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Chapter 3

EXPOSURE AND HEALTH EFFECTS

CONTENTS

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Chapter 3
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3.1 EXPOSURE ASSESSMENT

Given its ubiquitous nature in the environment, human exposure to arsenic is inevitable. Exposure can occur via all three principal routes, that is, through the inhalation of air, through the ingestion of food and water, and via dermal absorption. Worldwide, the degree of non-occupational exposure to arsenic varies greatly, being dependent on local geochemistry and the level and proximity of anthropogenic activity. Elevated environmental exposure to arsenic tends to be confined to relatively small, geologically arsenic-rich areas where levels of arsenic, particularly in drinking water, exceed those found elsewhere by an order of magnitude or more.

3.1.1 ENVIRONMENTAL LEVELS

Arsenic is a natural component of the earth's crust where it is present at an average concentration of 2 mg/kg. Trace concentrations are found in all environmental media, including air, water, soils/sediments and biota. Available data on typical environmental levels are summarized in the following subsections.

3.1.1.1 Air and rainwater

Levels of arsenic in ambient air are generally low. In most remote and rural areas, concentrations average between 0.02 and 4 ng/m^3. Higher concentrations are evident in many urban areas, with levels ranging typically from 3 to about 200 ng/m^3. Concentrations in excess of 1000 ng/m^3 have, however, been measured in the vicinity of industrial sources, especially near non-ferrous metal smelters (WHO, 2001). In air, arsenic exists predominantly absorbed on particulate matter, and is usually present as a mixture of arsenite and arsenate, with the organic species being of negligible importance except in areas of arsenic pesticide application or biotic activity. (Beavington & Cawse, 1978; Brimblecombe, 1979; Davidson et al., 1985; Peirson et al., 1974).

A recent Europe-wide survey has found evidence of a gradual decline in ambient arsenic concentrations over the past few decades. This reduction in air arsenic is attributed to the progressive introduction of dust abatement equipment at industrial facilities. Typical arsenic levels for the European region are currently quoted as being between 0.2 – 1.5 ng/m^3 in rural areas, 0.5 – 3 ng/m^3 in urban areas and no more than 50 ng/m^3 in industrial areas (DG Environment, 2000).

Arsenic has been detected in rainwater. In non-polluted areas, mean concentrations range from 0.013 to 0.5 ug/L (Scudlark & Church, 1988; Andreae, 1980), whereas near a North Sea gas platform, mean arsenic concentrations up to 45 ug/L have been reported (Peirson et al., 1974).

3.1.1.2 Soils

Background concentrations of arsenic in soil range from 1 to 40 mg/kg, with a mean value of 5 mg/kg (Beyer & Cromartie, 1987; Bowen, 1979). Soils overlying naturally arsenic-rich geological deposits, such as sulphide ores, may have significantly higher concentrations, in some cases up to two orders of magnitude higher (NAS, 1977).

Whereas non-contaminated soils typically contain low levels of arsenic, human activity (for example, waste disposal and pesticide applications) can increase substantially the concentrations found in soils. Extremely high arsenic concentrations have been reported in soils contaminated with mine or smelter wastes (up to 27 000 mg/kg), and levels of 20 100 to 35 500 mg/kg have been found in soils around the effluent dumping point of an arsenical pesticide manufacturing plant (US EPA, 1982; Chatterjee & Mukherjee, 1999). In addition, mean total arsenic concentrations of 50 to 550 mg/kg have been recorded in agricultural soils applied with various arsenical pesticides (Sanok et al., 1995; Takamatsu et al., 1982; Walsh & Keeney, 1975; Stilwell & Gorny, 1997). Some peats and sewage sludges have been reported to contain considerable quantities of arsenic. Reported concentrations in peats vary from around 4 mg/kg up to 340 mg/kg (Minkkinen & Yliruokanen, 1978; Shotyk, 1996). Zhu & Tabatabai (1995) monitored total arsenic levels in sewage sludge from waste treatment plants in Iowa (USA) and found concentrations which ranged from 2.4 to 39.6 mg/kg, with a mean of 9.8 mg/kg.

Relatively little of the total arsenic measured in soils has been found to be present in bioavailable forms. In one study, which looked at garden soils near or at sites of past mining activity, the water-soluble extractable arsenic fraction was found to be less than 1% of the total (Xu & Thornton, 1985). In similar studies, the proportion of water-extractable arsenic in agricultural top soils ranged from 0.05% to 0.3%, and in mine wastes from 0.02% to 1.2% (Kavanagh et al., 1997). Ng et al. (1998) reported total arsenic concentrations of 32 to 1 597 mg/kg in soils that had been contaminated 30 years previously with arsenical pesticides. Based on a rat model, it was estimated that the absolute bioavailability of these contaminated soils relative to arsenite and arsenate ranged from 1.0 to 9.9% and 0.3 to 3.0%, respectively.

3.1.1.3 Surface water

Arsenic is widely distributed in surface water. Concentrations of arsenic in surface waters are usually low, although higher concentrations can occur near natural mineral deposits or near anthropogenic sources.

Measured levels of arsenic in surface freshwaters (rivers and lakes) are summarized in **Table 3.1**. Surveys indicate that most values are below 10 ug/L, although some samples may exceed 1 mg/L

(Page, 1981; Smith et al., 1987; Welch et al., 1988). A total arsenic concentration of 2 mg/L has been recorded near one pesticide plant (Faust et al., 1983; Faust et al., 1987). Crearley (1973) reported mean arsenic levels of 3200 and 7900 ug/L in two lakes near a manufacturing plant that had been producing arsenic-based cotton defoliants for 30 years. High levels of arsenic have been recorded in some thermal waters. For example, Tanaka (1990) found a mean concentration of 570 ug/L in Japan's geothermal waters, with a maximum level of 25.7 mg/L.

Table 3.1 Concentrations of arsenic in surface freshwaters (Source: WHO, 2001)

Location	Sampling period	Sampling details and/or arsenic source	Concentration (µg/litre)[a]	Reference
Brazos River, Texas, U.S.A.	NS	0.2 µm filtered, arsenite	0.05	Chakraborti et al. (1986)
Madison River, Montana, U.S.A.	NS	Geothermal	51	Sonderegger & Ohguchi (1988)
Finfeather Lake, Texas, U.S.A.	1973	near manufacturing plant for arsenic-based cotton defoliants	7900 (6000-8600)	Crearley (1973)
Municipal Lake, Texas, U.S.A.	1973	as above	3200 (1700-4400)	Crearley (1973)
Maurice river, NJ, U.S.A.	1982-1983	Upstream of pesticide plant	3.3 (1.05-4.4)	Faust et al. (1987a)
	1982-1983	0.6 km downstream	2222 (1320-4160)	Faust et al. (1987a)
	1982-1983	4.2 km downstream	266 (118-578)	Faust et al. (1987a)
Union Lake, NJ, U.S.A.	1982-1983	14-17 km downstream	86.1 (27.1-267)	Faust et al. (1987a)
Bowron Lake, British Columbia, Canada	1992	Reference lake; no mining activity	0.26 (<0.2-0.42)	Azcue et al. (1994a)
Lake water, British Columbia, Canada	1992	near abandoned gold mine	0.25 (<0.2-0.3)	Azcue et al. (1994a)
Lake Asososca, Nicaragua	1991-1992	Volcanic crater; includes surface, intermediate and bottom samples	5.9 (0.85-15.8)	Cruz et al. (1994)
Moira Lake, Ontario, Canada	1987-1988	past mining activity; 15% particle sorbed	43 (4-94)	Diamond (1995)
Lakes, Northwest Territories, Canada	1975	gold mining activity	700-5500 (range)	Wagemann et al. (1978)
Subarctic lakes, Northwest Territories, Canada	1991	gold mining activity	270 (64-530)	Bright et al. (1996)
Yangtze river (source area), China	NS	filtered water (<0.45 µm)	3.1 (0.1-28.3)	Zhang & Zhou (1992)
Antofagasta, Chile	1958-1970	Toconce River, Andes Mountains	<800	Borgono et al. (1977)
Mutare river, Zimbabwe	1993	Near gold/arsenic mine dumps	13-96 (range of means)	Jonnalagadda & Nenzou (1996b)
Odzi river, Zimbabwe	1993	2.2 km downstream from gold/arsenic mine dumps (after confluence with Mutare river)	1-3 (range of means)	Jonnalagadda & Nenzou (1996b)
Lake Xolotlan, Nicaragua	NS	Volcanic crater; range of means	10.2-30.1 (range of means)	Lacayo et al. (1992)
Waikato river, New Zealand	1993-1994	Volcanic source	32.1 (28.4-35.8)	McLaren & Kim (1995)

Lake water, Lapland, Finland	1992	0.1 m below surface	0.17 (median)	Mannio et al. (1995)
Nakhon Si Thammarat Province, Thailand	1994	Mining activity	217.5 (4.8-583)	Williams et al. (1996)

NOTES: [a] - mean and ranges of total arsenic unless stated otherwise; NS - not stated

Sediments in aquatic systems often have higher arsenic concentrations than those of the overlying water. In most cases, concentrations are within the range 5-3000 mg/kg (WHO, 2001), with the higher levels occurring in areas of contamination, such as gold mining activity (Welch et al., 1988; Wagemann et al., 1978). Isolated reports of sediment concentrations in excess of 3000 mg/kg have been found in the literarature. Arsenic concentrations of up to 10 000 mg/kg (dry weight) were found in surface sediments near a copper smelter (Crecelius et al., 1975).

