行政院國家科學委員會補助專題研究計畫成果報告

※※※※※※※※※※※※※※※※※※※※※※※※※
※ ※
※ 晶圓廠離子植入機台維修人員尿中砷物種分析 ※
※ Speciation of Urinary Arsenic of the Ion Implanter ※
※ Maintenance Engineers in the Semiconductor ※
※ Fabircation Facility ※
※※※※※※※※※※※※※※※※※※※※※※※※※

計畫類別：□x 個別型計畫 □整合型計畫
計畫編號：NSC 89－2314－B－002－375
執行期間：89 年 8 月 1 日至 90 年 7 月 31 日

計畫主持人： 黃耀輝

執行單位： 國立台灣大學公共衛生學院
職業醫學與工業衛生研究所

中 華 民 國 90 年 10 月 15 日

行政院國家科學委員會專題研究計畫成果報告

計畫編號：NSC 90-2314-B-002-375
執行期限：88 年 8 月 1 日至 89 年 7 月 31 日

主持人：黃耀輝　臺灣大學公共衛生學院職業醫學與工業衛生研究所
計畫參與人員：李志洋、王瀅琇、姚婉林　臺灣大學公共衛生學院職業醫學與工業衛生研究所

摘要

半導體晶圓製造過程中，維修工程師在拆卸機台進行保修作業時有可能暴露到危害物質，特別是作業環境中的砷或砷化物。本研究以高效能液相層析儀結合原子吸收光譜儀進行維修工程師的尿中砷代謝物種分析，以瞭解其維修作業中可能的砷暴露。共有 30 名來自六家不同晶圓廠的維修工程師被列爲暴露組，另每家晶圓廠兩名工業衛生師共 12 人組成對照組。於機台維修當週，針對暴露組與對照組的研究對象連續七天採集每日早起第一泡尿液樣本。尿中三價砷、五價砷、單甲基砷酸、二甲基砷酸及總無機砷代謝物平均濃度分別爲 1.7±1.4 *u*g/L, 1.4±1.1 *u*g/L, 6.2±6.7 *u*g/L, 20.2±14.1 *u*g/L, 29.5±17.2 *u*g/L。單甲基砷酸及其佔尿中總無機砷代謝濃度百分比在對照組、無保養作業的維修工程師及有保樣作業的維修工程師之間分別呈現遞增趨勢($p<0.005$ 及 $p<0.0005$)。本研究也指出低濃度砷暴露情況下，尿中總無機砷代謝濃度可能會受食物中砷醣的干擾而誤導無機砷暴露量的測量。然而在此情況下，以尿中砷物種分析觀察單甲基砷酸比例的變化是一項適當有用的指標，足以確定暴露的存在。

關鍵字： 砷、尿、物種分離、離子植入、保養維修。

ABSTRACT

For the wafer fabrication in semiconductor industry, the maintenance engineers are potentially exposed to hazards during their work of disassembling machine compartments for clean-up. One special concern is arsenic or arsenic compounds in working environment. The present study analyzed speciated urinary inorganic arsenic metabolites of the maintenance engineers with HPLC-HG-AAS to study the potential arsenic exposure during their maintenance work. Totally, from 6 wafer fabrication facilities, 30 maintenance engineers were recruited as exposed group, so were the another 12 office-based industrial hygienists serving as control group. First morning voided urine samples of each study subject were collected for 7 consecutive days. Results show the levels of total urinary inorganic arsenic metabolites for exposed group were 1.7±1.4 *u*g/L, 1.4±1.1 *u*g/L, 6.2±6.7 *u*g/L, 20.2±14.1 *u*g/L, 29.5±17.2 *u*g/L for As^{3+}, As^{5+}, monomethylarsonic acid, dimethylarsinic acid and total inorganic arsenic, respectively. Both concentration of monomethylarsonic acid and its proportion among various urinary inorganic arsenic metabolites showed significantly ascending trend among control group, engineers without preventative maintenance work prior to their urine sampling, and those with such work prior to sampling ($p<0.005$, and $p<0.0005$, respectively). It was aslo suggested that, at low level occupational arsenic exposure, the concentration of total urinary inorganic arsenic metabolites might be misleading due to the confounding effect of arsenosuger coming from seafood. Nevertheless, speciation of urinary arsenic species is good and appropriate in such case to use the proportion change of monomethylarsonic acid as an indicator for the verification of

arsenic exposure.

Keywords: Arsenic, Urine, Speciation, Ion Implanter, Preventative Maintenance.

