Exposure to hardly soluble indium compounds in ITO production and recycling plants is a new risk for interstitial lung damage

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Exposure to hardly soluble indium compounds in ITO production and recycling plants is a new risk for interstitial lung damage

T Hamaguchi,1 K Omae,1 T Takebayashi,1 Y Kikuchi,1 N Yoshioka,1 Y Nishiwaki,1 A Tanaka,2 M Hirata,2 O Taguchi,3 T Chonan3

ABSTRACT
Objectives: To identify the effects of indium on the lung and to assess exposure-effect and exposure-response relations between indium exposure and effects on the lungs.

Methods: Ninety three male indium exposed and 93 male non-exposed workers from four ITO manufacturing or ITO recycling plants were analysed in a cross-sectional study. Indium in serum (In-S) was determined as a biological exposure index. Geometric means (GSD) of In-S were 8.25 ng/ml (4.55) in the exposed workers and 0.25 (2.64) in the non-exposed workers. The maximum concentration of In-S was 116.9 ng/ml. A questionnaire for respiratory symptoms and job histories, spirometry, high-resolution computerised tomography (HRCT) of the chest, serum KL-6, serum SP-A, serum SP-D and serum CRP were measured as the effect indices.

Results: Spirometry, subjective symptoms and the prevalence of interstitial or emphysematous changes on lung HRCT showed no differences between exposed and non-exposed workers. Geometric means (GSD) of KL-6, SP-D and SP-A in the exposed workers were 495.4 U/ml (2.26), 85.2 ng/ml (2.02) and 39.6 ng/ml (1.57), and were significantly higher than those in the non-exposed workers. The prevalence (%) of the exposed and non-exposed workers exceeding the reference values were also significantly higher in KL-6 (41.9 vs 2.2), SP-D (39.8 vs 7.5), and SP-A (43.0 vs 24.7). Very sharp exposure-effect and exposure-response relations were discovered between In-S and KL-6 and between In-S and SP-D when the exposed workers were classified into seven groups by In-S.

Conclusions: The study outcomes with regard to the basis of serum immunochemistry biomarkers and HRCT indicate that exposure to hardly soluble indium compound dust may represent a risk for interstitial lung damage.

Since the rapid expansion of compound semiconductors and liquid crystal display (LCD) production, the consumption of indium has been increasing.

Beginning in the mid-1990s, the authors’ institutions performed single or repeated intratracheal instillation experiments with fine particles of hardly soluble indium compounds such as indium phosphide (InP) and indium arsenide and found that these induce severe lung inflammation with fibrotic changes1–6 and have mild reproductive effects.7,8 The US National Toxicology Program (NTP) carried out an InP inhalation experiment for two years and concluded that there is clear evidence of carcinogenic activity of InP on the lungs in male and female rats and mice.9 The International Agency for Research on Cancer classified InP as Group 2A in 2006.10

In 1998, a worker was identified as having interstitial pneumonitis. He was engaged in a wet mirror grinding process of a high-density sintered alloy of 90% indium oxide-10% tin oxide (ITO) for making transparent, electrically-conductive thin film for liquid crystal display. In 2001 he died of bilateral pneumothorax. Lung biopsy and autopsy suggested that ITO accumulated in the lung might have been the cause of the interstitial pneumonitis.11 The second case of pulmonary fibrosis, which involved a worker from the same plant, was disclosed in 2002 and published in 2005.12 Chonan et al have reported the results of health check-ups of 108 male ITO exposed and ex-exposed workers in the same plant as the former two cases,11,12 and concluded that both serum Krebs von den Lungen-6 (KL-6) and abnormalities of chest high-resolution computed tomography (HRCT) were prevalent among indium workers, and that these abnormalities increased with the indium burden in workers, suggesting that inhaled indium could be a potential cause of occupational lung disease.13

To clarify whether indium dust inhalation induces the lung interstitial changes in current indium-exposed workers, and to assess exposure-effect and exposure-response relations between indium levels and health effects, we designed a cross-sectional survey that was carried out from December 2004 through February 2004 in two ITO manufacturing and two ITO recycling plants.