Arsenic levels in seawater are typically 1 to 2 ug/L. The dissolved forms of arsenic in seawater include arsenate, arsenite, methanearsonic acid (MMA) and dimethylarsinic acid (DMA) with adsorption onto particulate matter being the physical process most likely to limit dissolved arsenic concentrations (Maher & Butler, 1988). Reported concentrations in estuarine locations are generally a little higher (WHO, 2001). In one study conducted in the St Lawrence Estuary, Canada, it was noted that arsenic concentrations increased from 0.5 to 1.4 ug/L (or from 6.6 to 18.7 nM) with increasing salinity (from 0 to 31%) (Tremblay & Gobeil, 1990).

3.1.1.4 Groundwater

Arsenic levels in groundwater typically average around 1 to 2 ug/L (Table 3.2). However, in areas with volcanic rock and sulphide mineral deposits, arsenic levels in excess of 3000 ug/L have been measured (Page, 1981; Robertson, 1989; Welch et al., 1988).

Table 3.2: Concentrations of arsenic in groundwater (Source: WHO, 2001**)**

Location	Sampling period	Arsenic source	Concentration (µg/litre)[a]	Reference
Hungary	N.S.	deep groundwater	68 (1-174)	Varsanyi (1989)
South-west Finland	1993-1994	well waters; natural origin	17-980 (range)	Kurttio et al. (1998)
New Jersey, U.S.A.	1977-79	well waters	1 (median)	Page (1981)
			1160 (maximum)	Page (1981)
Western U.S.A.	N.S.	geochemical environments	48 000 (maximum)	Welch et al. (1988)
South-west U.S.A.	1970-	alluvial aquifers	16-62 (range of means)	Robertson (1989)
Southern Iowa & western Missouri, U.S.A.	N.S.	natural origin	34-490 (range)	Korte & Fernando (1991)
Northeastern Ohio, U.S.A.	N.S.	natural origin	<1-100 (range)	Matisoff et al. (1982)
Lagunera region, northern Mexico	N.S.	well waters	8-624 (range)	Del Razo et al. (1990)
Cordoba, Argentina			>100	Astolfi et al. (1981)
Chile			470-770 (range)	De Sastre et al. (1992)
Pampa, Cordoba, Argentina	N.S.	2-15m, 61°45'-63°W; 32°20'-35°00'S	100-3810 (range)	Nicolli et al. (1989)
Kuitun-Usum, Xinjiang, PR China	1980	well waters	850 (maximum)	Wang et al. (1993)
Hsinchu, Taiwan	N.S.	well waters	<0.7	Chen et al. (1994)
West Bengal, India	N.S.	arsenic-rich sediment	193-737 (range of means)	Chatterjee et al. (1995)
			3700 (maximum)	Chatterjee et al. (1995)
Calcutta, India	1990-1997	near pesticide production plant	<50-23080 (range)	Chakraborti et al. (1998)
Bangladesh	1996-1997	well waters	<10 - >1000 (range)	Dhar et al. (1997)
Nakhon Si Thammarat Province, Thailand	1994	shallow (alluvial) groundwater; mining activity	503.5 (1.25-5114)	Williams et al. (1996)
	1994	deep groundwater; mining activity	95.2 (1.25-1032)	Williams et al. (1996)

NOTES: [a] - mean and ranges of total arsenic unless stated otherwise; NS - not stated

According to the scientific literature, areas having elevated groundwater concentrations of arsenic, be they naturally occurring or due to human activity, can be found in all the major world regions. For example, in Iowa, Missouri and Ohio, arsenic, apparently of natural origin, was found in groundwaters at concentrations between 34 and 490 ug/L (Korte & Fernando, 1991; Matisoff et al., 1982). In Hungary, Varsanyi (1989) found that arsenic concentrations in deep groundwater ranged from 1 to 174 ug/L, with an average value of 68 ug/L. High arsenic levels originating from arsenic-rich bedrock were found in drilled wells in southwest Finland with concentrations ranging from 17 to 980 ug/L (Kurttio et al., 1998), while in parts of Mexico arsenic concentrations ranged from 8 to 624 ug/L with over 50% of samples in excess of 50 ug/L (Del Razo et al., 1990). Chen et al. (1994) reported mean arsenic levels in groundwaters of southwest Taiwan of 671 ug /L (as dissolved arsenic).

Arsenic contamination of groundwater from arsenic-rich sediment has been reported widely in both India and Bangladesh. Chatterjee et al. (1995) analysed groundwater from six districts of West Bengal, India. Mean total arsenic levels ranged from 193 to 737 ug/L with a maximum value of 3700 ug/L. Mandal et al. (1996) reported that 44% of groundwater samples collected in West Bengal up to January 1996 contained total arsenic levels greater than 50 ug/L. Dhar et al. (1997) found that 38% of groundwater samples collected from 27 districts of Bangladesh contained total arsenic levels greater than 50ug/L. During 1990 and 1991 Chatterjee et al. (1993) sampled groundwater in the vicinity of a chemical plant in Calcutta, India, which had produced the insecticide Paris-Green (acetocopper arsenite) for 20 years. Groundwater contained total arsenic levels ranging from <0.05 to 58 mg/L; the highest total arsenic level included 75% arsenite.

3.1.1.5 Biota

Levels of arsenic in marine organisms can range from < 1 mg/kg up to more than 100 mg/kg (Lunde, 1977; Maher & Butler, 1988; Phillips, 1990). Arsenic is present mainly in its organic forms, including for example as arsenosugars (in macroalgae) and arsenobetaine (in invertebrates and fish).

In freshwater organisms and terrestrial biota arsenic levels are normally less than 1 mg/kg (fresh weight). In the case of terrestrial biota, however, higher levels have been recorded in samples collected from areas with significant geothermal activity or from sites close to anthropogenic sources of arsenic. Mean concentrations of up to 3000 mg/kg have found at old arsenical mine sites (Porter & Peterson, 1975; Benson et al., 1981). Terrestrial plants accumulate arsenic by root uptake from the soil and by the adsorption of arsenic deposited on the leaves.

3.1.2 EXPOSURE IN THE GENERAL POPULATION

As previously mentioned, exposure to environmental contaminants including arsenic can occur through one or more of three pathways, inhalation, ingestion and dermal absorption. In the case of arsenic, available evidence suggests that non-occupational exposure occurs primarily through the ingestion of food and water, with the inhalation pathway playing only a minor role. Food is more commonly the main contributor to total intake but in areas where drinking waters contain relatively high levels of arsenic, drinking water may be the most important source of arsenic intake. Intake via dermal absorption is believed to be negligible, and is not considered further here.

3.1.2.1 Air

Human exposure to arsenic in ambient air will be primarily to the inorganic forms of arsenic, organic species generally being negligible in airborne particulates, except in areas of substantial use of arsenic pesticides or in areas with high biotic activity (section 3.1.1.1). To some extent exposure will be governed by the size of the particulates, the smaller (submicron) particles being more significant. Based on the currently available measurements of arsenic in ambient air, it is estimated that inhalation of airborne particles would result in a pulmonary exposure of around 1 ug/day in a non-smoker. In areas of elevated atmospheric arsenic, i.e. in the vicinity of industrial operations, the contribution may well be higher than this.

