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Occupational exposure to arsine

An epidemiologic reappraisal of current standards

by Philip J Landrigan, MD, MSc, Richard J Costello, PE, CIH, William T Stringer, MS[1]

LANDRIGAN PJ, COSTELLO RJ, STRINGER WT. Occupational exposure to arsine: An epidemiologic reappraisal of current standards. *Scand j work environ health* 8 (1982) 169—177. In an evaluation of chronic occupational exposure to arsine (AsH_3), an epidemiologic survey was conducted at a lead-acid battery manufacturing plant. Personal (breathing zone) air samples were obtained for the measurement of exposure to arsine and particulate arsenic (As), and area air samples were also collected for the determination of arsenic trioxide (As_2O_3) vapor concentrations. For the quantification of arsenic absorption, total arsenic content was determined in duplicate 24-h urine samples. Arsine in 177 breathing-zone air samples ranged from non-detectable to 49 $\mu g/m^3$. The highest levels were found in the battery formation area, where arsine is generated by the reaction of battery acid with lead-arsenic alloy. Exposures to particulate arsenic (maximum 5.1 $\mu g/m^3$) and to As_2O_3 (maximum 0.44 $\mu g/m^3$, expressed as As) were generally lower. Urine analysis showed that eight (20.5 %) of 39 production workers had urinary arsenic concentrations (corrected to a specific gravity of 1.024) of 50 $\mu g/l$ (0.67 $\mu mol/l$) or above, indicating increased arsenic absorption. None of eight office staff had elevated urinary arsenic levels. A close correlation was found between urinary arsenic concentration and arsine exposure ($N = 47$; $r = 0.84$; $p = 0.0001$). Arsine levels above 15.6 $\mu g/m^3$ were associated with urinary arsenic concentrations in excess of 50 $\mu g/l$ (0.67 $\mu mol/l$). No correlation was found between urinary arsenic content and exposures to particulate arsenic or to As_2O_3. Consumption of neither seafood, red wine, tobacco, nor contaminated drinking water accounted for urinary arsenic excretion. It was concluded that the current arsine exposure standard, 200 $\mu g/m^3$, fails to prevent chronic increased absorption of trivalent arsenic from the inhalation of arsine.

Key terms: arsenic, epidemiology, industrial hygiene, occupational medicine, workplace standards.

Arsine gas (AsH_3) is the most acutely toxic form of inorganic arsenic (10). Inhalation causes rapid intravascular hemolysis. Symptoms of headache, dyspnea, nausea, and vomiting begin 2 to 24 h after inhalation. In severe cases they are followed by the rapid appearance of an almost pathognomonic clinical triad of abdominal pain, hematuria, and jaundice (15, 27, 31). Death is caused by acute renal failure, apparently the result of massive tubular damage induced principally by the intratubular precipitation of hemoglobin (10).

Standards limiting occupational exposure to arsine have, for the most part, been intended to prevent acute toxicity (1). In the United States, the arsine exposure standard of the Occupational Safety and Health Administration (OSHA) is 200 $\mu g/m^3$, measured as an 8-h time-weighted average (46); the guidance in the United Kingdom is a hygienic limit of 200 $\mu g/m^3$ (8). The Scandinavian countries have also adopted an exposure standard of 200 $\mu g/m^3$, with the exception of Sweden which has adopted 50 $\mu g/m^3$ as its standard.

[1] Division of Surveillance, Hazard Evaluations and Field Studies, National Institute for Occupational Safety and Health, Cincinnati, Ohio, United States.

Reprint requests to: Dr PJ Landrigan, Division of Surveillance, Hazard Evaluations and Field Studies, NIOSH, 4676 Columbia Parkway, Cincinnati, OH 45226, USA.