SUBJECTS AND METHODS
Study subjects and indium exposure profiles
This study was approved by the ethics committee of the School of Medicine, Keio University. Candidates for both exposed and non-exposed study subjects in the four plants were informed of the purpose and significance of the study, the benefits of the study for themselves and other indium-exposed workers, and their rights as participants. In total, 227 male workers volunteered for this study, but of these, 11 did not ultimately participate. One hundred and twelve male indium-exposed workers and 104 male non-exposed workers agreed to join the study and signed the form indicating informed consent. The rate of participation was 95.2%. Among the 112 exposed workers, 19 workers were excluded from the statistical analysis because their working period at indium-exposed sections was less than one year.
Eleven non-exposed workers were also excluded because they sometimes had a chance to enter the indium plants as a plant inspector, process supervisor, and so on. It may be reasonable to exclude them since their In-S levels did not seem to correspond to non-exposed levels. Finally, 93 indium-exposed and 93 non-exposed workers were used for statistical analysis.

More than half of the exposed workers had inhaled primary ITO dust, about 40% mainly indium trioxide and/or indium hydroxide dust, and about 10% mainly indium metal. Some of the exposed and non-exposed workers had job histories of exposure to non-ferrous metal compounds such as zinc, cadmium, lead, copper, gallium, selenium, and so on.

Table 1 shows the characteristics and indium exposure profiles of the study subjects. The exposed workers were significantly younger in age and smaller in BMI than the non-exposed workers. The proportion of smokers was significantly higher in the exposed workers, but the Brinkman index (daily number of cigarettes consumed multiplied by year of smoking) for smokers and ex-smokers was significantly lower in the exposed workers.

The exposed workers inhaled dusts of ITO, indium trioxide, indium hydroxide, and/or metal indium, all of which are hardly soluble in water. Unfortunately, we could not measure the size distribution of the fine dusts, but company staff of all four

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**Table 1** Characteristics of the study subjects and indium exposure profile

<table>
<thead>
<tr>
<th></th>
<th>Exposed workers (n = 93)</th>
<th>Non-exposed workers (n = 93)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean SD Range</td>
<td>Mean SD Range</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>36.8 12.2 20–67</td>
<td>43.6 11.1 22–70</td>
<td>0.0001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64.9 9.5 48–93</td>
<td>67.3 9.9 44–95</td>
<td>0.1101</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169.9 5.6 155–183</td>
<td>169.2 6 156–185</td>
<td>0.4509</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>67.7 52.7</td>
<td>52.7</td>
<td>0.0555</td>
</tr>
<tr>
<td>Indium in serum (In-S, ng/ml)*</td>
<td>8.25 4.55 ND–116.9</td>
<td>0.25 2.64 ND–1.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Duration of indium exposure (months)</td>
<td>94.9 54† 13–488</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ND, below detection limit.  
*Geometric mean and geometric standard deviation.  
†Median.

For test of difference in mean, Student or Welch t test (In-S) was adopted. For test of smoking prevalence, $\chi^2$ test was applied.

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**Table 2** Results of medical examinations

<table>
<thead>
<tr>
<th></th>
<th>Exposed workers</th>
<th>Non-exposed workers</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GM GSD</td>
<td>GM GSD</td>
<td></td>
</tr>
<tr>
<td>Serum immunochemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KL-6 (U/ml)</td>
<td>495.4 2.26</td>
<td>240.1 1.44</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SP-D (ng/ml)</td>
<td>85.2 2.02</td>
<td>51.7 1.73</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SP-A (ng/ml)</td>
<td>39.6 1.57</td>
<td>33.8 1.52</td>
<td>0.0133</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>0.05 3.24</td>
<td>0.05 3.07</td>
<td>0.2937</td>
</tr>
<tr>
<td>Spirometry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%FVC</td>
<td>101.9 11.8</td>
<td>100.4 12.7</td>
<td>0.3998</td>
</tr>
<tr>
<td>%FEV₁</td>
<td>99.1 11.6</td>
<td>98.4 12.8</td>
<td>0.6850</td>
</tr>
<tr>
<td>%FEV₁/forced exp.</td>
<td>97.4 6.7</td>
<td>98.3 7.3</td>
<td>0.3809</td>
</tr>
<tr>
<td>%MMF</td>
<td>94.5 28.0</td>
<td>94.7 27.9</td>
<td>0.9561</td>
</tr>
<tr>
<td>%PEF</td>
<td>105.6 15.0</td>
<td>106.3 14.9</td>
<td>0.7401</td>
</tr>
</tbody>
</table>