3.1.2.2 Food and Beverages

Food monitoring data indicate that trace concentrations of arsenic are present in all foodstuffs. Total arsenic concentrations in food from various countries vary widely, being dependent upon the food type, growing conditions (type of soil, water, geochemical activity, use of arsenical pesticides) and processing techniques. In general, however, the highest concentrations of total arsenic are found in seafood, followed by meats and grain; fruit, vegetables and diary products tend to have lower total concentrations (Gunderson, 1995; Yost et al., 1998; NRC, 1999; MAFF, 1997; Dabeka et al, 1993; ANZFA, 1994). Concentrations of total arsenic in found in various food groups in North America are given in Table 3.3. Analysis of various beverages from Denmark found low levels of arsenic (3-11 ug/L) (Pedersen et al., 1994).

Table 3.3 Total arsenic concentrations in various food groups from Canada[a]

(Source: WHO, 2001)

Food Category	Sample Size	Mean (µg As/kg wet weight)	Range (µg As/kg wet weight)
Milk and dairy products	89	3.8	<0.4-26
Meat and poultry	124	24.3	<1.3-536.0
Fish and shellfish	40	1662.4	77.0-4830.0
Soups	28	4.2	<0.2-11.0
Bakery goods and cereals	177	24.5	<0.1-365.0
Vegetables	262	7.0	<0.1-84.0
Fruit and fruit juices	176	4.5	<0.1-37.0
Fats and oils	21	19.0	<1.0-57.0
Sugar and candies	49	10.9	1.4-105
Beverages[b]	45	3.0	0.4-9.0
Miscellaneous[c]	33	12.5	<0.8-41.0

(a) Data from Dabeka *et al*., (1993); [b] Includes: coffee, tea, soft drinks, wine and canned and bottled beer; [c] Includes: bran muffins, muffins with and without raisins, gelatin desserts, raisins, baked beans, weiners, and raw & canned beets

There are few data on the concentration of arsenic in human breast milk. What data are available suggest that levels are low; for example Grandjean et al. (1995) reported low concentrations of arsenic in breast milk from a population consuming large amounts of marine mammals. One study of ten lactating women by Concha et al. (1998a) found arsenic concentrations of between 0.83 and 7.6 ug/kg fresh weight (median 2.3 ug/kg) in breast milk from women consuming in excess of 200 ug/L in their drinking water. It was concluded that breast feeding provided 1-2 ug/day compared with 100-200 ug/day from formula milk made up with the arsenic-rich water.

Arsenic in foods occurs as a mixture of inorganic species and the less toxic organic arsenicals, including trimethyl species such as arsenobetaine. Preliminary findings suggest that inorganic arsenic accounts for 75% of the total arsenic burden in meats, 65% in poultry, 75% in dairy products and 65% in cereals (US EPA, 1988; Yost et al., 1998). In contrast, in fruits and vegetables, and fish/seafood, the organic species tend to predominate with inorganic arsenic contributing only 10%, 5%, and 0-10%, respectively.

A few studies have looked specifically at the relative proportions of organic and inorganic arsenic species in food. According to a report from the Netherlands (Vaessen and van Ooik, 1989), inorganic arsenic accounts for between 0.1 and 41% of the total arsenic burden in seafood. Edmonds and Francesconi (1993), in their review of data on inorganic arsenic in seafood, concluded that inorganic arsenic represented less than 1% of the total amount of arsenic. Mohri et al. (1990) estimated that a typical Japanese diet contained 5.7% inorganic arsenic; the corresponding intake was estimated to be 27-376 ug total arsenic/day. In another study, Toa and Bolger (1998) estimated an intake of inorganic arsenic in US males and females, aged 60-65 years, of 12.5 and 9.7 ug/day, respectively. Other age groups had lower daily intakes, which varied from 1.3 ug/day for infants to 9.9 ug/day for young males (aged 25-30 years).

Collectively such studies indicate that inorganic arsenic levels in fish and shellfish are generally low (< 1%), but that other foodstuffs (meat, poultry, diary products and cereals) contain higher proportions of inorganic arsenic. Based on preliminary data it has been estimated that approximately 25% of the daily intake of dietary arsenic is as the inorganic forms; this is, however, highly dependent on the type and range of foods ingested (US EPA, 1988, Yost et al, 1998). More data are needed to obtain satisfactory information on the normal range of inorganic arsenic in food.

Representative mean daily intakes of total arsenic from food and beverages in several countries are summarized in Table 3.4. The variation in dietary intake of total arsenic in adults reflects in large part the variability in the consumption patterns worldwide of arsenic-rich food groups (fish/shellfish and meats) and confirms the need to consider such regional variations in arsenic intake when carrying out human health risk assessments for arsenic.

Table 3.4 Estimated average dietary intake of arsenic in various countries (Source: WHO, 2001)

Country	Method of Sampling[a]	Intake of Total Arsenic (µg/day)	Reference
Australia	MB (adult male) (adult female) (2 year old)	73.3 52.8 17.3	ANZFA, 1994
Brazil	DD[b](students) (S. Catarina 1 region) (Manaus region)	18.7-19.5 49.2-52.9 139.6-159.3 16.5-17.0	Fávaro et al, 1994
Canada	TD (5 cities-adult male) (5 cities-1 to 4 yrs)	59.2 14.9	Dabeka *et al*., 1993
Croatia	MB	11.7	Sapunar-Postruznik *et al*., 1996
Japan	DD (adult-male&female)	182	Mohri *et al*., 1990
Spain	TD (Basque Region-adult)	291	Urieta *et al*., 1996
UK	TD (adults)	63	MAFF, 1997
USA	MB (adults) (0.5-2 yrs)	52.6 27.6	Yost *et al*., 1998

[a] MB- Market basket survey; TD- Total diet study; DD- Duplicate diet study; [b] Mean values not reported.

3.1.2.3 Drinking-water

Concentrations of total arsenic in fresh surface and groundwaters, both potential sources of drinking-water, are given in Sections 3.1.1.3 and 3.1.1.4 (Tables 3.1 and 3.2). Although arsenic levels in natural waters are usually low (a few µg/L), drinking waters in some areas in the world contain concentrations of total arsenic well in excess of 100 of µg/L. These elevated arsenic concentrations are generally a result of natural geochemical activity. Arsenate is usually the predominant species; however, some groundwaters have been found to contain up to 50% arsenite. Concentrations of methylated species in natural waters are usually low, that is less than 0.3 µg/L (ATSDR, 1993). Unless stated otherwise, monitoring data for drinking water given in this section are reported as total arsenic.

A review of water quality monitoring data collected during the period 1976-1993 revealed that concentrations of arsenic in drinking waters in the USA lie between < 2.5 and 28 µg/L in surface

waters, and between < 5 to 48 µg/L in groundwater sources. (Detection limits of 2 or 5 µg/L precluded more accurate estimates of the lower limit of these ranges). Based on these data, it was estimated that approximately 2% of the US population is exposed to drinking water containing more than 10 µg/L of arsenic (Borum & Abernathy, 1994). Areas of especially high arsenic concentrations have been identified by the US EPA in a detailed analysis of 1978 water quality monitoring data. These include parts of California and Neveda, were levels are arsenic in the bedrock are naturally high; mean arsenic concentrations of up to 80 µg/L and maximum levels of more than 1,400 µg/L have been reported. Arsenic was detected in 67% of 3,834 drinking water samples taken in this year (detection limit 0.1 µg/L); the mean concentration was reported to be 2.4 µg/L (US EPA, 1993).

Water quality monitoring data obtained from six Canadian Provinces over a four-year period (1985-1988) have also been compiled and analysed (NHW/DOE, 1993). It was found that the percentage of drinking water samples having total arsenic concentrations of > 5 µg/L varied from 0 to 32%. However, when 28 samples from 7 ground water sources in Nova Scotia were excluded from the analysis the range was reduced to 0-12%. In areas dominated by naturally occurring high arsenic-containing ores, or where gold mining had previously occurred, arsenic concentrations in drinking water supplies of between 150 and >500 µg/L were reported.

In the West Bengal Region of India, it has been estimated that over 1 million people are consuming drinking-water containing arsenic at concentrations above 50 µg/L. Levels as high as 3.7 mg/L have been recorded at some locations (Das et al, 1995; Choudry et al., 1997). Similarly, in areas of Bangladesh bordering India, 38% of ground water samples in 27 districts were found to contain arsenic at levels > 50ug/L (Dhar et al, 1997). In Southwest Taiwan, about 100,000 people are believed to have been exposed (i.e. prior to 1970) to high concentrations of arsenic in drinking-water (range 10 to 1800 µg/L, mean 500 µg/L) (Guo et al, 1994). Similar problems have been reported in Chile, where 100,000 people have consumed drinking water containing 800 ug/L of arsenic for up to12 years (Borgono et al., 1977) and in North Central Mexico, where 200,000 people were exposed to >50 µg/L arsenic in drinking-water (and to as much as 410 µg/L in at least one village (Cebrian et al., 1983). In the major Australian drinking water systems, levels of arsenic of up to 15 µg/L have been recorded; however, typical concentrations are usually below 5 µg/L (NHMRC, 1996).