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Current occupational exposure standards for arsine are not intended to protect against any toxic consequences which may result from chronic inhalation of the gas (4). Chronic inhalation of arsine in concentrations below those required to produce acute toxicity would appear however to be widespread in modern industry. Potentially exposed workers include metal smelters and refiners, metallurgists, solderers, lead platers, battery makers, and manufacturers of semiconductors (10, 45). In such workers, inhaled arsine is rapidly removed from lung tissue (35) and is oxidized to form elemental trivalent arsenic (As^{+3}) and arsenous oxide (arsenic trioxide, As_2O_3) (10, 27). Both of these species of arsenic have been shown to be human carcinogens (26).

To evaluate arsenic absorption in workers with chronic occupational exposure to arsine, we conducted an industrial hygiene and medical survey at a lead-acid battery manufacturing plant (25). We found chronic arsine exposure at levels below the current OSHA standard, and we found a strongly positive correlation between arsine concentrations in the air and the urinary excretion of arsenic. Arsine exposures of less than one-tenth the current OSHA exposure standard were associated with the urinary excretion of arsenic in amounts significantly greater than a population norm of 50 μg/l (18). These observations suggest a need for a downward revision of the arsine standard to protect workers against the possibly carcinogenic consequences of the chronic absorption of trivalent arsenic through the inhalation of arsine gas.

Background

The plant which we evaluated has been in operation since 1965. It employs approximately 200 workers and produces lead-acid storage batteries according to conventional technology (fig 1) (48). Lead oxide is produced during the tumbling of lead pigs in air in a ball mill. The oxide is then mixed with sulfuric acid and other minor additives to form a paste, and the paste is applied to grids cast of metallic lead. The lead-lead oxide plates are assembled into groups, welded together, placed in plastic casings, and attached to posts and terminals. The assembled batteries are filled with acid, and in the battery formation area of the plant are "formed" electrically by the application of direct electrical current. After formation, batteries are either drained and shipped dry or sealed and shipped with acid.

Arsenic is used in battery production as an alloy with lead in concentrations of 0.5 to 0.7 % (48). The arsenic increases breakage resistance ("hardens" the lead) and increases resistance to electrochemical corrosion (41).

The introduction of arsenic to battery

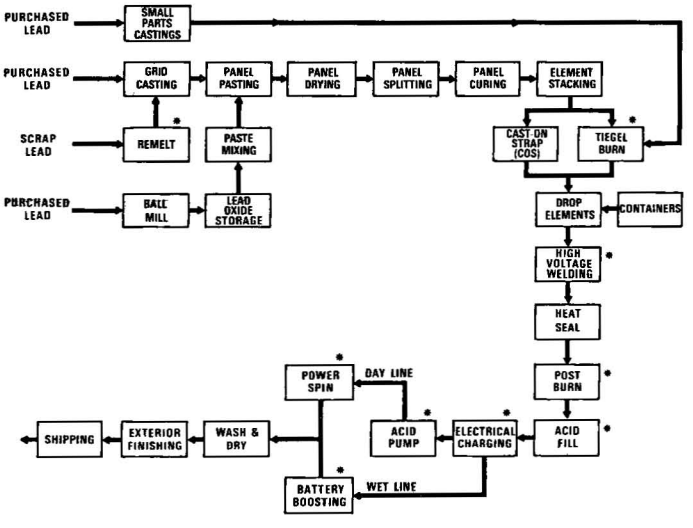

Fig 1. Process flow — Lead-acid battery plant, November 1980. (* = job category with potential exposure to airborne arsenic species)

manufacturing creates a hazard of potential exposure to several species of arsenic. Arsine may be generated in the battery formation process when lead-arsenic alloy comes into contact with acid (24). Arsine may be formed also in scrap recovery operations. Particulate arsenic can be released into the air whenever lead-arsenic alloys are cut or fragmented. Finally, arsenic trioxide fumes or vapors may be generated by the heating of lead-arsenic alloy, such as occurs in welding (7).

