Assessment of occupational exposure to inorganic arsenic based on urinary concentrations and speciation of arsenic

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Abstract

An analytical speciation method, capable of separating inorganic arsenic (As (V), As (III)) and its methylated metabolites (MMAA, DMAA) from common, inert, dietary organoarsenicals, was applied to the determination of arsenic in urine from a variety of workers occupationally exposed to inorganic arsenic compounds. Mean urinary arsenic (As (V) + As (III) + MMAA + DMAA) concentrations ranged from 4.4 µg/g creatinine for controls to <10 µg/g for those in the electronics industry, 47.9 µg/g for timber treatment workers applying arsenical wood preservatives, 79.4 µg/g for a group of glassworkers using arsenic trioxide, and 245 µg/g for chemical workers engaged in manufacturing and handling inorganic arsenicals. The maximum recorded concentration was 956 µg/g. For the most exposed groups, the ranges in the average urinary arsenic speciation pattern were 1-6% As (V), 11-14% As (III), 14-18% MMAA, and 63-70% DMAA. The highly raised urinary arsenic concentrations for the chemical workers, in particular, and some glassworkers are shown to correspond to possible atmospheric concentrations in the workplace and intakes in excess of, or close to, recommended and statutory limits and those associated with inorganic arsenic related diseases.

Long term occupational exposure to inorganic arsenic compounds may lead to various diseases such as cancer of the respiratory tract, skin cancer,

hyperkeratosis, hyperpigmentation, cardiovascular disease, and disturbances of the peripheral vascular and nervous systems.¹⁻⁴ These chronic effects, while different from those of acute arsenic intoxication, are similar to those resulting from long term environmental exposure of the general population in certain parts of the world to naturally raised inorganic arsenic concentrations in drinking water.¹⁻⁴ Despite improved awareness and stricter legal requirements, there is still potential for occupational exposure to inorganic arsenic in a range of industries, most notably non-ferrous smelting, glass making, and the manufacture and application of arsenical pesticides. Inhalation or ingestion of arsenic containing airborne dusts, or a combination of both, are two of the most important exposure pathways.

Assessment of exposure to airborne arsenic by direct atmospheric measurements alone is imprecise and unreliable. Biological markers are inherently more satisfactory as indicators of exposure.^{5,6} Hair, which has proved successful in forensic investigations of deliberate acute arsenic poisoning,¹ is of rather less value in studies of occupational exposure, however, because of the problem of external contamination. Urine, more conveniently collected than blood, is the preferred indicator as excretion via the kidneys is the major route of elimination of inorganic arsenic (pentavalent, As (V); trivalent, As (III)) and its metabolites (monomethylarsonic acid, MMAA, CH₃AsO(OH)₂; dimethylarsinic acid, DMAA, (CH₃)₂AsO(OH)) from the human body.^{2,7-9} It is extremely important that the analytical method used is capable of distinguishing these forms, separately or in toto, from the more complex but non-toxic organoarsenicals, such as arsenobetaine ((CH₃)₃As⁺CH₂COOH), whose presence in seafood constitutes the major source of dietary arsenic.¹⁰ Consumption of a meal of fish or shellfish can raise urinary arsenic to concentrations in excess of 500 µg/l, more than 50 times the typical background level.^{7,11,12} Some studies of occupational, environmental, and dietary exposure to arsenic have overlooked or made insufficient allowance for this important effect.¹³

The initial purpose of this study was to establish the concentration and speciation of arsenic in urine

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from United Kingdom workers from a range of occupations subject to varying degrees and types of exposure to inorganic arsenic and to compare the results with control group data. Thereafter, the calculated intakes of inorganic arsenic, based partly on the measured urinary arsenic concentrations, could be compared with recommended limits and the doses associated with inorganic arsenic related ill health.

Materials and methods

Urine samples (first void or spot) were provided by a selected number of individuals working within the following occupational groups:

Semiconductor industry where arsenic is used as arsine gas in the doping of chips to enhance the conduction of the silicon or germanium crystal. Operators may be exposed to minute quantities of arsenic trioxide through the handling of the wafers¹⁴ but those more at risk are engaged in plant cleaning and maintenance ($n = 14$; first void).