3.1.2.4 Soil

Although ingestion of arsenic in soil and dust is unlikely to be a significant source of arsenic intake in adults, it may be so in the case of children, particularly in locations near industrial and hazardous waste sites. There is some evidence to suggest that children living near arsenic-contaminated sites do have elevated body burdens relative to children from uncontaminated sites (see section 3.2.1.5). The bioavailability of the arsenic in these soils is often low (see section

3.1.1.2); however, more data on the bioavailability of arsenic from such sources is necessary for a more accurate assessment of human risk from soil exposures.

3.1.2.5 Miscellaneous Exposures

Smokers are exposed to arsenic by the inhalation of mainstream cigarette smoke. It has been estimated that a person in the USA smoking 40 cigarettes per day would inhale about 10 µg of arsenic (ATSDR, 1993). Some dietary supplements, such as Chinese herbal medicines, may contain undesirable high arsenic concentrations (Chan, 1994).

3.1.3 OCCUPATIONAL EXPOSURES

There is the potential for significant occupational exposure to arsenic in several industries, in particular, non-ferrous smelting, electronics, wood preservation, wood joinery shops, arsenic production, glass manufacturing and, the production and application of arsenical pesticides. Exposure is primarily through the inhalation of arsenic-containing particulates; however, ingestion and dermal exposure may be significant in particular situations. It is extremely rare that workers are exposed to arsenic alone, but are usually exposed to arsenic in combination with other substances. At present a number of countries have established occupational regulations for arsenic which set limits on the permissible concentration of inorganic arsenic in the workplace. These range from 0.01 to 0.1 mg/m^3 (ILO, 1991; DFG, 1999; OSHA, 2000; MSZW, 2000).

The following examples are given to illustrate the range of arsenic levels and exposures that have been reported in specific industries in various locations world-wide. It is stressed that they should not be considered as representative of all similar industrial sites.

Exposure to arsenic in copper smelters has been assessed in a number of studies. For example, measurements of arsenic in air were made between 1943 and 1965 at one copper smelter in the USA.Very high airborne concentrations (>5 mg/m^3) were estimated in the following departments: arsenic roaster (20 mg/m^3), electrostatic precipitator (13 mg/m^3), arsenic refinery (7.5 mg/m^3) and main flue (6.9 mg/m^3). High concentrations (0.5-4.99 mg/m^3) were reported in four departments: masons shop (2.6 mg/m^3), ore roaster (1.4 mg/m^3), materials crushing (1.0 mg/m^3) and reverbatory furnaces (0.6 mg/m^3). The remaining 10 departments of the smelter had only medium (0.1-0.49 mg/m^3) to low (<0.1 mg/m^3) concentrations of arsenic (Welch et al., 1982).

Data on airborne arsenic concentrations inside a second US copper smelter have been reviewed by Enterline and Marsh (1982). As in Welch's study, reported levels varied by department, but in this

case the arsenic concentrations were universally high. For example, between 1947 and 1953, a total of 25 samples from the arsenic plant found airborne arsenic concentrations ranging from 0.8 to 41.4 mg/m^3. As part of their study, Enterline and Marsh (1982) also measured the urinary excretion rates of workers; it was concluded, on the basis of measurements made during the period 1938-1957, that airborne arsenic concentrations in ug/m ^{3} are about one-third the urinary excretion concentrations in ug As/L of urine.

Arsenic exposures of workers in a copper mine and smelter complex in Chile have been assessed by Ferreccio et al. (1996). Using data obtained from 1952 to 1991, Ferreccio et al. (1996) reported that workers' exposure to airborne arsenic varied from 1.6 to 201.7 in ug As/m^3, with workers in the administration area experiencing the lowest arsenic levels and those in the smelter itself the highest. Similarly, Offergelt et al. (1992) reported levels of arsenic (as a time-weighted average or TWA) of between 6 and 502 ug/m^3 in a sulphuric acid plant. As part of an epidemiological investigation on lung cancer mortality of workers in non-ferrous mines, Liu and Chen (1996) measured airborne arsenic concentrations in 1978, 1981 and 1988. In chronological order, the concentrations of arsenic reported were: 0.23 mg/m^3 (range 0.004-0.577; 6 samples); 0.06 mg/m^3 (range 0.003-0.166; 14 samples), and 0.32 mg/m^3 (range 0.028-1.442; 8 samples).

Workers in selected glass manufacturing industries may be exposed to airborne arsenic through the use of arsenic trioxide (IARC, 1993). In Germany, for example, workers were found to have urinary arsenic concentrations ranging from 3 to 114 ug/g creatinine. In 1976, 36% of the cases were above the upper normal limit of 25 ug As/g creatinine; by 1981 this had dropped to 18% of cases (Schaller et al., 1982). The mean urinary arsenic excretion in 18 workers involved in weighing and mixing chemicals in a UK specialist glass manufacturing facility was 79.4 ug/g creatinine compared to 4.4 ug/g creatinine in controls (Farmer & Johnson, 1990). Similarly, in a Belgian glass factory, urinary excretion rates of arsenic in 10 workers ranged between 10 and 941 ug/g creatinine compared with a range of 7.6-59 ug/g creatinine in control workers (Roels et al., 1982). The authors concluded that the high urinary arsenic concentrations in the glass factory workers were more likely to be related to oral intake due to poor hygiene, rather than as a result of pulmonary uptake.

Exposure to arsenic in the air has been documented in 19 out of 27 workers using arsenic-containing materials in the following occupations and activities: taxidermy; workers producing garden fences, weekend cottages and new houses; workers impregnating wood with copper:chromium:arsenic (CCA) solutions, and workers impregnating electric pylons with arsenic solutions (Jensen & Olsen, 1995). Median arsenic exposures of indoor workers preparing fences and weekend cottages were 3.7 and 0.9 ug/m^3, respectively. Mean urine arsenic levels in taxidermists were 1.8 times the reference level of 14.5 nmoles As/mmole creatinine.

Airborne arsenic concentrations in a wood joinery shop handling treated wood were reported to be 0.043 - 0.36 mg/m^3 (WHO, 1981). In a more recent study involving wood joinery shops, airborne arsenic concentrations between 0.54 and 3.1 ug/m^3 were reported (Nygren et al, 1992). In two workshops machining CCA-treated wood, concentrations of arsenic in personal air samples ranged from 10 to 67 ug/m^3 (Subra et al., 1999).

Workers in coal-powered power plants may also be exposed to the arsenic found in the coal, or more likely to that found in fly ash during cleaning. Yager et al. (1997) have reported arsenic concentrations (8-hour TWA concentrations) of between 0.17 and 375.2 ug/m^3 (mean = 48.3 ug/m^3) in the breathing zone of maintenance workers from a coal-fired power plant in Slovakia. The urinary excretion of total urinary arsenic metabolites ranged between 2.6 and 50.8 ug As/g creatinine (with a mean of 16.9 ug As/g creatinine). The authors estimated a mean urinary excretion of 13.2 ug As/g creatinine in workers exposed to fly ash, from an 8-hr TWA exposure to 10 ug As/m^3, suggesting that the bioavailability of arsenic in coal fly ash is approximately one-third that seen in smelters.

It should be noted that some of the above studies refer to measurements made 20 to 40 years ago, and it is unlikely that present-day levels are as high as the earlier reports might indicate. Nowadays, levels of arsenic in workplaces with up-to-date control equipment and good hygiene practices are generally below 10 ug/m^3 (expressed as a 8 hour TWA concentration) (WHO, 2001).

3.1.4 TOTAL INTAKE FROM ALL ENVIRONMENTAL PATHWAYS

On the basis of available data, it is estimated the daily intake of total arsenic from the consumption of food and beverages in the general population typically lies between 20 and 300 ug/day (WHO, 2001). This wide variation in intake reflects large differences in the composition of diets worldwide, particularly with regard to the proportion of fish/shellfish. It should also be noted that intake data refer to total arsenic and do not reflect the possible variation in intake of the less toxic organic derivatives versus the more toxic inorganic arsenic species. Limited data suggest that approximately 25% of the arsenic present in food is inorganic.

