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Exposure and Health Risk of Gallium, Indium, and Arsenic from Semiconductor Manufacturing Industry Workers

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The semiconductor manufacturing industry is a chemically-intensive, modern industry in which workers are potentially exposed to toxic metals of the IIIA, IVA, and VA families, including gallium (Ga), indium (In), and arsenic (As) (Liao et al., 2006; Chen, 2006). These metals or metalloids are known to have several toxicities and to cause carcinogenesis in animals and humans (Chepesiuk, 1999; Fowler et al., 1993). Symptoms of acute poisoning (including gastrointestinal discomfort, vomiting, coma, and sometimes death) usually occur within 30 min of ingestion of GaAs and InAs, whereas the consequences of chronic poisoning (including anemia, leucopenia, skin cancer, and other internal cancers) are much more insidious (Betoulle et al., 2002). A single dose of 100 mg/kg of GaAs and InAs resulted in acute pulmonary inflammation and pneumocyte hyperplasia after 14 days (Betoulle et al., 2002; Tanaka et al., 1996; Webb et al., 1986). Chronic exposure (2-year observation period) to lower doses (<1 mg/L) of GaAs and InAs produced systemic toxicity and definite pulmonary lesions (Ohyama et al., 1988). In addition, testicular toxicity was observed, and tumor occurrence increased significantly in mice when GaAs and InAs were injected intraperitoneally (Omura et al., 2000). There was also evidence of renal toxicity. CD rats exposed to GaAs developed mitochondrial swelling of renal proximal tubule cells and dose-dependent inhibition of δ-aminolevulinic acid dehydratase (ALAD) in the blood, kidney, and liver (Goering et al., 1988; Conner et al., 1995).

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Arsenic has been classified by International Agency for Research in Cancer (IARC) as a Group I carcinogen, which means that it is a documented human carcinogen. Much of the information linking arsenic to cancer has been obtained through studies of human exposure. Chronic exposure to inorganic arsenic is a potential occupational hazard. The Occupational Safety and Health Administration (OSHA) mandate permissible limits for occupational exposures to ensure the safety and health of workers. The permissible exposure limit (PEL) for arsenic was set at 10 $\mu g/m^3$ for an 8-hr day in a 40-hr workweek, and the short-term exposure limit (STEL) measured over a 15-min period was set at 2 $\mu g/m^3$ (ATSDR, 2006). Moreover, the biological exposure index (BEI) of total arsenic in urine was set at 35 µg/L (ACGIH, 2004).

Taiwan's history of economic development is well known. The semiconductor manufacturing industry, in particular, has played a decisive role in the development of Taiwan's economy. Taiwan is the largest producer of CD-ROMs and light emitting diodes (LEDs) with integrated circuit (IC) products, accounting for 70% and 50% of total worldwide production, respectively. Semiconductor production increased 54% in Taiwan from 1993 to 2000. Currently, about 350 companies in Hsinchu Science-based Industrial Park (HSIP) manufacture ICs, computers and peripheral devices, telecommunication devices, optoelectronics, biotechnology products, and precision machinery. These companies employ over 30,000 people (Chen and Huang, 2004; Chen, 2006). Because workers in the semiconductor manufacturing industry are potentially exposed to a variety of heavy metals, their health may be at risk. In this study, we examined workers' personal exposure to gallium (Ga), indium (In), and arsenic (As) by monitoring the concentrations of these substances in inhalable-air and urine. We then evaluated the potential health risk of working in the semiconductor manufacturing industry.