Serum immunochemistry exceeding the reference values

<table>
<thead>
<tr>
<th></th>
<th>n Prev</th>
<th>n Prev</th>
</tr>
</thead>
<tbody>
<tr>
<td>KL-6 &gt;500</td>
<td>39 2</td>
<td>7 2</td>
</tr>
<tr>
<td>SP-D &gt;110</td>
<td>37 7</td>
<td>40 8</td>
</tr>
<tr>
<td>SP-A &gt;43.8</td>
<td>40 23</td>
<td>24 7</td>
</tr>
<tr>
<td>CRP &gt;0.3</td>
<td>7 5</td>
<td>8 4</td>
</tr>
</tbody>
</table>

Positive HRCT changes

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Interstitial changes</td>
<td>6 9</td>
<td>0.4177</td>
</tr>
<tr>
<td>Emphysematous changes</td>
<td>7 5</td>
<td>0.5497</td>
</tr>
</tbody>
</table>

Respiratory symptom complaints

| Current smokers          |        |        |
| Cough in winter          | 10 6   | 16.2   | 0.5841 |
| Cough in all seasons     | 10 6   | 6.1    | 0.1402 |
| Phlegm in winter         | 12 25  | 0.4784 |
| Phlegm in all seasons    | 12 19.8| 0.8901 |

Ex or never smoked

|                          |        |        |
| Cough in winter          | 8 13.6 | 0.1636 |
| Cough in all seasons     | 7 11.4 | 0.1742 |
| Phlegm in winter         | 7 6.8  | 0.0792 |
| Phlegm in all seasons    | 5 6.8  | 0.2569 |

GM, geometric mean; GSD, geometric standard deviation. Prev, prevalence (%).  
For test of difference in mean, Student t test or Welch t test (KL-6 and SP-D) was adopted. For test of prevalence, $\chi^2$ test or, if number in a cell was 4 or less, Fisher’s exact method was applied.
plants said that the dusts consisted largely of respirable-sized particles.

In this study, we selected In-S as a biological exposure index rather than indium in urine or indium in whole blood taking; this index results in narrower variation and an easier pretreatment process. For pretreatment, 1 ml of serum was digested with 5 ml of 68% ultra-pure nitric acid (TAMAPURE-AA-100, Tama Chemicals Co, Japan) and 0.5 ml of 35% ultra-pure hydrogen peroxide (TAMAPURE-AA-100) by a microwave digestion apparatus (Multiwave 3000, Perkin-Elmer, Japan). Digested sample was diluted to 20 ml with ultra-pure water and was introduced into the inductively coupled plasma mass spectrometer (ICP-MS, Agilent 7500c, Yokogawa Analytical Systems, Japan) at the Center of Advanced Instrumental Analysis, Kyushu University. Rhodium was used as an internal standard for indium measurement. The detection limit of In-S was 0.1 ng/ml. If In-S was below the detection limit, 0.05 ng/ml was given for the statistical analysis.

Medical examinations
Respiratory symptoms were examined using the Japanese version of the self-administered ATS-DLD (American Thoracic Society-Division of Lung Disease) questionnaire with additional questions for job histories. All questionnaire answers were confirmed and, if necessary, rewritten in more detail based on doctors’ interviews.

Serum KL-6, serum surfactant protein D (SP-D), serum surfactant protein A (SP-A), and CRP were determined by a nationwide clinical laboratory for assessing lung interstitial changes and inflammation. They were sampled during work hours in the middle of the week.

A forced maximal expiratory flow-volume test (spirometry) was carried out using electronic autospirometers (Chestgraph HI-701, Chest Co, Tokyo, Japan) by experienced examiners. Because the reliability and reproducibility of the measurement of spirometry depended strongly on the cooperation and effort of the examinees, the significance of and method for the spirometry were explained to all examinees, who were then trained in mastering the manoeuvre. The flow-volume test was repeated at least three times for each study subject, and the trial satisfying the criteria recommended by the Japanese Respiratory Society (JRS) was chosen. From the spirogram, forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), FEV1/FVC multiplied by 100 (FEV1%), maximal mid-expiratory flow (MMF), and peak expiratory flow (PEF) were recorded.