Although food is the main contributor to the daily intake of arsenic for much of the non-occupationally exposed population, in areas where drinking water contains elevated levels of arsenic, drinking water will be a significant source of both total and inorganic arsenic. In some cases, i.e. where levels of arsenic exceed 50 ug/L, arsenic in drinking water may even be the major contributor. For example, consumption of 1.4 litres of drinking water containing >50 ug As/L could provide over 70 ug inorganic arsenic compared with an estimated intake of inorganic

arsenic from food of between 12 and 14 ug, assuming a typical North American diet (Yost et al., 1998; NRC, 1999).

All other intakes of arsenic (inhalation and dermal) are usually small in comparison to the oral route (ATSDR, 1993). Inhalation would add about 1 ug As/day from airborne particulates in a non-smoker; this would rise to approximately 10 ug/day in a smoker on 40 cigarettes per day. Contaminated soils may be a significant source of arsenic intake in children in certain locations; however, the low bioavailability of soil arsenic would need to be taken into account in an exposure assessment (see section 3.1.2.5).

The most appropriate way to determine the internal (absorbed) dose of arsenic in individuals in specific populations is to measure the concentrations of arsenic species in urine. Concentrations of total urinary arsenic and metabolites of inorganic arsenic (i.e. inorganic arsenic + MMA + DMA) reflect the level of intake of total arsenic and inorganic arsenic, respectively.

Reported concentrations of metabolites of inorganic arsenic in urine of individuals with no known history of arsenic exposure are generally below 10 ug/L in European countries. Similar or slightly higher concentrations are reported in studies from the US and Japan. However, arsenic concentrations exceeding 1 mg/L have frequently been observed in the urine of individuals from in West Bengal and Bangladesh (WHO, 2001).

In general, the concentration of arsenic metabolites in urine correlate well with concentrations of arsenic in drinking water. Moreover, several studies conducted in the US have shown that the urinary arsenic concentration is approximately half that in drinking water (Harrington et al., 1978; Valentine et al., 1979). In other populations, for example in Argentina and Taiwan where a much greater proportion of the intake of fluids was from drinking water or drinks made from drinking water (as opposed to prepared beverages), the concentration of arsenic in urine was proportionately much higher (WHO, 2001).

3.2 KINETICS AND METABOLISM

Humans are exposed to many different forms of inorganic and organic arsenic species (arsenicals) in food, water and other environmental media. Each of the forms of arsenic has different physicochemical properties and bioavailability and therefore the study of the kinetics and metabolism of arsenicals in animals and humans is a complex matter. Arsenic metabolism is also characterised by large interspecies differences compared with other metals and metalloids.

3.2.1 INORGANIC ARSENIC

The fate of ingested or inhaled inorganic arsenic in the human body is largely dependent on its valence state. The two most common valence states to which humans might be environmentally exposed are the trivalent and pentavalent forms, arsenite (AsIII) and arsenate (AsV). Since arsenicals may change valence state depending on handling and preparation methodologies, studies cited in this review were evaluated with particular attention to the use of appropriate methods to ensure that the inorganic arsenic valence state was maintained.

3.2.1.1 Absorption

Respiratory deposition and absorption

Human inhalation exposure to inorganic arsenic can occur as a consequence of industrial activity (e.g., smelting of ores), production of energy (e.g., coal-fired power plants) and during cigarette smoking. The extent of arsenic deposition of inhaled arsenic will depend largely on the size of the inhaled particulates, while the absorption of deposited arsenic is highly dependent on the solubility of the arsenical.

Available human data are insufficient to estimate quantitatively regional arsenic deposition in the respiratory tract. However, occupational studies in which both the concentration of inorganic arsenic in the breathing zone and urinary excretion of inorganic arsenic and its metabolites were determined provide some information on arsenic absorption. Studies of this type demonstrate that the excretion of arsenic and methylated metabolites is significantly increased in exposed workers compared to unexposed workers (e.g. Vahter et al., 1986; Yamauchi et al., 1989; Offergelt et al., 1992; Hakala and Pyy, 1995; Yager et al., 1997). While this confirms that arsenic is absorbed from the respiratory tract, such studies do not provide enough information to estimate quantitatively arsenic absorption after inhalation because of the influence of confounding factors, such as the possible contribution of oral exposures.

Gastrointestinal absorption

Arsenic can be absorbed from the gastrointestinal tract following the ingestion of arsenic-containing food, water, beverages or medicines, or as a result of inhalation and subsequent mucociliary clearance. The bioavailability of ingested inorganic arsenic will vary depending on the matrix in which it is ingested (i.e. be it food, water, beverages or soil), the solubility of the arsenical compound itself and the presence of other food constituents and nutrients in the gastrointestinal tract.

In common with experimental animals, controlled ingestion studies in humans indicate that both tri- and pentavalent arsenic are readily absorbed from the gastrointestinal tract. For example, Pomroy et al. (1980) reported that healthy male human volunteers excreted 62.3 ± 4.0% of a 0.06

ng dose of ^{74}As-arsenic acid (AsV) in urine over a period of 7 days, whereas only 6.1 ± 2.8% of the dose was excreted in the faeces. Results obtained from similar studies show that between 45% and 75% of the trivalent forms of arsenic are excreted in the urine within a few days, indicating that gastrointestinal absorption is both relatively rapid and extensive (WHO, 2001).

Dermal absorption

Few investigations of dermal absorption rates for arsenicals have been undertaken. What data are available indicate that absorption rates are generally low (<10 %); however, for certain forms of arsenic higher rates may be observed (WHO, 2001). Wester et al. (1993) studied the percutaneous absorption of arsenic acid (H_3AsO_4) from water and soil. In rhesus monkeys, arsenic uptake ranged from 6 to 2%. The same authors also reported that human cadaver skin absorbed approximately 1 to 2% of the administered dose over a 24-hr period.

Placental transfer

Both As(III) and As(V) have been found to cross the placenta of laboratory animals (WHO, 2001). Case reports of arsenic poisoning in pregnant women, in which the foetus died and was subsequently found to have toxic levels of arsenic in its organs and tissues, demonstrate that arsenite (arsenic trioxide) also readily passes through the placenta of humans (Lugo et al., 1969; Bollinger et al., 1992). This conclusion is substantiated by a more recent study conducted by Concha et al. (1998b) who observed that similar arsenic concentrations were found in cord blood and maternal blood (~9 ug/L) of maternal-infant pairs exposed to high arsenic-containing drinking water (~200 ug/L).

3.2.1.2 Distribution

Fate of inorganic arsenic in blood

Inorganic arsenic is rapidly cleared from the blood of most laboratory animals and humans; for this reason blood arsenic is considered to be a useful bioindicator of recent, relatively high-level exposures (see also section 3.2.3.2). Older studies (WHO, 1981) have indicated that the kinetics of arsenic clearance in the plasma and erythrocytes are similar, although levels in erythrocytes tended to be approximately 3-fold higher a few hours after exposure.

More recently, Zhang et al. (1996, 1997, 1998) have reported on the distribution of arsenical species in serum and arsenic-protein binding in serum of patients with renal disease. The predominant arsenic species present in serum were DMA (~15-30%) and arsenobetaine (~54 - 76%), with the remainder being protein-bound. Inorganic arsenic and MMA were undetectable (Zhang et al. 1996, 1997). Zhang et al. (1998) further reported that only inorganic arsenic was bound to serum proteins and that transferrin is the main carrier protein. It should be noted that

since individuals with renal disease tend to accumulate arsenic in serum, these results may not be typical of the general population.

Tissue distribution

As in experimental animals, analysis of post mortem human tissues reveals that arsenic is widely distributed in the body following either long-term relatively low-level exposure or poisoning (Raie, 1996; Gerhardsson et al., 1988; Dang et al., 1983). Dang et al. (1983), using neutron activation analysis (NAA), found that arsenic concentrations were quite low in both the blood and brain of Bombay accident victims relative to other tissues, and that arsenic concentrations in any given tissue was quite variable.

Levels of total arsenic and major arsenic metabolites were measured by HGAAS in a variety of human tissues obtained from adult patients (aged between 36 and 79) suffering from cerebral haemorrhage, pneumonia or cancer in Kawasaki, Japan (Yamauchi & Yamamura, 1983). No sex-dependent differences in arsenical tissue levels were observed and inorganic arsenic was found to be the predominant form in tissues, followed by DMA. MMA levels were uniformly low and detected only in liver and kidney. It is interesting to note that total arsenic levels were higher than those reported in the Indian study of Dang et al. (1983) and that levels in the brain tended to be more comparable to arsenic levels in other tissues. Interindividual variation in total tissue arsenic was again quite high, as observed in the Dang study.