Methods

Industrial hygiene survey

The environmental sampling undertaken in the present investigation was intended to measure personal (breathing zone) exposures to arsine and to airborne particulate arsenic and to determine area air concentrations of arsenic trioxide vapor. The survey focused on those job categories and plant areas where the likelihood of exposure to one or more species of arsenic appeared to be the greatest (fig 1). At the time of the survey, 42 production workers were employed over three shifts in these areas.

To measure breathing zone exposures to particulate arsenic and arsine, we developed a two-component sampling train comprised of a 13-mm mixed cellulose ester filter followed in series by a 150-mg charcoal tube operated at a flow rate of 0.2 l/min (7). The inlet of this sampling train was restricted to provide a casette inlet and filter face velocity equivalent to that of a conventional 37-mm filter cassette operated at a flow rate of 2 l/min (13). The collection characteristics of this system were shown to be comparable to those of the conventional method (7). We collected full-shift breathing zone samples on each of the 4 d of the survey (Monday through Thursday) for all volunteer workers on all three shifts with potential exposure to arsenic species. In addition we collected full-shift samples on the day shift each day for 4 d from the eight office staff who had agreed to participate as a reference group.

To measure area air concentrations of arsenic trioxide, we developed a collection system comprised of a 37-mm mixed cellulose ester filter pretreated with sodium carbonate and glycerol (CARB filter system) (5, 7). Development of this system was necessary because arsenic trioxide can exist in both particulate (fume) and vapor states at normal plant temperatures. Earlier studies had demonstrated that 25 to 90 % of arsenic trioxide vapors pass through a conventional mixed cellulose ester filter and that 4 to 40 % through both the conventional filter and its backup pad. The CARB system, by contrast, was shown to be more than 90 % efficient in the collection of arsenic trioxide (5, 7). Area air samplers were positioned at six plant locations that offered a wide range of exposure to airborne species of arsenic. Full-shift samples were collected at each of these locations for each of the 4 d of the survey.

All air samples, both personal and area, were collected with personal sampling pumps equipped with automatic flow rate controllers. All samples were analyzed for arsenic content by atomic absorption spectroscopy at the Utah Biomedical Test Laboratory with a modification of method S309 of the National Institute for Occupational Safety and Health.

To evaluate the possibility that plant workers might have been exposed to arsenic in drinking water, six tap-water samples were collected from sinks and drinking fountains at the plant. These samples were collected in acid-washed plastic bottles, to which 0.5 g of sodium ethylenediaminetetraacetate (EDTA) was added as a preservative. The samples were refrigerated and shipped to the same laboratory as the air samples for arsenic analysis by atomic absorption spectroscopy with a hydride evolution technique (36). No drinking water samples were collected elsewhere in the community outside the plant.

Medical examination

The medical component of this survey was intended to measure workers' absorption of arsenic and to correlate absorption with exposure to arsine and to other species of airborne arsenic.

To measure arsenic absorption, we collected 24-h urine samples on the second and third days of the workweek (Tuesday and Wednesday) from all production and

office workers who had agreed to participate in the air sampling survey. (Make-up samples were collected on Thursday and Friday from workers who had missed the previous collections.) Workers were given arsenic-free plastic collection bottles with written instructions for the collection of complete 24-h urine output and for sanitary precautions to be observed during the urine collection. At the conclusion of each 24-h period samples were collected at the plant and shaken by hand until they appeared homogeneous. The volume was measured, and the specific gravity determined by a refractometer. A 125-ml aliquot was taken from each sample and placed in an acid-washed plastic bottle, to which was added 0.5 g of sodium EDTA as a preservative. These aliquots were held at the plant at 4°C for the duration of the study and were then shipped refrigerated to the laboratory for arsenic analysis.

As a quality control measure, two separate 125-ml aliquots were taken from each of 12 urine samples. These duplicate aliquots were separately numbered, and sent to the laboratory with no indication that they represented paired samples. Also, four sample collection bottles were washed in the field with distilled water, and the washings sent to the laboratory with EDTA preservative for arsenic analysis.