According to JRS Guidelines for the Diagnosis and Management of Chronic Obstructive Pulmonary Disease (COPD), chest HRCT was carried out at four hospitals near the study sites. Two experts in respiratory medicine certified by the JRS independently interpreted interstitial and emphysematous changes on HRCT of six lung fields—the upper, middle and lower lung fields of right and left sides. Because the quality of the HRCT photographs among the hospitals could not be made sufficiently uniform, primarily because of differences in CT equipment, we defined the HRCT photographs as being evident of HRCT change if at least one of the two experts identified interstitial or emphysematous changes of 10% or above in an area in at least one of the six lung fields.

All medical examinations and radiological diagnosis except for interviews regarding job histories were carried out without any knowledge of whether or not the examinees were exposed workers.

Statistical analysis
For continuous data, data distribution was examined, and an appropriate transformation was performed to approximate a normal distribution before the analysis. The mean values of the variables were compared by the Student t test, Welch t test or analysis of variance followed by Dunnett test for adjusting multiple comparisons. Wilcoxon rank sum test was applied when an appropriate transformation was not valid. The logit model was applied to assess exposure-response relations. For prevalence data, proportions were compared by the chi² test or Fisher’s exact method. All statistical analysis was performed using JMP version 5.1.2 (SAS Institute Inc, Cary, NC, USA) and ToxTools version 1.0 (Cytel Software Co, Cambridge, MA, USA).
RESULTS

Table 2 shows the results of the medical examinations. GM (GSD) of KL-6, SP-D, and SP-A in the exposed workers were 495.4 U/ml (2.26), 85.2 ng/ml (2.02), and 59.6 ng/ml (1.57). These were significantly higher than those in the non-exposed workers. CRP showed no changes.

The prevalence (%) of the exposed workers above the reference values of KL-6 (>500), SP-D (>110) and SP-A (>43.8) were 41.9, 39.5 and 43.1, and that of the non-exposed workers was 2.2, 7.5 and 24.7 respectively. The differences in the prevalence were statistically significant.

Parameters of spirometry adjusted by age and height by smoking habit showed no differences between exposed and non-exposed workers. Six exposed and 10 non-exposed workers showed interstitial changes on lung HRCT.

There was no difference in the prevalence of the interstitial changes between the exposed and non-exposed workers. Smoking did not affect the interstitial changes in this study population. Seven exposed and five non-exposed workers, all of whom were ex or current smokers, showed emphysematous changes on lung HRCT. There were no differences in the prevalence of emphysematous changes between exposed and non-exposed workers. Three of the six exposed and two of the 10 non-exposed workers with the interstitial changes also had emphysematous changes.

In currently smoking workers, the prevalence (%) of respiratory symptoms showed no trends and no difference between exposed and non-exposed workers. In ex-smoking or never-smoked workers, the prevalence was higher in exposed workers than in non-exposed workers, but the differences were not statistically significant. Subjective symptoms and the lung changes on HRCT showed no relation to each other.

To clarify the dose-effect and dose-response relations between In-S and KL-6, SP-D, SP-A and HRCT, the exposed workers were divided into seven groups by In-S levels—namely, groups 0 to 6 with In-S of less than 1.0, 1.0–4.9, 5.0–9.9, 10.0–19.9, 20.0–29.9, 30.0–49.9 and 50.0 ng/ml or above, respectively. Table 3 shows the results of the medical examinations. GM (GSD) of KL-6, SP-D and SP-A, and the prevalence (%) of workers exceeding the reference values of KL-6, SP-D and SP-A, and the prevalence of the interstitial and emphysematous changes on lung HRCT in each group. Dose-effect and dose-response relations were very clear in all of these parameters. Compared to group 0, statistically significant increases in means were found in groups 4 to 6 for KL-6, groups 4 and 6 for SP-D, and groups 5 and 6 for SP-A by Dunnett multiple comparison test. Applying a multiple regression model, age- and smoking-adjusted dose-dependent trends were statistically significant for the three parameters. A dose-response trend was revealed significantly for all of the five parameters after age and smoking adjustment by applying a logistic regression model. Best-fit approximate logit functions between In-S of each group and the prevalence of KL-6 and SP-D were estimated to be logit \( p = \frac{-2.09 + 0.112 \times \text{In-S}}{1 + \exp(0.112 \times \text{In-S})} \) for KL-6 (\( p < 0.001 \)) and logit \( p = \frac{-1.55 + 0.0612 \times \text{In-S}}{1 + \exp(0.0612 \times \text{In-S})} \) for SP-D (\( p < 0.001 \)), which indicate extremely sharp dose-response relations (fig 1). For SP-A and the HRCT changes, the dose-dependent increases were significant but not as sharp as those for KL-6 and SP-D.