Materials and Methods

In this study, workers were selected from two major semiconductor companies in the Hsinchu Science-based Industrial Park (HSIP). We selected 144 exposed workers (including one group of 72 production workers known as operators and one group of 72 engineers) and 72 unexposed workers (office administrators, also known as the referent group). Both sample collection and biological monitoring were conducted for all selected workers. Samples were collected as described by Chen et al. (2002) and Katchen et al. (1998) using an IOM personal sampler (Institute of Occupational Medicine, SKC, USA) equipped with a cylindrical body, 37 mm cassette, and PVC filter. The flow rate was set at 2.0 L/min. At the end of the shift on the sampling day, a spot urine specimen was collected from each selected worker in PVC bottles that were previously soaked in 20% nitric acid, followed by 20% hydrochloric acid, and rinsed with deionized water (>18.2 MΩ). After sampling, all urine samples were stored at –70° and analyzed within 24 hr of collection. Personal air-exposure samples and urine samples were digested with 30 mL of nitric acid in a microwave digestion bomb (MD2000, CEM Corporation, Matthews, NC, USA). Samples were analyzed three times by an inductively coupled mass spectrometry method (Hall et al., 1996; Matschat et al., 1997) using a Perkin-Elmer Elan 5000 Inductively Coupled Plasma Mass Spectrometer (ICP-MS). The operating conditions were as follows: (1) carrier gas (argon, 99.999%): 0.8 L/min; (2) plasma gas (argon, 99.999%): 13 L/min; (3) auxiliary gas (argon, 99.999%): 0.8 L/min; (4) pump rate: 1.5 mL/min; and (5) power: 1055 KW.

All chemicals were of analytical reagent grade. Aqueous stock solutions (1000 mg/L) of Ga(III) and In(III) were prepared using $Ga(SO_4)_3$ and $In(SO_4)_3$ (Fluka Chemie AG, Basel, Switzerland). The As(V) stock solution containing 1000 mg/L As was prepared by dissolving sodium arsenate (Na_2HAsO_4; ACS reagent) (Sigma, St. Louis, MO, USA) in a 1% (v/v) HCl solution, diluted from 12 M HCl (Optima; Fisher, Pittsburgh, PA, USA). As(III) stock solution at 1000 mg/L was prepared by dissolving sodium m-arsenite ($NaAsO_2$) (Sigma, 96.7% purity) in 1% (v/v) HCl solution. Calibration curves were plotted from various concentrations (0.002 to 10 μg/L) of Ga(III), In(III), As(III), and As(V) standards. The recovery yields of three metals were 93%, 95%, 97%, and 98% for Ga(III), In(III), As(III), and As(V), respectively. The detection limits of the three target metals were <5 ng/L. Arsenic concentrations reported in this study include both the concentrations of As(III) and As(V). The maximal value of relative standard deviation (RSD) for the five replicate analyses of an individual sample was less than 4%.

The analyses of Student's t tests were performed to compare the concentration differences between the two exposed groups and one referent group. Statistical analyses were conducted using SPSS/PC$^+$ (SPSS, Inc., Chicago, IL, USA). All tests were regarded as significant when $p < 0.05$.

Results and Discussion

Our results provide a database that could be used to gauge the potential health risk of workplace metal pollutants contributed by the semiconductor manufacturing industry and to develop an environmental strategy for controlling exposure to the pollutants.

Levels of exposed workers' and referents' personal exposure to inhalable metals are shown in Table 1. In operators, metal concentrations in inhalable air samples were 0.34–101.26, 0.14–100.62, and 5.26–106.12 μg/m^3 for Ga, In, and As, respectively, and were averaged to be 12.25, 8.43, and 25.66 μg/m^3, respectively. The decreasing order of concentration in inhalable air was arsenic > gallium > indium, and the concentration of arsenic was about 2.1 and 3.0 times that of gallium and indium, respectively. This decreasing order was also apparent in engineers (10.72, 7.38, and 22.42 μg/m^3 for Ga, In, and As) and administrators (2.59, 2.08, and 3.56 μg/m^3 for Ga, In, and As). The results agreed with those of past studies (Chepesiuk, 1999, Van Zant, 2000, and Chen, 2006), indicating that manufacture of high brightness LEDs, telecommunication laser diodes, optical storage lasers, electric devices, and solar cells, were the main contributors of metal pollutants. A survey of five manufacturing districts ranked semiconductor metals (in decreasing order of usage) as follows: As > Ga > In, with As ranked as the main inhalable hazard. In our study, mean exposures to the three metals were consistently and significantly ($p < 0.05$) higher in the exposed groups than in the referent group. Differences in the levels of the three metals between the operators (production workers) and engineers were not statistically significant ($p > 0.05$). Results indicated that high levels of these inhalable metals had not spread to nonmanufacturing (referent) areas of the factory. Monitoring the workplace concentrations of these metals should continue in these areas.