At the time of the collection of the urine samples, each worker was asked whether he or she had eaten any salt water fish, shellfish, or crabs during the preceding week. This procedure was designed to assess the major possible dietary source of arsenic. Also, by means of a supplementary questionnaire, the workers were queried concerning their typical use of tobacco and consumption of red wine.

After extraction with nitric, perchloric, and sulfuric acids, urine samples were analyzed for total arsenic content by atomic absorption spectroscopy with an automated hydride evolution technique. This technique does not distinguish among species of arsenic, but measures the total urinary excretion of the absorbed arsenic of any species. The results of the analyses were corrected to the specific gravity of "standard" urine (SG 1.024). The lower limit of detection for arsenic in urine was 1 μg/l (0.013 μmol/l).

Results

Industrial hygiene survey

A total of 179 breathing-zone air samples were collected from 48 workers for arsine analysis (table 1). Arsine concentrations ranged from less than the limit of detection to 49 $\mu g/m^3$. The highest mean exposures were found for the battery formation job categories: process attendants (20.6 $\mu g/m^3$), power spin operators (14.5 $\mu g/m^3$), and conveyor formation handlers (13.7 $\mu g/m^3$). There were no differences for the arsine exposures between days. The evening shift had significantly higher arsine exposures than either of the other two shifts ($p < 0.05$).

A total of 177 air samples were collected for 48 workers for the measurement of particulate arsenic (table 1). Arsenic concentrations ranged from less than the limit of detection to 5.1 $\mu g/m^3$. Nine values (5.1 %) were above 2 $\mu g/m^3$, the recommended exposure standard of the National Institute for Occupational Safety and Health (23). The highest mean exposures were found for assembly line (post burn) (0.9 $\mu g/m^3$), element battery repair (0.87 $\mu g/m^3$), and salvage and remelt 0.69 $\mu g/m^3$) workers. There were no significant differences for the particulate arsenic exposures between days or shifts.

Forty-nine area air samples were collected for the measurement of arsenic trioxide vapor (table 2). The highest mean concentrations were found for the element battery repair (0.36 $\mu g/m^3$) and post burn (0.18 $\mu g/m^3$) areas.

The six drinking water samples collected in the plant contained no detectable arsenic.

Medical examination

Thirty-nine (93 %) of 42 production workers with potential exposure to airborne arsenic species participated in the medical survey. Eight office workers participated as a reference group.

Forty-three of the participating workers provided two 24-h urine samples, and four provided a single sample. The mean urinary arsenic concentration (corrected for specific gravity) from the first day of collection was 31.5 μg/l (0.42 μmol/l), and on the second day 24.9 μg/l (0.33 μmol/l).

Table 1. Personal (breathing zone) exposures to airborne particulate arsenic and arsine by job category — Lead-acid battery plant, November 1980.

Job category	Number of workers	Particulate arsenic ($\mu g/m^3$)			Arsine ($\mu g/m^3$)		
		Number of samples	Mean	SD	Number of samples	Mean	SD
Assembly line (post burn)	4	16	0.93	1.38	16	1.92	1.09
Battery stacker [a]	2	8	0.08	0.0	8	8.12	3.98
Boosted stock [a]	2	8	0.08	0.0	8	4.42	1.67
Conveyor formation handler [a]	6	23	0.09	0.02	24	13.74	10.89
Element battery repair	5	19	0.87	1.53	20	10.82	8.64
Gravity check acid leveler	4	12	0.08	0.0	12	2.78	1.95
High rate tester	2	8	0.08	0.01	8	11.63	3.94
Immersion filler	2	8	0.66	1.64	8	2.00	1.20
Power spin operator [a]	2	6	0.08	0.01	7	14.48	7.15
Process attendant [a]	3	12	0.11	0.08	12	20.57	8.56
Salvage and remelt operator	3	12	0.69	1.15	12	0.15	0.19
Scrap coordinator	3	11	0.09	0.04	11	0.95	0.52
Tiegel operator	2	6	0.32	0.43	6	0.51	0.34
Office	8	28	0.08	0.00	27	0.06	0.11
Total	48	177			179		

[a] Job category in the battery formation area.