DISCUSSION

This is the first analytic epidemiology focusing on the relations between indium dust exposure and effects on the lungs.

KL-6 is increased in patients with interstitial lung diseases such as idiopathic interstitial pneumonitis, hypersensitivity pneumonitis, and collagen disease-associated interstitial
pneumonitis, and is a sensitive indicator for the active phase of interstitial lung diseases. Meanwhile, KL-6 is not increased in patients with non-interstitial lung diseases, including emphysema. SP-D and SP-A are also increased in patients with interstitial lung diseases. Among these three indices, KL-6 has been evaluated as being the best marker for interstitial lung disorders, with SP-D being the next best.

In our study population, the indium-exposed workers showed significantly higher values of KL-6 and SP-D than the non-exposed workers, and the exposure-effect and exposure-response relations between In-S and KL-6, and between In-S and SP-D were very sharp. These results were consistent with those observed in other indium-exposed workers, as reported by Chonan et al. From these findings, we can conclude that lung interstitial tissues of highly indium-exposed workers actively respond to the indium inhaled, regardless of whether radiologically detectable lung fibrosis has developed.

Two cases reported in 2003 and 2005 had inhaled ITO dust, which is made of indium and tin oxides. Tin is known to cause stannosis, which is benign pneumoconiosis without symptoms of interference with pulmonary function and with no necrosis, foreign body giant cell reaction, or collagen formation. The pathological and radiological findings of the lungs of the two reported cases did not appear to be explained by stannosis. In this study population, approximately half of the exposed workers inhaled tin-free indium compounds such as indium trioxide, indium hydroxide, and/or indium metal fume, and they showed no differences in effects on the lungs compared to the workers who had primarily inhaled ITO. Other non-ferrous metal compounds might be possible candidates for causing the interstitial changes. In exposed workers with an experience of non-ferrous metal exposure (n = 58), geometric means of In-S, KL-6, SP-D and SP-A were 7.5, 553.9, 90.1 and 45.1, all of which were not statistically different from 8.8, 458.6, 81.9 and 35.7 in In-exposed workers without this experience (n = 55). The same outcomes were also found in non-exposed workers. In the non-exposed workers, there were no differences in KL-6 and SP-D between smokers and non-smokers (data not shown). Thus, tin, other non-ferrous metal compounds except for indium, and smoking are unlikely to cause the interstitial changes on the lungs observed in this study.

We used In-S as a biological exposure index of indium in this study. In the report based on the NTP study, In-S increased in proportion to concentration and the duration of exposure, though In-S was quite low relative to indium in the lungs. However, after exposure termination, the decreasing rate of In-S seemed to be very slow compared to that of indium in the lungs. These results suggest that the toxicokinetics of In-S might be different from that of indium in the lungs. Further evidence is necessary to confirm whether or not In-S is an appropriate biological exposure index reflecting indium load in the lungs.

Because the quality of HRCT films was not sufficiently uniform in this study, we could not read the HRCT findings with sufficient comparability among the four hospitals. Therefore, we chose to define HRCT findings as positive if the area of interstitial or emphysematous changes in at least one of the six HRCT lung fields exceeded 10% or above, but this definition was not universal and might be biased toward underestimation of the prevalence of HRCT findings. Relations between indium exposure and HRCT changes might have been found if CT quality had been uniform, as reported by Chonan et al.

Despite the limitations of the study described above, two case reports, one a field study and another observations of animals exposed to hardly soluble indium compounds, are consistent with the results of this cross-sectional study. Thus, we conclude that exposure to hardly soluble indium dust represents a risk for interstitial lung damage.

Acknowledgements: The authors thank all staff members and participants of the four plants for their helpful and cordial cooperation. This study was supported in part by Grants-in-aid for Scientific Research (Project No 15390191) from the Ministry of Education, Culture, Sports, Science and Technology of Japan (2003–4).

Competing interests: None declared.

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