University electronics research group engaged in manufacturing gallium arsenide semiconductors, with potential for exposure to arsenic trioxide when cleaning out equipment ($n = 7$; first void).

Glass manufacturing industry where arsenic trioxide is used as a decolourising agent in the manufacture of specialist glass. Possible exposure to airborne arsenic trioxide may occur during the weighing out of the constituents for each batch of glass and during the mixing of the chemicals ($n = 30$; first void 18, spot 12).

Timber treatment firm where pentavalent inorganic arsenic is used in combination with chromium and copper to prevent wood decay. Exposure is to airborne pentavalent inorganic arsenic during the mixing of the chemicals and via possible skin contact in handling the dried wood after treatment and removal from the solution. Again, exposure may be enhanced during the cleaning of equipment, in this case the tanks used to contain the wood preservative ($n = 5$; first void).

Chemical firm engaged in manufacturing arsenic containing compounds. For plant operators, there is the possibility of exposure to (a) arsenic trioxide as a result of dust escaping during the discharge of material into the reactor system and (b) arsenic pentoxide and sodium arsenate due to possible dust escaping during the filling of drums with the final product. Again, greater exposure may be experienced during maintenance work than normal production work. Urine samples were provided from those individuals thought to be subject to increased exposure ($n = 24$; spot).

Where possible, first void samples were collected in polypropylene bottles, preferably towards the end of the working week to allow the pattern of arsenic excretion to be established. Spot samples were

collected when first void samples were not available. The samples were not subjected to any chemical pretreatment before storage under refrigeration at 4°C or -20°C if longer storage periods were required.

In addition, first void urine samples were provided in the Glasgow area by 40 adults of the general population who were believed not to have been exposed to inorganic arsenic other than to the small amounts present in the typical United Kingdom diet.^{10,15} A further 28 spot urine samples from glass-workers were also provided by the Health and Safety Executive in London during an intercalibration exercise.

Individual arsenic species, As(V), As(III), MMAA, and DMAA, were separated from a 4 ml aliquot of each urine sample on a combined cation anion exchange resin column¹⁶ and determined by hydride generation atomic absorption spectrometry (HGAAS).¹⁵ The detection limit for each species in the original urine sample was 0.5 µg/l.¹⁵ The total concentration of arsenic in each urine sample—that is, including any seafood organoarsenicals—was obtained by HGAAS after appropriate dilution of a nitric/sulphuric/perchloric acid digest.^{17,18}

An intercomparison study, based on the analysis of urine samples supplied by the Health and Safety Executive in London, where analytical arsenic speciation is performed using a continuous HPLC/HGAAS technique,¹⁹ showed good agreement in both speciation and total arsenic data.^{15,18} Additional confirmation of the latter was provided by accurate analysis of NBS freeze dried urine SRM 2670 (480 µg/l).

The fact that inorganic arsenic and its metabolites MMAA and DMAA may form hydrides directly from an acidified (1.5% w/v HCl) sample solution, whereas the stable dietary organoarsenicals do not, afforded an opportunity for the rapid semi-quantitative screening of urine samples to estimate the sum of the four species, As(V), As(III), MMAA, and DMAA. As a result of the differing rates of response of these species to hydride generation,^{20,21} the determination of a range of concentrations was all that could be achieved with the use here of signal peak heights. Peak areas may yield more precise estimates.²²

Creatinine concentrations, necessary for the normalisation or correction of arsenic concentrations for fluctuations in urinary volume, were routinely determined, using an automatic method based on the Jaffe reaction, by the department of clinical biochemistry, Glasgow Royal Infirmary.

Results

Table 1 shows good agreement between the direct hydride generation range and the sum of hydride forming arsenic species' concentrations over a wide

range of urinary arsenic concentrations. The ability of these techniques to distinguish between occupational exposure to inorganic arsenic and dietary exposure to inert organoarsenicals in seafood is evident in several samples, notably Nos 1, 3, 5, 6, 7, 9 and 12. When exposure to inorganic arsenic is raised but seafood consumption is low, the total concentration of arsenic approximates well to the sum of species concentration—for instance, Nos 8, 10, 11, 13, 14, and 15).