Each worker's results from the 2d were averaged, and the arithmetic mean of the two corrected values was employed in the subsequent calculations. For those workers who had provided only a single specimen, the corrected arsenic concentration of that sample was used in the subsequent analyses.

Duplicate aliquots were prepared at the plant from 12 urine samples and sent separately to the laboratory. Excellent agreement was seen for the blind analysis of these duplicate specimens [correlation coefficient (r) = 0.99].

The washings of four sample collection bottles were sent to the laboratory for arsenic analysis. No arsenic was detected in any of these samples.

Eight (11.0 %) workers had corrected urinary arsenic concentrations of 50 $\mu g/l$ (0.68 $\mu mol/l$) or above; none had concentrations of 100 $\mu g/l$ (1.34 $\mu mol/l$) or higher (table 3). All the workers with urinary arsenic concentrations of 50 $\mu g/l$ or above were employed in production areas, and the greatest number (six) were employed in battery formation. The highest mean urinary arsenic concentration [44.6 $\mu g/l$ (0.60 $\mu mol/l$)] was also found among the battery formation workers. The mean urinary arsenic concentration of the eight office workers was 14.4 $\mu g/l$ (0.19 $\mu mol/l$).

Table 2. Arsenic trioxide (As_2O_3) vapor concentrations by plant area — Lead-acid battery plant, November 1980.

Area	Number of samples	As_2O_3 (in μg arsenic/m^3)	
		Mean	SD
Boosted stock	10	0.02	—
Element battery repair	3	0.36	0.06
Battery formation	11	0.11	0.07
Post burn	7	0.18	0.14
Salvage and remelt	11	0.07	0.12
Tiegel	7	0.06	0.07
Total	49		

Six workers reported that they had eaten seafood or shellfish during the week prior to this investigation. The urinary arsenic concentrations of these six workers ranged from 4.25 to 53.5 $\mu g/l$ (0.06—0.71 $\mu mol/l$); the one value over 50 $\mu g/l$ (0.68 $\mu mol/l$) was that of a battery formation worker. The mean urinary arsenic concentration of the six workers who had eaten seafood was 20.8 $\mu g/l$ (0.28 $\mu mol/l$), and the corresponding mean of the remaining 41 participants was 28.7 $\mu g/l$ (0.38 $\mu mol/l$). Five of the 22 workers who completed a supplementary history ques-

tionnaire reported that they occasionally drank red wine (maximum 1 glass/month). The mean urinary arsenic concentration of these five workers was 22.9 μg/l (0.31 μmol/l), while that of the 17 workers who reported no red wine consumption was 23.4 μg/l (0.31 μmol/l). Thirteen of the 22 workers who completed the supplementary questionnaire reported that they smoked tobacco. Their mean urinary arsenic concentration was 21.2 μg/l (0.28 μmol/l), while that of the nine nonsmokers was 26.7 μg/l (0.36 μmol/l). The respondents to the supplementary questionnaire did not differ significantly from the nonrespondents with respect to urinary arsenic concentration.

To evaluate quantitative relationships between the urinary arsenic concentrations and concomitant exposures to airborne arsenic species, we examined product moment correlations (6) between the mean (corrected) urinary arsenic concentration of each worker and his or her mean

Table 3. Urinary arsenic concentrations, mean and distribution by job category — Lead-acid battery plant, November 1980.