Table 2 shows the urinary concentrations of these metals. Mean urinary arsenic levels in the exposed groups (39.35 vs 36.25 μg/L for operators vs engineers) were in good agreement with the values reported by Horng et al. (2002). These authors reported urinary arsenic levels of

Table 1 Metal levels in inhalable air of exposed workers and unexposed workers (referents)

Metals (μg/m^3)	Exposed groups		Reference group
	Operators (1)	Engineers (2)	Administrators (3)
Number	72	72	72
Gallium (Ga)			
Range	0.34–101.26	0.25–100.27	0.14–18.00
Mean	12.25	10.72	2.59
p value	$p < 0.05$ for (1) vs (3) and (2) vs (3); $p > 0.05$ for (1) vs (2)		
Indium (In)			
Range	0.14–100.62	0.25–99.23	0.12–17.66
Mean	8.43	7.38	2.08
p value	$p < 0.05$ for (1) vs (3) and (2) vs (3); $p > 0.05$ for (1) vs (2)		
Arsenic (As)			
Range	5.26–106.12	4.71–102.35	0.35–18.77
Mean	25.66	22.42	3.56
p value	$p < 0.05$ for (1) vs (3) and (2) vs (3); $p > 0.05$ for (1) *vs* (2)		

Table 2 Metal levels in urine of exposed workers and unexposed workers

Metals (μg/L)	Exposed groups		Reference group
	Operators (1)	Engineers (2)	Administrators (3)
Number	72	72	72
Gallium (Ga)			
Range	5.56–56.31	4.42–51.36	0.09–8.05
Mean	10.15	9.06	1.32
p value	$p < 0.05$ for (1) vs (3) and (2) vs (3); $p > 0.05$ for (1) vs (2)		
Indium (In)			
Range	3.05–35.89	3.02–34.09	0.05–7.27
Mean	6.98	5.88	1.24
p value	$p <0.05$ for (1) vs (3) and (2) vs (3); $p >0.05$ for (1) vs (2)		
Arsenic (As)			
Range	12.26–70.08	11.95–68.12	5.56–46.52
Mean	39.35	36.25	15.60
p value	$p <0.05$ for (1) vs (3) and (2) vs (3); $p >0.05$ for (1) vs (2)		

38.1–76.8 μg/L for steel industry workers. Total arsenic in the urine at levels of 100 μg/L or less is considered normal. Both values were significantly higher in the exposed groups than the referent group (15.60 μg/L). The mean urinary gallium and indium levels were similar (gallium: 10.15 vs 9.06 μg/L, with ranges of 5.56–56.31 vs 4.42–51.36 μg/L for operators vs engineers, respectively; indium: 6.98 vs 5.88 μg/L for operators vs engineers, respectively) and are in agreement with previously published values in liquid crystal display (LCD) facility workers (5.8–33.4 μg/L, In) (Miyaki et al., 2003).

Table 3 and Table 4 list the distribution and the percentage that metal concentrations in exposed and unexposed workers are determined by personal exposure and biological monitoring. Levels of exposure to inhalable gallium and indium were lower than PEL levels (100 μg/L; NIOSH, 2005) or failed to exceed them by more than 3% in all three groups (operators, engineers, and administrators), suggesting that workplace Ga and In exposure has a negligible effect on workers' health. However, in the exposed groups, arsenic exposures exceeded PEL limits (10 μg/L) by 76.39 vs 70.83% (operators vs engineers) and BEI limits for urinary arsenic (35 μg/L) by 66.67 vs 55.56%. In administrators, arsenic levels were only 6.94% and 5.56% above PEL and BEI limits, and gallium and indium levels did not exceed the PEL limit. Thus, more attention should be paid to exposed workers than referents. Notably, no BEI limit for gallium or indium has been suggested by ACGIH or NIOSH for semiconductor manufacturing industry. Moreover, the data were processed through the Pearson's

Table 3 Distribution and percentage of metal concentrations by personal exposure in exposed and unexposed workers