Urinary sum of species (As(V), As(III), MMAA, DMAA) concentrations for workers from various occupations increased in the order controls (geom mean 4.4 µg/g) < semiconductor (5.9 µg/g) < electronics (9.7 µg/g) < glass manufacture (10.2 µg/g) < timber treatment (47.9 µg/g) < glass manufacture (HSE) (79.4 µg/g) < arsenical manufacture (245 µg/g) (figure). In much the same order of occupations, inorganic arsenic (As(V), As(III)) and the monomethylated metabolite (MMAA) became more frequently detected and achieved higher concentrations (table 2). Dimethylarsinic acid (DMAA), observed in all samples (table 2), was the major single species excreted and usually constituted considerably more than 50% of the sum but its relative importance tended to decline with increasing sum concentrations (table 3). This is illustrated in more detail for various ranges of arsenic concentrations in urine from the arsenical manufacture workers, DMAA declining from 76.0% (40–99 µg/g) before levelling out at 58.2% (200–499 µg/g) and 59.6% (500–999 µg/g). With MMAA fairly constant at 15.6–19.0%, inorganic arsenic increased from 8.3% to 22–23% over the same concentration ranges. Whereas for the controls DMAA always (40/40) exceeded 80% of the sum of species, averaging a nominal 97.6%, the corresponding figures for the arsenical manufacture workers were 2/24 (>80%) and 63.6% (table 3).

Table 1 A comparison of urinary arsenic concentrations determined by direct hydride generation, analytical speciation, and total digestion methods

Sample No	Direct hydride generation	Sum concn* (µg/l)	Total
1	5–9	5.0	441
2	5–9	5.6	34
3	8–12	8.1	430
4	8–12	10.0	24
5	9–15	12.3	159
6	10–14	15.2	2500
7	14–22	19.7	204
8	27–44	38.6	44
9	44–63	57.8	135
10	96–150	138	145
11	112–180	169	178
12	138–198	181	300
13	410–580	530	610
14	640–1020	967	1150
15	860–1380	1291	1450

*Sum concentration ≡ ΣAs(V), As(III), MMAA, DMAA.

Sum of arsenic species (As(V), As(III), MMAA, DMAA) concentrations (µg/g creatinine) in urine of Glasgow controls (A) and of workers engaged in semiconductor manufacture (B), electronics research (C), glass manufacture (D), timber treatment (E), glass manufacture—HSE (F), and arsenical manufacture (G). Geometric mean for each data set is shown by broken line (-----).

Discussion

For occupationally exposed groups of workers, there have been only a few studies, based on urine analysis, that have differentiated between inorganic arsenic + methylated metabolites and total arsenic, including dietary organoarsenicals (table 4). Although the nature of this information is inconsistent with respect to concentration units, calculation of average concentration and speciation pattern detail, the pronounced presence of inorganic arsenic (9–35.8%), despite the predominance of methylated species (64.1–91%) with DMAA (54.5–78%) as the major species throughout, and raised sum concentrations are similar to the findings of this study (tables 2 and 3, figure). As with arsenical manufacture workers in this study, greater exposure to inorganic arsenic is marked by a decline in the relative contribution of

Table 2 Maximum concentration (and frequency of detection) of individual arsenic species in urine from various groups of workers

Category	No	As(V) ($\mu\text{g/g}$)	As(III)	MMAA	DMAA
Glasgow controls	40	<0.5* (0)	1.0 (5)	0.6 (4)	39.0 (40)
Semiconductor manufacture	14	2.8 (1)	2.0 (1)	1.4 (2)	22.2 (14)
Electronics research	7	2.0 (3)	3.4 (4)	2.4 (4)	13.1 (7)
Glass manufacture	30	3.8 (2)	12.1 (26)	6.2 (24)	27.1 (30)
Timber treatment	5	6.7 (3)	20.9 (5)	21.3 (4)	80.7 (5)
Glass manufacture (HSE)	28	12.2 (21)	54.7 (26)	146 (28)	304 (28)
Arsenical manufacture	24	185 (22)	187 (24)	190 (24)	540 (24)

*Detection limit 0.5 $\mu\text{g/l}$.