INTRODUCTION

The semiconductor industry has been an enormous worldwide growth industry. Among many sources of potential exposure to chemicals, occupational arsenic exposure is one of the most concerned problems since inorganic arsenic is frequently used as a dopant material in diffusion furnaces (Williams and Baldwin 1994, Tu 1996, Ungers and Jones 1986). Chemical concerns with the operations of diffusion furnace and ion implanter center on the possibility of toxic gas releases and exposures to residues during maintenance activities. During the maintenance process, arsenic-containing byproducts, such as arsenic trioxide, are deposited on surfaces inside the reaction chamber. These byproducts can generate arsenic-containing particles, which creates the potential for exposure to workers when maintenance is performed on the reactor.

On the other hand, researches also indicated that a substantial fraction of absorbed arsenate (As^{5+}) is reduced in the blood to arsenite (As^{3+}) (Bertolero et al. 1981, McBride et al. 1978), which is in turn methylated through the hepatic detoxification mechanism and made much less reactive with tissue constitutes in comparison with inorganic arsenic (Tam et al. 1978). By the way, there seems to exist the individual susceptibility to arseniasis, with the viewpoint of either acquired and genetic susceptibility (Chen et al. 2001). In response to this issue, research with urinary arsenic speciation analysis would be useful and helpful in exploring the potential occupational arsenic exposure through the monitoring of urinary arsenic species fluctuation in a certain period. The present study is therefore proposed to investigate the distributions of the maintenance engineers' urinary arsenic species, and, in turn, to elucidate the possible occupational arsenic exposure from their ion implanter maintenance works.

MATERIALS AND METHODS

The present study was conducted in a semiconductor company's six wafer fabrication facilities. Of these fabrication facilities, all their ion implanters used elemental arsenic and/or gaseous hydride arsenic (AsH_3) as the ion source for implantation in the manufacturing process. Among these six wafer fabrication facilities, totally 30 preventative maintenance engineers were recruited as exposed group, while two designated industrial hygienists from each wafer fabrication facility were assigned as control group.

For the urine sampling, study subjects of both exposed and control groups were asked to provide with their first morning voided urine in seven successive days of the preventative maintenance week. Urinary creatinine was measured with a colorimetric method using the Hitachi Special Automatic Analyzer (Model 7450). If a sample contained an abnormally low or high level of creatinine, i.e., less than 0.5 g/L or greater than 3.0 g/L, the urinary arsenic result was excluded from analysis (ACGIH 2000).

The urine samples were analyzed for levels of As^{3+}, As^{5+}, monomethylarsonic acid (MMA), and dimethylarsinic acid (DMA) using HPLC linked with HGAAS (Perkin Elmer FIAS 400, Perkin Elmer AAnalyst 100) (Norin & Vahter, 1981). Recovery rates for As^{3+}, As^{5+}, MMA, and DMA were 97.6%, 98.5%, 104.7%, and 100.6%, respectively, and the detection limits were 0.14 μg/L, 0.39 μg/L, 0.56 μg/L, and 0.76 μg/L, respectively. Detailed information on the urinary arsenic speciation and the description of QA/QC process can be found elsewhere (Lee 2001).

Personal and area air samples were obtained for 1~2 hours during the major period of preventative maintenance task, and analyzed for both arsenic and arsine with hydride generation atomic absorption spectrometer（HGAAS, Perkin Elmer FIAS 400, Perkin Elmer AAS 3110）and graphite furnace atomic absorption spectrometer（GFAAS, Perkin Elmer AAS 5100）, respectively. In addition, wipe samples were

collected with moistened No.1 Advantec filter paper from a pre-defined 10x10 cm^2 hot spot of ion implanter and the nearby work areas, and the cleaning room area to characterize arsenic deposition, and analyzed for arsenic with HGAAS. Besides, individual information on study subjects was collected with standard questionnaire, including demographic and behavioral information, work history, work-related syndrome and symptoms, general environmental conditions related to potential arsenic exposure, consumption of seafood, and drinking water, etc. Statistical methods including Student's t test and general linear model (GLM), correlation and regression were applied and run on the Statistical Analysis System for data analysis of urinary arsenic levels with related leading factors.

RESULTS

The average age of 28.3(±3.1) years old for the preventative maintenance engineers was younger, but not significantly, than the control group, i.e., 30.5(±2.5) years old. Most of the preventative maintenance engineers were potentially exposed to chemicals at work, such as arsine (AsH_3), phosphine (PH_3), BF_3, isopropyl alcohol (IPA), and hydrogen peroxide (H_2O_2). Besides, around one-third of the preventative maintenance engineers were smokers, i.e., 10 out of 30 subjects, while half of the control group were smokers (6 out of 12). Meanwhile, results of the seafood consuming indicated that around 26.7% (8 out of 30) preventative maintenance engineers and 41.7% (5 out of 12) of the control group did eat seafood prior to the week of their urine sampling.