Metals (μg/L)	Personal exposure					
	Total Number	No. >PEL	Percentage (%)	No. <PEL	Percentage (%)	PEL
Gallium (Ga)						
Operators	72	2	2.78	70	97.22	100
Engineers	72	1	1.39	71	98.61	100
Administrators	72	0	0		100	100
Indium (In)						
Operators	72	1	1.39	71	98.61	100
Engineers	72	0	0	72	0	100
Administrators	72	0	0	72	0	100
Arsenic (As)						
Operators	72	55	76.39	17	23.61	10
Engineers	72	51	70.83	21	29.17	10
Administrators	72	5	6.94	67	93.06	10

Table 4 Distribution and percentage of metal concentrations by biological monitoring in exposed and unexposed workers

Metals (μg/L)	Biological monitoring					
	Total Number	No. >35 μg/L	Percentage (%)	No. <35 μg/L	Percentage (%)	PEL
Gallium (Ga)						
Operators	72	1	1.38	71	98.62	–
Engineers	72	0	0	72	100	–
Administrators	72	0	0	72	100	–
Indium (In)						
Operators	72	0	0	72	100	–
Engineers	72	0	0	72	100	–
Administrators	72	0	0	72	100	–
Arsenic (As)						
Operators	72	48	66.67	24	33.33	35
Engineers	72	40	55.56	32	44.44	35
Administrators	72	4	5.56	68	94.44	35

correlation coefficient (r) analysis to see the relation between personal exposure and biological monitoring. The results show that there is a high extent of relationship ($r = 0.75–0.86$) between the urinary metal concentrations and inhalable metal exposure levels for all three types of semiconductor manufacturing workers, indicating significant consistency in the personal exposure and biological monitoring of these workers.

The workers in this study were mainly exposed to inhalable arsenic-containing dusts. Exposure (occupational and environmental) to inorganic arsenic compounds is associated with a higher frequency of skin and lung cancer. Long-term exposures may result in chronic poisoning, which is characterized by nausea, vomiting, diarrhea, peripheral neuropathy, and renal damage. Chronic signs of toxicity are related chiefly to disorders of the skin, mucous membranes, gastrointestinal system, nervous system, circulatory system, and the liver (Aoki et al., 1990; Horng et al., 2002). In this study, 20% of workers in the exposed groups had proteinuria and abnormal liver function, and 12% had hypertension. Cancer risk has also been calculated in semiconductor manufacturing industry workers, but since no arsenic health risk data for Taiwan has been published, the data available to assess risk was collected by the US EPA Carcinogen Assessment Group, as presented in the Integrated Risk Information System (IRIS) summary (US EPA, 1988). The risk assessment forum has completed an assessment of the carcinogenicity risk associated with inhalation of inorganic arsenic in the workplace. The multistage model was used to predict dose-specific cancer risk associated with inhalation of inorganic arsenic. In exposed semiconductor manufacturing industry workers, the cancer unit risk (CR) associated with exposure to airborne arsenic (expressed as a single formula CR = Mean × Factor) was 4.29×10^{-3} per (μg/L), and the risk of cancer mortality was about 1.10×10^{-1}, which was significantly

Table 5 Assessment of cancer risk to exposed workers and referents on the basis of arsenic concentration in inhalable air

Groups	Mean (μg/m^3, arsenic)	Factor (μg/m^3)$^{-1}$	Cancer risk
Operators	25.66	4.29×10^{-3}	1.10×10^{-1}
Engineers	23.42	4.29×10^{-3}	1.00×10^{-1}
Administrators	3.56	4.29×10^{-3}	1.52×10^{-2}

higher than the US EPA's acceptable risk (10^{-6}) in general nonoccupational residents, suggesting that occupational exposure to arsenic increased cancer incidence and mortality among workers (Table 5).

The higher Ga, In, and As exposure levels and urinary concentrations in workers and engineers in administrators indicated that semiconductor manufacturing in the workplace adversely affects workers' health. Cancer risk, estimated by the level of inhaled arsenic, was higher than the allowable risk based on US EPA's acceptable risk limits. Our results suggest that semiconductor manufacturing industry workers should be better protected from these pollutants. Considering that no BEI limits for gallium and indium have been suggested by ACGIH, our results might be used to establish such regulations. Levels of Ga, In, and As in inhalable-air and urinary levels of these metals need to be continually monitored to evaluate the potential risks of long-term exposure and to protect workers' health.

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