Creatinine concentrations were not available for one semiconductor manufacture worker, five glass manufacture workers, and one glass manufacture (HSE) worker.

DMAA during or immediately after working hours (table 4).^{25 29}

The predominance of methylated species—that is, MMAA + DMAA—in urine (table 3) is consistent with the natural mechanism for detoxification of inorganic arsenic via the reduction/methylation sequence $\text{As(V)} \longrightarrow \text{As(III)} \longrightarrow \text{MMAA} \longrightarrow \text{DMAA}$.^{8 9} The decline in the relative contribution of the methylated species, and of DMAA in particular, with increasing sum concentration is consistent with the observation from acute intoxication investigations and controlled metabolic studies that with increasing dose of inorganic arsenic the methylation efficiency decreases, perhaps as a consequence of approaching or exceeding the body's methylation capacity.³⁰ More specifically, the conversion of MMAA to DMAA can be inhibited by high concentrations of As(III) in the liver, where methylation is believed to take place.^{9 31}

Although excretion via the kidney is by far the major route of elimination of arsenic from the body, the relation of urinary arsenic concentrations to actual occupational exposure to, intake and uptake of inorganic arsenic, and the assessment of their significance with respect to health and recommended exposure limits are not straightforward. The absorption of inorganic arsenic via ingestion, inhalation,

and percutaneous routes of intake may depend on factors such as chemical form, solubility, and particle size and less quantifiable parameters such as hand to mouth transfer, particle retention in lungs, and mucociliary clearance from the upper respiratory tract to the gastrointestinal tract.^{5 7 13 23 32} Best estimates of absorption range from 80% to 100% of intake via the gastrointestinal tract but only 20–30% from the lungs, largely because of the low ($\sim 35\%$) retention factor for particles in the lung.^{13 33} Unfortunately, the most authoritative recommended limits for the intake of arsenic are based largely on the ingestion of readily soluble inorganic arsenic compounds (or inorganic arsenic already in solution), a situation clearly not directly extrapolable to the most common types and routes of occupational exposure, which usually include both inhalation and ingestion of airborne particles. None the less, it is instructive, as a first measure, to derive inorganic intakes based on the urinary output of inorganic arsenic and its metabolites, assuming efficient absorption (as occurs with ingestion) and using an experimentally determined relation between intake and output. On the basis of metabolic studies involving regular, repeated oral ingestion of inorganic arsenic in solution by volunteers, it has been shown, both in this laboratory (L R Johnson, J G Farmer, unpublished data) and

Table 3 The relative mean proportions* of the individual arsenic species excreted in urine by various groups of workers

Category	Sum concn range ($\mu\text{g/g}$)	No	As(V) (%)	As(III)	MMAA	DMAA	Inorganic	Methylated
Controls	1.2–39.0	40	0	1.7	0.7	97.6	1.7	98.3
Semiconductor	1.7–22.2	14	1.0	0.8	1.5	96.7	1.8	98.2
Electronics	4.6–18.6	7	8.9	7.7	8.0	75.4	16.6	83.4
Glass	2.0–37.2	30	0.9	14.0	15.4	69.7	14.9	85.1
Timber	12.3–126	5	4.6	14.2	13.9	67.4	18.8	81.3
Glass (HSE)	25.3–517	28	2.3	11.3	17.8	68.7	13.6	86.5
Arsenical	45.2–956	24	6.1	12.1	18.2	63.6	18.2	81.8
	40–99	3	0.4	7.9	15.6	76.0	8.3	91.6
	100–199	8	3.6	11.3	18.4	66.8	14.9	85.2
	200–499	8	9.4	13.5	19.0	58.2	22.9	77.2
	500–999	5	8.3	13.7	18.4	59.6	22.0	78.0

*Where individual arsenic species were not detected—that is, <0.5 $\mu\text{g/l}$ —their concentration was taken as 0 $\mu\text{g/l}$ and, therefore, 0 $\mu\text{g/g}$ creatinine.