Raie (1996) compared tissue arsenic levels in infants (aged 1 day to 5 months) and adults from Glasgow, Scotland using NAA. Mean levels of arsenic (ppm or ug/g dry weight) in liver, lung and spleen in infants versus adults were 0.0099 vs. 0.048, 0.007 vs. 0.044, and 0.0049 vs. 0.015, respectively. These data suggest that arsenic accumulates in tissues with age, a finding that is wholly consistent with observations in laboratory animals (Marafante et al., 1982).

A number of studies have been conducted in humans with a view to determining whether there are differences in tissue arsenic accumulation in differing disease states. In the case of multiple sclerosis and non-multiple sclerosis patients, no significant differences were found (Warren et al., 1983). Narang & Datta (1983) have reported that concentrations of arsenic in both liver and brain of patients who died of fulminant hepatitis are high compared to patients who died of non-hepatic related causes. Collecchi et al. (1985) found that malignant laryngeal tissue had significantly higher levels of arsenic compared with normal tissue; plasma arsenic levels were also significantly higher in cancer patients compared with controls. Zhang et al. (1996, 1997) have reported that arsenic levels in serum are significantly elevated (~5 to 6-fold) in patients with chronic renal disease.

3.2.1.3 Metabolic transformation

Arsenic metabolism is characterized in many species by two main types of reactions: (1) oxidation/reduction reactions which interconvert arsenite and arsenate, and (2) methylation reactions in which trivalent forms of arsenic are sequentially methylated to form mono-, di- and trimethylated products using S-adenosyl methionine (SAM) as the methyl donor and GSH as an essential co-factor (see Figure 3.1). One striking feature of arsenic metabolism is that there are extreme qualitative and quantitative interspecies differences in methylation to the extent that some species do not appear to methylate arsenic at all (Styblo et al., 1995; Vahter, 1999).

Figure 3.1 Arsenic methylation in mammals
Source: WHO, 2001 (PENDING)

In common with that which is observed in most laboratory animal species, controlled ingestion studies indicate that both arsenate and arsenite are extensively methylated in humans, with DMA being the main methylated metabolite excreted in human urine. A noteworthy difference between humans and laboratory animals is that MMA is excreted in the urine of humans to a greater extent. The biological basis for this difference is unknown.

Several studies involving populations exposed to relatively high levels of arsenic in drinking water indicate that methylation patterns are not highly correlated with exposure level (Warner et al., 1994; Hopenhayn-Rich et al., 1996a). Hopenhayn-Rich et al. (1996b) compared methylation patterns in Chilean subjects (n=73) before and after changing from higher (600 ug/L) to lower (45 ug/L) arsenic-containing drinking water. There was a small but significant decrease in urinary inorganic arsenic (17.8% to 14.1%) and a decrease in the MMA to DMA ratio (0.23 to 0.18). The authors further noted that there was large interindividual variation in methylation profiles, and that factors such as smoking, gender, age, years of residence and ethnicity only accounted for ~20% of the variation observed. They speculated that much of the interindividual variation observed might be explained by genetic differences in the activity of methylating enzymes and related co-factors.

Vahter et al. (1995a) reported a unique pattern of urinary methylated metabolite excretion in a population of healthy native Andean women in north-western Argentina consuming an apparently protein-adequate diet. Reported arsenic concentrations in the drinking water of this population were ~200 ug/L. These women excreted mainly inorganic arsenic (median 25%, range 6.5 to 42%) and DMA (median 74%, range 54 to 93%) in their urine and very little MMA (median 2.1% with a range of 0.6 to 8.3%). The authors suggested that this finding indicates the existence of genetic polymorphism in the control of arsenic methyltransferases. They also suggested that the higher urinary DMA excretion in women in the village with the highest arsenic in drinking water (~200 ug/L) compared with women in the villages with lower arsenic in drinking water (2.5 to 31 ug/L) indicates induction of DMA excretion. It is interesting to note that differences in the activities of

other methyltransferases have been explained by the existence of genetic polymorphisms (Weinshilboum, 1992).

In further studies of the same Andean population, Concha et al. (1998c) reported striking differences in urinary excretion patterns of arsenic metabolites in children compared to adult women. In one village, children (age 3-15 years) excreted a much higher median percentage of inorganic arsenic in urine (49% vs. 25%) and a much lower median percentage of DMA in urine (47% vs. 74%) compared to adult women (age 20-47 years). A low median % MMA excreted in urine was also observed in both the women (2.1%) and children (3.6%) which is consistent with previously reported results (Vahter et al., 1995a). Another significant finding in these children was that with increasing excretion of total arsenic metabolites in urine, the percentage of inorganic arsenic decreased and the percentage of DMA increased; the authors interpreted this as evidence for induction of arsenic methylation with increasing exposure (Concha et al., 1998c). In the few studies that have looked at methylation patterns in children, percentages of metabolites excreted in urine are similar to adults (Buchet et al., 1980; Kalman et al., 1990). However, in both these latter studies arsenic exposure was relatively low as indicated by total concentration of arsenic metabolites excreted in urine (i.e. < 20 ug/L).

Data suggestive of gender differences in arsenic metabolism have been reported in studies conducted in Chile and Taiwan (Hopenhayn-Rich et al., 1996a; Hsu et al., 1997). In both of these studies males were reported to have a significantly higher MMA:DMA ratio in urine, indicating that more DMA was being excreted by females compared to males. This has been interpreted to mean that females have greater methylation capacity compared to males (Hopenhayn-Rich et al., 1996a). Concha et al. (1998c) reported significant increases in the percentage DMA excreted in urine in Argentinean women during pregnancy, a possible reason for gender differences reported in some studies.

Inorganic arsenic metabolism is affected by liver disease. In patients with various forms of liver disease, the presence of disease had no effect on the total amount of arsenic excreted, but dramatically shifted the proportion of MMA and DMA excreted in the urine. The percentage of arsenic excreted as MMA was decreased in liver disease compared to controls (6.1±0.7 vs. 12.8±0.7), while DMA was increased (40.7±1.9 vs. 24.3±1.6) (Buchet et al., 1984). Geubel et al. (1988) reported similar findings in healthy subjects compared to subjects with cirrhotic liver disease; they further noted that in patients with other non-hepatic diseases arsenic methylation was unaffected.

3.2.1.4 Elimination and excretion

Inorganic arsenic and its metabolites are eliminated primarily via the kidney. Studies in adult human males voluntarily ingesting a known amount of either trivalent or pentavalent arsenic

indicate that between 45% and 75% of the dose is excreted in the urine within a few days to a week. Although relatively few studies in volunteers have included measurement of arsenic in both faeces and urine, (Pomroy et al., 1980) reported that 6.1%±2.8% of a single oral dose of arsenic acid (pentavalent As) was excreted in the faeces over a period of 7 days compared to the 62.3%±4.0% in urine. No quantitative data was available that directly addressed the issue of biliary excretion of tri- or pentavalent arsenic in humans.

Although arsenic is excreted by other routes than via urine and faeces (e.g. in sweat), these routes of excretion are generally minor (WHO, 1981). Since arsenic can accumulate in keratin-containing tissues, skin, hair and nails could also be considered as potentially minor excretory routes. Both older (WHO, 1981) and recent studies indicate that arsenic can be excreted in human milk, although the levels are low (Dang et al., 1983; Grandjean et al., 1995; Concha et al., 1998a).

3.2.1.5 Retention and turnover

Pomroy et al. (1980) studied the whole body retention of radio labelled arsenic (^{74}As; 6.4 ci, 0.06 ng As) administered once orally as arsenic acid (AsV) in healthy male volunteers (aged 28 to 60 years) using whole body counting for periods of up to 103 days. While the averaged whole body clearance data for the six subjects in the study were best described by a triexponential model, the interindividual variation was quite high. It was reported that 65.9% of the dose was cleared with a half-life of 2.09 days, 30.4% with a half-life of 9.5 days and 3.7% with a half-life of 38.4 days. No comparable data for humans exist for trivalent inorganic arsenic.

Some studies have been conducted for the purpose of evaluating whether there is an increased body burden of arsenic in children living near arsenic contaminated sites relative to either children from low arsenic exposure areas or compared to adults. For example, Binder et al. (1987) reported that total urinary arsenic excretion was significantly increased in children living in a Montana (USA) community with high levels of arsenic in soil (average ~400 - 700 ppm) compared with a community with low levels (44 ppm) in soil. In urine samples taken in the high-arsenic soil community, mean total arsenic was 54 ug/L (53.8 ug/g creatinine) compared with 16.6 ug/L (17.1 ug/g creatinine) in the low-arsenic community.