Table 1 presents airborne arsenic levels and arsine levels of the study areas and subjects. It was noticed that these arsenic and arsine levels were all below the ACGIH TLVs for airborne arsenic of 10 $\mu g/m^3$ and arsine of 50 ppb, except arsenic level found in ion source chamber (ACGIH 2000). The maintenance engineer who experienced relatively high arsine exposure level of 0.129 ppb was known with the working task of on site dismounting the major parts of equipment, scrubbing and cleaning the ion implanter itself. Arsenic contents on the surfaces of work areas were shown in Table 2 with the highest level presented at the wiping site on passageway.

Totally, 210 and 82 urine samples were collected in the maintenance week from participating preventative maintenance engineers and the control group, respectively. The concentrations and proportions of various arsenic species in urine by study groups and fabrication facilities are presented in Table 3. Concentrations and proportions of both As^{5+} and monomethylarsonic acid (MMA) of the maintenance engineers were significantly different from the control group. On the other hand, the total urinary inorganic arsenic metabolite levels of the facilities A and E, i.e., 20.3±7.0 $\mu g/L$ and 43.5±27.3 $\mu g/L$, respectively, were either significantly lower or higher than the grand average of 29.5±17.2 $\mu g/L$.

Proportion of various arsenic species among total inorganic arsenic metabolites in urine, by preventative maintenance work prior to their urine sampling, was shown in Table 4. The engineers with preventative maintenance work prior to urine sampling showed the highest monomethylarsonic acid (MMA) proportion than those without preventative maintenance work prior to urine sampling. Results of general linear model (GLM) analysis indicated that fabrication facility had significant effect on all urinary arsenic species levels and proportion except As^{3+} concentration, while the effect of preventative maintenance work prior to urine sampling influenced only the proportion of monomethylarsonic acid (MMA). Results of stepwise regression indicated that preventative work (PM Work) ($p=0.063$), potential exposure to AsH_3 ($p<0.05$), PH_3 ($p<0.05$), and smoking ($p<0.005$) were the leading predictors for monomethylarsonic acid level (MMA) while preventative work (PM Work) ($p<0.0005$) and smoking ($p<0.005$) were those for monomethylarsonic acid (MMA) (Table 5). On the other hand, both eating seafood and alcoholic drinking were among those significant predictors for dimethyl arsinic acid level (DMA) and total

urinary inorganic arsenic metabolites (Total As_i) ($p<0.05$).

DISCUSSION

In the present study, with the urinary arsenic levels of these control and exposed groups close to the BEI value published by the ACGIH, it might not be possible to expect any significant adverse health effects happen to them, and is hard to tell the elevation of urinary arsenic due to occupational exposure. However, the finding of the present study indicated a consistent association of ion implanter maintenance work and total urinary inorganic arsenic metabolites in a previous study at low level arsenic exposure (Hwang and Chen, 2000). Besides, facilitated with urinary arsenic speciation, this study was able to compare the urinary arsenic species distribution from the viewpoint of occupational exposure and identify the potential leading causes, and, accordingly, provide with appropriate intervention measures.

Recent researches indicated that dimethylarsinic acid in urine might be partly contributed by the metabolites of arsenosugar after consumption of arsenosugar-containing seafood such as seaweed, mussels, clams, and oyster (Ma and Le 1998, Velez and Montoro 1998). In the present study, total urinary arsenic levels of engineers of the facilities A and E were significantly either lower or higher than the grand average (Table 3). Such difference was probably attributable to their food sources at work since the facilities of B, C, D, F are at the same location with one common dinning room offering four meals a day, while the facilities A, and E are located in another two different areas, each having their own dinning room, and seafoods were common and frequently supplied for meals in these dinning rooms. The finding of obvious variation of total urinary inorganic arsenic metabolite levels among maintenance engineers of the facilities in different locations shed light on that such biomarker for inorganic arsenic exposure might be misleading and unreliable. Accordingly, the BEI value of 35 *u*g/L for arsenic exposure, recommended by ACGIH, may be appropriate in the western developed countries with relative low background urinary arsenic levels, but may not be good for the people in oriental island countries, such as Taiwan and Japan, where seafoods are more common in daily meals, and their background urinary arsenic levels are relative high.

Although severe acute arsenic poisoning from semiconductor manufacturing operations is an extremely rare event, urinary arsenic monitoring is still worth for documentation purposes and to trigger further investigation for exposure source identification. However, should the total urinary inorganic arsenic metabolite levels applied as indicator, it must be very cautious to interpret such conventional levels for arsenic exposure in order to prevent any confounding effect of arsenosugar from seafood. In contrast, speciation of urinary arsenic species is more appropriate in such case to clearly differentiate the contributions of arsenic species in urine, and avoid further misinterpretation of the results of urinary arsenic levels. In the present study, it was demonstrated that, for low level occupational arsenic exposure, urinary arsenic speciation is more appropriate from the viewpoint of industrial hygiene to use the proportion change of monomethylarsonic acid as an indicator for arsenic exposure verification.