Table 4 Summary of published data on the sum concentrations of urinary arsenic species (*As(V)*, *As(III)*, MMAA, and DMAA) excreted by workers in various industries and on the associated arsenic speciation patterns

Industry	Sum Concn		Speciation pattern			
	Maxm ($\mu\text{g/l}$)	Arith mean	<i>As(V)</i> (%)	<i>As(III)</i>	MMAA	DMAA
Glass manufacture ^{12,23}	941*	81.2 304*	(21.6)		16.9	61.6
Pesticides:						
Mixing ²⁴	654	227	(10)		23	67
Spraying ²⁴	269	83	(18)		20	62
Arsenical manufacture ²⁵ :						
Before work		135.1	13.4	15.3	10.7	60.6
After work	273	158.9	16.9	18.9	9.6	54.5
Smelting ²⁶⁻²⁸ :		96.6†	3.2	8.9	21.5	66.4
	340	70				
	580	61				
	328*	79*†				
Continuous ²⁹	300†		(19)		20	61
After weekend ²⁹	140†		(9)		13	78

* $\mu\text{g/g}$ creatinine.

†Geometric mean.

elsewhere,³⁰ that 40–60% of the daily intake of inorganic arsenic is excreted each day in urine, once equilibrium between intake and output is established—usually about one to five days after the start of intake for intakes increasing to 1000 $\mu\text{g/day}$. Confidence in applying this relation to the case of workers exposed to atmospheric particulate arsenic is provided by the observation⁵ that the average daily urinary excretion of arsenic by smelter workers was 42% of the inhaled amount derived from direct measurements of airborne inorganic arsenic.

The WHO recommend a provisional maximum tolerable daily intake of ingested inorganic arsenic of 2 $\mu\text{g/kg}$ body weight.³⁴ For a 70 kg man this is equal to a provisional tolerable daily intake of 140 μg inorganic arsenic. This corresponds to an output of 56–84 μg arsenic based on an output of 40–60% of the intake. Assuming that an average 1.5 g creatinine—that is, 1.5 l urine with a concentration of 1 g/l¹⁸—is excreted daily, this gives a urinary arsenic concentration of 37–56 $\mu\text{g/g}$ creatinine. Similarly, the daily intake of 150 μg inorganic arsenic (equivalent to drinking 1.5 l water with an average concentration of arsenic of 0.1 mg/l), considered by the Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment (COT)³⁵ to give rise to “presumptive toxicity,” corresponds to a urinary arsenic concentration of 40–60 $\mu\text{g/g}$. With one exception, the controls are well below this level (figure); indeed, the geometric mean concentration of 4.4 $\mu\text{g/g}$ corresponds to a calculated daily intake of inorganic arsenic of 11.0–16.5 $\mu\text{g/g}$, comparable with the estimate of 22 $\mu\text{g/day}$ which may be derived from the MAFF¹⁰ value for the average dietary intake of total arsenic of 89 $\mu\text{g/d}$ to which seafood contributes 75%, almost all in the form of inert organoarsenicals. Of the workers in the various occupationally exposed groups (figure), two of five in group E (timber

treatment), 20 of 27 in group F (glass manufacture—HSE), and 22 of 24 in group G (arsenical manufacture) exceeded the upper level of 60 $\mu\text{g/g}$.