Job category	Number of samples	Urinary arsenic (μg/l [a])		
		50—99 μg/l (N)	Mean	SD
Assembly line (post burn)	4	0	16.9	3.8
Battery stacker [b]	2	1	42.0	21.9
Boosted stock [b]	2	0	13.6	9.0
Conveyor formation handler [b]	6	2	46.3	28.2
Element battery repair	5	2	38.4	18.5
Gravity check acid leveler	3	0	17.6	10.3
High rate tester	2	0	33.2	12.4
Immersion filler	2	0	34.2	6.7
Power spin operator [b]	2	0	36.4	5.4
Process attendant [b]	3	3	69.0	14.1
Salvage and remelt operator	3	0	8.3	4.0
Scrap coordinator	3	0	9.7	1.2
Tiegel operator	2	0	7.9	3.7
Office	8	0	14.4	14.9
Total	47	8		

[a] 1 μg/l = 0.01335 μmol/l.
[b] Job category in the battery formation area.

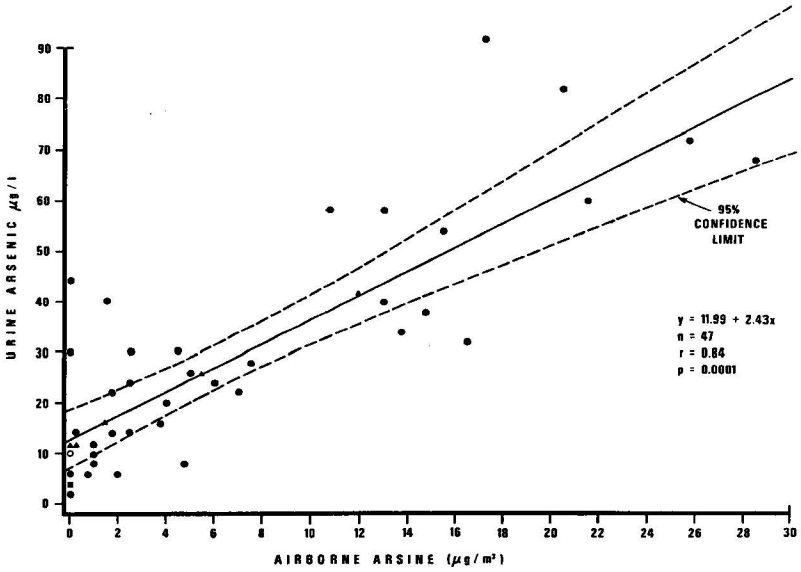

Fig 2. Correlation between arsine exposure and urinary arsenic excretion — Lead-acid battery plant, November 1980. (1 μg arsenic/l urine = 0.01335 μmol arsenic/l urine)

breathing-zone exposures (mean of four full-shift samples) to arsine and to particulate arsenic. No correlation analysis was undertaken in the case of arsenic trioxide because only area air samples were available.

The correlation of the workers' mean urinary arsenic concentrations with their mean personal (breathing-zone) exposures to arsine showed a close quantitative relationship ($N = 47$; $r = 0.84$; $p = 0.0001$) (fig 2). Little correlation was found, on the other hand, with exposure to particulate arsenic ($N = 47$; $r = 0.075$; $p = 0.62$), a possible reflection of the much lower concentrations of particulate arsenic in air as compared to arsine. The highest urinary arsenic concentrations were found for the battery formation workers, the group the most heavily exposed to arsine at the plant.

Mean arsine exposures of 15.6 $\mu g/m^3$ (95 % confidence interval 13.2—19.4 $\mu g/m^3$) or greater were found to be associated with urinary arsenic concentrations of 50 $\mu g/l$ (0.68 $\mu mol/l$) and above (fig 2); by linear extrapolation, mean arsine exposures of 31.2 $\mu g/m^3$ and above would be associated with urinary arsenic concentrations of 100 $\mu g/l$ (1.34 $\mu mol/l$) and higher.

Discussion

The data from this study confirm the results of previous investigations which have shown arsine to be an occupational hazard in the manufacture of lead-acid storage batteries (16, 24). In battery production, the likelihood of arsine exposure is the greatest during electrical formation, when lead-arsenic alloy comes into contact with battery acid.

