am J Respir Crit Care Med* 2002; 165: 378–81.
 - 11) Honda Y, Kuroki Y, Matsuura E, et al. Pulmonary surfactant protein D in sera and bronchoalveolar lavage fluids. *Am J Respir Crit Care Med* 1995; 152(6 Pt 1): 1860–6.
 - 12) The Japanese Respiratory Society. Guidelines for pulmonary function testing. Tokyo, Japan: Medical Review; 2004 (in Japanese).
 - 13) Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J*. 2005; 26: 720–35.
 - 14) The Clinical Pulmonary Functions Committee. Standard criteria of spirometry and arterial blood gas partial pressure measurement in Japanese. *J Jap Respir Soc* 2001; 39: 383–99.
 - 15) Department of Health and Human Services (DHHS). 1996. National Center for Health Statistics. Third National Health and Nutrition Examination survey, 1988–1994, NHANES III Adult and Examination Data Files (CD-ROM). Public Use Data File Documentation Number 76200. Hyattsville (MD): Centers for Disease Control and Prevention.
 - 16) Nishida O. A clinical study of the carbon monoxide diffusing capacity. The 3rd reports. *Medical Journal of Hiroshima University* 1970; 18: 223–33 (in Japanese) .
 - 17) Japan Public Health Association. Research on Method Of Measuring Influence On Health Due To Air Pollution. Tokyo: Japan Public Health Association; 1979 (in Japanese).
 - 18) Ferris BG. Epidemiology Standardization Project (American Thoracic Society). *Am Rev Respir Dis* 1978; 118(6 Pt 2): 1–120.
 - 19) Nakano M, Omae K, Uchida K, et al. Five-year cohort study: emphysematous progression of indium-exposed workers. *Chest* 2014; 146: 1166–75.
 - 20) Iida et al. Steam pressure. *Physical Constants New Edition*; Tokyo: Asakura Publishing Co., Ltd; 1978. p. 133 (in Japanese).
 - 21) Tanaka A, Hirata M, Homma T, et al. Chronic pulmonary toxicity study of indium-tin oxide and indium oxide following intratracheal instillations into the lungs of hamsters. *J Occup Health* 2010; 52: 14–22.
 - 22) Indium Oxide. Patty's toxicology Fifth Edition; New York (USA): John Wiley & Sons, Inc; 2001. p. 471–5.