Largely on the basis of epidemiological evidence linking inorganic arsenic exposure, via consumption of drinking water of raised arsenic concentration, to a range of diseases in certain parts of the world, COT also reported that a daily intake of 1500 μg inorganic arsenic (equivalent to drinking 1.5 l water with an inorganic arsenic concentration of 1 mg/l) could produce signs of “overt chronic arsenicism” in some individuals.³⁵ This corresponds to a daily output of 600–900 μg arsenic and gives a urinary arsenic concentration of 400–600 $\mu\text{g/g}$. In group G (arsenical manufacture) five of the urine samples exceeded 600 $\mu\text{g/g}$, with seven of this group and one of group F (glass manufacture—HSE) higher than 400 $\mu\text{g/g}$ (figure). The maximum urinary arsenic concentration for group G was 956 $\mu\text{g/g}$, which is equivalent to an intake of 2390–3585 μg inorganic arsenic a day, far in excess of the WHO and COT recommended limits.^{34,35} It is worth noting that if absorption of inorganic arsenic by the bodies of these occupationally exposed workers is not 100% efficient, then the derived intakes may underestimate the actual combined intake via inhalation and ingestion. Although the extent of uptake, rather than intake, is clearly of greater significance with respect to health, recommended limits of exposure are often set in terms—for instance, $\mu\text{g/l}$ water, $\mu\text{g/m}^3$ air^{10,13,35-37} that serve as reference benchmarks against which ambient environmental or workplace arsenic concentrations may be directly compared.

A few studies, based largely on smelter workers, have attempted to quantify possible correlations between the levels of airborne arsenic and the concentrations of urinary arsenic. Vahter *et al* found that urinary concentrations (*As(V)*, *As(III)*,

MMAA, DMAA) of 50–200 µg/l were equivalent to airborne As levels of 1.7–53 µg/m³,⁵ with a best fit empirically established linear relation

$$\text{As}_{\text{urine}}(\mu\text{g/l}) = 45 + 2.9 \text{As}_{\text{air}}(\mu\text{g/m}^3) \\ \text{that is, } \text{As}_{\text{air}}(\mu\text{g/m}^3) = 0.345 \text{As}_{\text{urine}}(\mu\text{g/l}) - 15.5$$

Insertion of the threshold 60 µg/g and 600 µg/g concentrations derived from COT³⁵ arsenic exposure considerations into the above equations (assuming a creatinine concentration of 1 g/l) yields airborne arsenic concentrations of 5.2 µg/m³ and 191 µg/m³, the latter being close to the former Health and Safety Executive³⁶ eight hour time weighted average control limit of 200 µg/m³, reduced³⁷ since 1 January 1989 to 100 µg/m³. This corresponds to a urinary arsenic concentration of 335 µg/g, exceeded by one of 27 in group F (glass manufacture—HSE) and 10 of 24 in group G (arsenical manufacture).

The use of atmospheric/urinary arsenic correlations and extrapolations in evaluating health risks, especially the contraction of lung cancer,⁶ should be viewed with caution.¹³ Both Vahter *et al* and Roels *et al* have shown the potential importance of the direct oral ingestion route for some employees in workplaces such as glassworks and smelters where inhalation and absorption of airborne arsenic via the lungs might be expected to predominate.^{5,28} The critical effect following the latter exposure route is lung cancer whereas several effects, such as skin cancer, are more likely after oral exposure. Such considerations, however, actually reinforce the need for biological markers of exposure—for example, urine—as opposed to external markers of exposure, such as airborne arsenic, which can provide an estimate of exposure via one route only—namely, inhalation. The determination of arsenic (inorganic arsenic + metabolites) in urine, on the other hand, provides an estimate of total exposure and is also more relevant to an assessment of the exposure of each individual worker.

We have attempted to show the importance of urinary arsenic determination in the monitoring and assessment of occupational exposure to inorganic arsenic. In particular, the separation of inorganic arsenic and its metabolites from dietary organo-arsenicals is essential. Detailed analytical speciation of urinary arsenic into As(V), As (III), MMAA, and DMAA is the most reliable way to measure ΣAs(V), As(III), MMAA, DMAA and may be of additional value in investigating the chemical nature (As(V) or As(III)) and duration of exposure to arsenic, as well as the status of the body's detoxifying methylation capacity. A rapid alternative for screening purposes is direct hydride generation from acidified urine for estimation of the sum of the four hydride forming species by AAS. The range of data obtained in this study for individuals occupationally exposed to inorganic arsenic in the United Kingdom shows the

need for vigilance and regular monitoring of urinary arsenic by methods of adequate sophistication.

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