Trepka et al. (1996) studied differences in arsenic burden among children in Germany. No striking age or gender-related differences were reported, although urinary arsenic excretion was slightly, but significantly increased in children from the most polluted area. However, the authors did not consider this increase to be toxicologically significant. In contrast, Diaz-Barriga et al. (1993) reported striking increases in body burden in children living closest to a copper smelter (median soil levels ~500 ppm arsenic) compared with children living 7 to 25 km away (median

soil levels ~11 to 14 ppm arsenic). Urinary arsenic excretion (normalized to creatinine) was more than doubled and arsenic levels in hair were more than 10-fold higher.

3.2.1.6 Reaction with body components

Numerous mechanistic studies have documented basic differences in the interaction of pentavalent compared to trivalent inorganic arsenic with body components; this is an important determinant in observed differences in tissue distribution.

Pentavalent inorganic arsenic and phosphate are analogs; this means that arsenate (As(V)) can compete with phosphate for active transport processes. Consequently, the addition of phosphate can decrease the intestinal uptake and renal tubular reabsorption of arsenate (Gonzalez **e**t al., 1995; Ginsburg & Lotspeich, 1963). Arsenate can also substitute for phosphate in the hydroxyapatite crystal of bone; this accounts for the higher concentrations of arsenic-derived radioactivity in bone after administration of arsenate compared to arsenite (Lindgren et al., 1982). At the biochemical level, arsenate can uncouple oxidative phosphorylation in mitochondria by substituting for inorganic phosphate in the synthesis of ATP (Gresser, 1981). It can also uncouple glycolysis by forming the dysfunctional compound, 1-arseno-3-phosphoglycerate, rather than 1:3-diphosphoglycerate (Mayes, 1983).

Arsenite (AsIII) reacts readily with vicinal sulfhydryl groups of a variety of enzymes and proteins. This affinity for sulfhydryl groups accounts for its accumulation in keratin-rich tissues such as skin, hair and nails. Arsenite also interacts with the ubiquitous sulfhydryl-containing cellular tripeptide, glutathione, at many different levels in the methylation process. Since arsenate can be reduced to arsenite in humans, administration of arsenate can cause inhibiton of enzymes and react with cellular enzymes and peptides. These may include the reduction of arsenic from pentavalency to trivalency following the addition of a methyl group and the formation of complexes with trivalent arsenicals which may be substrates for methylation (Styblo et al., 1996).

3.2.2 ORGANIC ARSENIC COMPOUNDS

The kinetics and metabolism of MMA, DMA, trimethylarsine (TMA) and trimethylarsine oxide (TMAO) as well as arsenobetaine and arsenocholine are discussed in this section. In general, relative to inorganic arsenic, organoarsenicals are less extensively metabolised and more rapidly eliminated.

3.2.2.1 Absorption

Respiratory deposition and absorption

No quantitative data concerning the respiratory deposition and absorption of organoarsenicals are available for humans or laboratory animals. However, the fact that increased urinary excretion of

arsenic during the workweek with a return to baseline levels on weekends was observed in workers spraying the herbicide monosodium methanearsonate indicates that respiratory absorption of organoarsenicals can occur (Abdelghani et al., 1986).

Gastrointestinal absorption

Limited experimental studies in human volunteers suggest that both MMA and DMA are readily absorbed from the gastrointestinal tract. Buchet et al. (1981a) reported that on average 78.3% of an oral dose of 500 ug of MMA and 75.1% of an oral dose of 500 ug DMA were excreted in urine within 4 days.

Studies have been conducted on the metabolism of organoarsenicals ingested in seafood. In one such study, an adult Japanese male consumed prawns containing ~10 ug (As)/kg trimethyl arsenic (98.8% trimethylarsenic - presumably as arsenobetaine). About 90% of the ingested arsenic was excreted in urine within 72 hours (Yamauchi & Yamamura, 1984). In human volunteers consuming flounder (containing arsenic as arsenobetaine), an average of 60% of the ingested dose was excreted in the urine within two days (Freeman et al., 1979). These data suggest that arsenobetaine is extensively and rapidly absorbed from the gastrointestinal tract.

Dermal absorption

No data concerning the dermal absorption of organoarsenicals in humans have been located, but both *in vivo* and *in vitro* dermal absorption data have been reported for arsenical herbicides in laboratory animals. Using clipped dorsal skin of B6C3F1 mice, Rahman and Hughes (1994) found that a constant fraction of the applied dose of MMA sodium salts (~ 12.4%) in a water vehicle was absorbed during a 24-hr period over the entire dose range (10 to 500 ug). Absorption appeared to be unaffected by vehicle volume. Using the same experimental system with DMA, Hughes et al. (1995) again found no significant dose-dependency in absorption over a 24-hr period. However, vehicle volume exerted a significant effect on absorption (rates ranged from around 7% to 40%) and decreased with increasing volume of water. In both studies, skin absorption of the arsenical herbicides from soil was very low (<1%). Shah et al. (1987) studied the *in vivo* percutaneous absorption of MMA and DMA in young (33-day old) and adult (82-day old) Fischer 344 rats. On average, the old and young rats absorbed 15.1% and 3.0% of the recovered dose, respectively, indicating that the young animals absorbed significantly less via this route.

Placental transfer

Older studies have demonstrated that DMA is capable of crossing the placenta of rats (Stevens et al., 1977) and that the organoarsenical feed additive Roxarsone (3-nitro-4-hydroxyphenylarsonic acid) accumulates in eggs (Chiou et al., 1997). However, more recent human or animal data are not available to substantiate these findings.

3.2.2.2 Distribution

Fate of organic arsenic in blood

Studies concerning the fate of organoarsenicals in human blood are almost totally lacking. Following ingestion of 10 ug/kg of trimethyl arsenic (98.8% by analysis, presumably arsenobetaine) in prawns, trimethylarsenic levels were reported to be approximately 2.5 times higher in blood plasma compared with erythrocytes at two hours post ingestion in the single subject studied. Levels declined thereafter and were at background by 24 hours (Yamauchi & Yamamura, 1984). In rodents, dimethyl- and trimethylarsenic compounds are rapidly cleared from the blood stream (Yamauchi et al, 1988; 1990).

Tissue distribution

Tissue distribution data in humans are derived from limited studies in which human volunteers have ingested ^{74}As labelled organoarsenicals. Brown et al. (1990) reported that arsenobetaine is rapidly and widely distributed in soft tissues with no major concentration in any region or organ and that greater than 99% of tracer activity was eliminated from the body within 24 days. Similar studies were unavailable for other organoarsenicals.

3.2.2.3 Metabolic transformation

There are limited data on the metabolism of MMA and DMA in humans. Buchet et al. (1981a) have reported that after a single oral dose of 500 ug MMA (as As), 87.4% of the total metabolites excreted in urine after 4 days were in the form of MMA and 12.6% were in the form of DMA. In the same study, it was reported that all of the ingested DMA (500 ug as As) excreted in the urine was in the form of DMA. However in a later study, Marafante et al. (1987) reported that 3.5% of a single oral dose of DMA (0.1 mg As/kg) was eliminated in urine as TMAO within 3 days. No metabolism studies were identified in which humans specifically consumed TMA or TMAO alone rather than in seafood.

It appears that, in common with laboratory animals, humans eliminate arsenobetaine from seafood unchanged in their urine. This implies that arsenobetaine is not metabolized (Tam et al., 1982). Recently, Goessler et al. (1997) have suggested that humans can metabolise inhaled trimethylarsine to arsenobetaine; their conclusion is based on the fact that elevated levels of arsenobetaine appeared in the urine of a chemist synthesizing trimethylarsine.

3.2.2.4 Elimination and excretion

Humans eliminate orally administered MMA and DMA predominantly in urine. Buchet et al. (1981a) reported that an average of 78.3% and 75.1% of a single oral dose (500 ug as As) of MMA and DMA, respectively, were eliminated in urine of human volunteers within a four-day

period. Arsenic ingested in seafood (where it is most likely to be present as arsenobetaine) is rapidly eliminated in urine. It is worthy of note that the percentage of the dose eliminated in urine following ingestion of arsenic in seafood is quite similar to that seen in laboratory animals dosed orally with arsenobetaine. No studies were identified that addressed the issue of biliary excretion or other routes of elimination for organoarsenicals in humans.