Inhaled arsine is rapidly dissolved in body fluids (35) and is degraded metabolically to yield trivalent arsenic (10). Trivalent arsenic is well established as a human carcinogen (18, 26, 33). It has been associated with the occurrence of three types of skin cancer — Bowen's disease, basal cell carcinoma, and squamous cell carcinoma (28). Arsenic-induced skin cancers have been observed among persons exposed occupationally to arsenic in the chemical (32) and wine-making (41) industries, as well as among persons exposed through the consumption of contaminated drinking water (44) or through the use of arsenical medications (28). The prevalence of arsenic-induced skin cancer appears to be related to total arsenic dose (29, 44). Exposure to trivalent arsenic has also been associated with angiosarcoma of the liver. In such cases, exposure has been through the drinking of arsenic-contaminated wine (41), or through the use of Fowler's solution (9). Trivalent arsenic has, in addition, been found to cause cancer of the lungs and bronchi. Excess mortality from lung cancer has been observed in several studies of smelter workers (17, 19, 34, 37, 39), as well as in studies of pesticide manufacturers and formulators (12, 20, 30), vineyard sprayers (41), and underground gold miners (29). In general, the frequency of excess lung cancer for workers exposed occupationally to trivalent arsenic or to arsenic trioxide has been related directly to their cumulative lifetime arsenic exposure (26). Trivalent arsenic has, finally, been associated in two studies with increased mortality from malignant neoplasms of the lymphatic and hematopoietic tissues (2, 30). The number of cases cited in each of these reports is however small, and further evaluation of the possible relationship will be required.

Inhaled arsenic is, for the most part, excreted via the urine (18), and the urinary arsenic concentration appears to be the most accurate indicator of current or recent (1—3 d) absorption of inorganic arsenic (11). Urinary arsenic concentration may provide an especially accurate reflection of recent arsine absorption, given the high solubility and rapid metabolism of inhaled arsine. Although the range of values considered "normal" in previous studies of urinary arsenic concentrations has varied, due primarily to differences in laboratory methods, over 95 % of the urinary arsenic concentrations of populations without occupational or other specifically identified exposures to arsenic has been found to be below 50 $\mu g/l$ (0.68 $\mu mol/l$) (3, 11, 21, 22, 40, 47). Three studies (32, 38, 42) have reported mean urinary arsenic concentrations of 80, 85, and 130 $\mu g/l$ (1.07, 1.13, and 1.74 $\mu mol/l$), respectively, for allegedly nonexposed groups; however, in each of the studies, persons in the "control" groups either

worked in proximity to arsenic-contaminated areas or had had previous occupational exposure to arsenic.

The data from this investigation indicate that the current OSHA standard for occupational exposure to arsine — 200 μg of arsine/m^3 of air (46) — a standard which is intended principally to prevent the acute toxic effects of arsine inhalation (1), does not prevent chronic increased absorption of trivalent arsenic from the inhalation of arsine. The data indicate that a mean arsine exposure of 15.6 μg/m^3, less than one-tenth the current legal standard in the United States, is associated with the excretion of 50 μg of total arsenic/l of urine (0.68 μmol/l), and, by linear extrapolation, the data indicate that a mean arsine exposure of 31.2 μg/m^3 would be associated with the excretion of 100 μg of arsenic/l of urine (1.34 μmol/l).

To prevent potential chronic toxicity among workers exposed to arsine, consideration should be given to a downward revision of the OSHA arsine exposure standard. The current OSHA standard for exposure to other species of airborne arsenic is 10 μg/m^3 (46), and the National Institute for Occupational Safety and Health recommends 2 μ/m^3 as the standard for occupational exposure to all species of inorganic arsenic, including arsine (23). It would seem reasonable that the arsine exposure standard be made compatible with those for other species of arsenic.

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