REFERENCE

ACGIH. (2000). Threshold Limit Values for chemical substances and physical agents and Biological Exposure Indices, 2000. Cincinnati, Ohio; American Conference of Governmental Industrial Hygienists.

Bertolero, F., Marafante, E., Edel, R. J., Pietro, R., Sabbioni, E. (1981). Biotransformation and introcellular binding of arsenic in tissues of rabbits after intraperitoneal administration of As-74 labeled arsenite. *Toxicology* **20**, 35-44.

Chen, C. J., Hsueh, Y. M., Tseng, M.P., et al. (2001) Individual susceptibility to arseniasis. In: Chappell, W.R., Abernathy, C.O., Calderon, R.L. eds. Arsenic

Exposure and Health Effects. Elsevier Science.

Hwang, Y.H., Chen, S.C. (2000). Monitoring of low level arsenic exposure during maintenance of ion implanters. *Arch. Environ. Health.* **55**, 347-354.

Lee, Z.Y. (2001). Occupational arsenic exposure and urinary inorganic arsenic metabolites of ion implanter maintenance engineers. [Master Thesis] National Taiwan University, Taipei, Taiwan.

Ma, M.S., Le, X.C. (1998). Effect of arsenosugars ingestion on urinary arsenic speciation. *Clin. Chem.* **44(3)**, 539-550.

McBride, B.C., Merilees, H., Cullen, W.R., Pickett, W. (1978). Anaerobic and aerobic alkylation of arsenic. *In* "Organometals and organometalloids, occurrence and fate in the enivornment" (F.E. Brinckman and J.M. Bellama, Eds.), pp 94-115. ACS Symp. Ser. 82, Washington, DC: American Chemical Society.

Norin, H., Vahter, M. (1981). A rapid method for the selective analysis of total urinary metabolites of inorganic arsenic. *Scan J. Work Environ. Health* **7**, 38-44.

Tam, K. H., Charbonneau, S. M., Bryce, F., Lacroix, G. (1978). Separation of arsenic methabolites in dog plasma and urine following intravenous ingestion of ^{74}As. *Anal Biochem.* **86**, 505-511.

Tu, L. J. (1996). Survey of potential hazards in a wafer manufacturing factory. [Master Thesis] National Taiwan University, Taipei, Taiwan.

Ungers, L. J., Jones, J. H. (1986). Industrial hygiene and control technology assessment of ion implantation operations. *Am. Ind. Hyg. Assoc. J.* **47(10)**, 607-614.

Velez, D., Montoro, R. (1998). Arsenic speciation in manufactured seafood products. *J Food Protection.* **61(9)**, 1240-1245.

Williams, M. E., Baldwin, D.G. (1994). Semiconductor industrial hygiene handbook. Noyes Publications.

Table 1. Concentrations of airborne arsenic and arsine during the ion implanter maintenance.

Sample Types	Chemical	# of Sample	# of Samples with Concentration > DL*	Range** As, $\mu g/m^3$ AsH_3, ppb
Area Sample				
At Ion Implanter	Arsenic	6	6	0.007~0.055
	Arsine	6	1	0.014
End Station	Arsenic	1	1	0.016
	Arsine	1	0	-
Ion Source	Arsenic	1	1	15.6
Chamber	Arsine	1	1	0.683***
Passageway	Arsenic	3	2	0.011~0.031
	Arsine	3	1	0.039
Wiping Site on	Arsenic	1	1	0.019
Passageway	Arsine	1	1	0.123
Inside Hood in	Arsenic	4	2	0.036~0.037
Cleaning Room	Arsine	4	2	0.028~0.098
Outside Hood in	Arsenic	1	0	-
Cleaning Room	Arsine	1	1	0.178
Subtotal	Arsenic	17	13	0.007~15.6
	Arsine	17	7	0.014~0.683
Personal Sample				
Maintenance	Arsenic	-	-	-
Engineers	Arsine	2	1	0.129***

* Detection Limit --- Arsenic: 0.005 $\mu g/m^3$, Arsine: 0.009 ppb.

** Only samples with concentration greater than detection limit were included.

*** Underestimate of exposure since breakthrough occurred during the sampling.

Table 2. Arsenic loading on the work surface.

Location	# of Sample	# of Sample with Concentration > DL*	Range* $\mu g/cm^2$
At Ion Implanter	3	3	0.001~0.007
Passageway	4	3	0.001~0.002
End Station	1	1	0.008
Ion Source Chamber	1	1	0.004
Wiping Site on	2	2	0.002~0.031
Passageway	4	2	0.001~0.006
Cleaning Room Floor	15	12	0.001~0.031
Total			

* Detection limit of wipe sample for arsenic loading was 0.0002 $\mu g/cm^2$. Only samples with arsenic loading greater than detection limit were included in range presentation.