3.2.2.5 Retention and turnover

To date only animal studies have specifically measured retention and turnover rates of organoarsenicals. Vahter et al. (1984), for example, have compared the whole body retention of ^{74}As-DMA in mice and rats following a single oral dose of 0.4 mg (As)/kg. In mice, whole body clearance of DMA was triphasic, with 85% of the dose eliminated with a half-time of 2.5 hours, 14% with a half-time of 10 hours and the remainder (<0.5%) with a half-time of 20 days. In rats elimination was biphasic with 45% of the dose having a half-time of ~13 hours and the remaining 55% having a half-time of ~50 days. The longer retention of DMA in the rat was attributed to its greater tendency to accumulate arsenic in red blood cells.

Yamauchi et al. (1990) calculated the biological half-lives following oral administration of organoarsenicals to hamsters from multiple studies conducted in their laboratory. They reported half-lives of 7.4 hours for MMA, 5.6 hours for DMA, 5.3 hours for TMAO, 3.7 hours for TMA and 6.1 hours for arsenobetaine.

3.2.3 BIOMARKERS OF ARSENIC EXPOSURE

The three most commonly employed biomarkers used to identify or quantify arsenic exposure are total arsenic in hair or nails, blood arsenic, and total or speciated metabolites of arsenic in urine.

3.2.3.1 Arsenic in hair and nails

Because arsenic (as the trivalent form) accumulates in keratin-rich tissues such as skin, hair and nails (see section 3.2.1.2), arsenic levels in hair and nails have been used as indicators of past arsenic exposure. Hair and nails have the advantage of being readily and non-invasively sampled, but can suffer from problems of external contamination. In the case of hair, sampling from less readily contaminated sites (e.g. the occipital area or the nape of neck) and closer to the scalp can minimize some of these problems.

Several studies have reported hair-As levels in subjects without known exposure to arsenic. In one such study, conducted by Zhuang et al. (1990), levels of 0.40 ± 0.22 ug/g were measured in the hair of adult male Chinese subjects who had died as a result of accidents. These authors also reported a significant positive correlation (r=0.75) of hair- arsenic with arsenic levels in kidney

cortex, but not in lung or liver. Similar studies performed in other parts of the world (USA and Europe) have found lower levels of hair arsenic (Paschal et al., 1989; Wolfsperger et al., 1994)

Following acute poisoning, arsenic levels in both hair and nails are elevated within one to a few weeks and return to background levels within a few months (Choucair et al., 1988). Since the relative rate of hair growth is known (around 1 cm per month), the segmental distribution of arsenic along the hair shaft has been used to distinguish between acute and chronic poisoning, as well as to estimate length of time since a poisoning incident (Koons & Peters, 1994).

Arsenic levels in hair and nails can also be influenced by arsenic-induced disease state. Lin et al. (1998) have reported that both hair and fingernail arsenic are elevated in patients with black foot disease and Armienta et al. (1997) have reported that arsenic levels in hair are significantly elevated in patients displaying arsenic-induced hyperkeratosis compared to patients showing only hyper- or hypo-pigmentation. Hair samples from residents of Szolnok County, Hungary indicated that hair arsenic values were approximately 10-fold higher among those consuming drinking water containing increased arsenic concentrations (50-780 ug/L) compared with those whose drinking water contained only low levels of arsenic (1.02 +/- 0.08 mg/kg hair versus 0.14 +/- 0.04 mg/kg hair). There were also reports of skin effects (i.e. a higher prevalence for hyperkeratosis) in the Lokoshaza area among children exposed to increased arsenic concentrations.

The arsenic content of both fingernails and toenails has also been used as a bioindicator of past arsenic exposure. Fingernail arsenic has been reported to be significantly correlated with hair arsenic content (Lin et al., 1998). Agahian et al. (1990) reported that fingernail arsenic was elevated due to occupational arsenic exposure and correlated significantly (r=0.89) with mean arsenic air concentrations.

The use of toenails over fingernails has been recommended in some studies due to the larger amount of sample that can generally be provided. Toenails have the added advantages of slower growth (and so reflect exposures in the more distant past) and fewer external contamination problems (Karagas et al., 1996; Garland et al., 1993). Karagas et al. (1996) reported that mean toenail arsenic was significantly elevated in individuals using well water known to be high in arsenic (0.39±0.12) compared with individuals using water from low arsenic wells (0.14±0.02). Based on a regression analysis of these data, a 10-fold increase in arsenic concentration in water was associated with a two-fold increase in toenail arsenic levels.

3.2.3.2 Blood arsenic

As previously mentioned (section 3.2.1.2) inorganic arsenic is very quickly cleared from human blood. For this reason blood arsenic is only used only an indicator of very recent and/or relatively

high level exposure, for example, in poisoning cases (Ellenhorn, 1997) or in cases of chronic stable exposure (i.e from drinking water).

Studies have shown that in general blood arsenic does not correlate well with arsenic exposure in drinking water, particularly at low levels. In five Californian communities having average concentrations of 6, 51, 98, 123 and 393 ug/L arsenic in their drinking water, blood arsenic concentrations (mean ± SD) were 0.49±0.12, 0.51±0.65, 0.29±0.18, 0.42±0.17 and 1.33±1.18 ug/dL, respectively. However, arsenic levels in drinking water were significantly correlated with increased total arsenic in both hair and urine (Valentine et al., 1979).

3.2.3.3 Arsenic and metabolites in urine

In common with other biomarkers of arsenic exposure, arsenic levels in urine may result from inhalation exposure as well as ingestion from food, water and soils (ATSDR, 1993) and as such provide a measure of the total absorbed dose. However, since arsenic is rapidly metabolised and excreted into the urine, levels in urine are best suited to indicate recent arsenic exposure. Total arsenic, inorganic arsenic and the sum of arsenic metabolites (inorganic arsenic + MMA + DMA) in urine have all been used as biomarkers of recent arsenic exposure.

In many older studies, total urinary arsenic was used as a biomarker of recent arsenic exposure. This approach has become increasingly uncommon because certain organoarsenicals (for example, the practically non-toxic compound arsenobetaine) present in substantial amounts in certain foodstuffs are excreted mainly unchanged in urine (Cullen & Reimer, 1989; Kaise & Fukui, 1992; Le et al., 1994a) (see also section 3.2.2.3.). Since consumption of seafood (e.g., marine fishes, crustaceans, bivalves, seaweeds) by human volunteers is associated with increased total urinary arsenic excretion (Arbouine & Wilson, 1992; Buchet et al., 1994, 1996), assessment of inorganic arsenic exposure using total urinary arsenic under these conditions would result in overestimation of inorganic arsenic exposure.

To avoid the potential for over-estimation of inorganic arsenic exposure inherent in using total urinary arsenic, most studies now measure speciated metabolites in urine, and use either inorganic arsenic or the sum of arsenic metabolites (inorganic arsenic + MMA + DMA) as an index of arsenic exposure. However, this can give misleading results unless a careful diet history is taken and/or seafood consumption is prohibited for two to three days prior to urine collection. There are two reasons for this. First, some seafoods contain the arsenic metabolites MMA and DMA, particularly DMA, in fairly high amounts. Secondly, arsenosugars present in seaweeds and some bivalves are extensively metabolised to DMA (either by the body itself or the gut microbiota), which is then excreted in urine (Le, et al., 1994b; Ma & Le, 1998; WHO, 2001).

3.3 HEALTH EFFECTS

Arsenic has long been associated with toxic effects, producing marked impacts on health after both oral and inhalation exposure. Effects range from acute lethality to chronic effects, such as cancer and diseases of the vascular system. Studies in laboratory animals have demonstrated that the toxicity of arsenic is dependent on its form and its oxidation state. It is generally recognised that the soluble inorganic arsenicals are more toxic than the organic ones, and the trivalent forms (AsIII) are more toxic than the pentavalent ones (AsV). There are multiple end-points, with several different organ systems being affected, including the skin and the respiratory, cardiovascular, immune, genitourinary, reproductive, gastrointestinal and nervous systems.

Much of the information about the human health effects of arsenic, in particular in relation to its carcinogenicity, comes from evidence obtained through the study of exposed human populations. Unusually, it has been difficult to find any suitable animal model for the study of arsenic carcinogenicity. The human health effects of arsenic have been comprehensively reviewed by several leading national and international bodies including, WHO, IARC and the US NRC (IARC, 1973, 1980, 1987; ATSDR, 1993, 2000; NRC 1999; WHO, 1981, 2001).

3.3.1 Short-term effects

Ingestion of large doses of arsenic usually results in symptoms within 30 to 60 minutes, but may be delayed when taken with food. Acute arsenic poisoning usually starts with a metallic or garlic-like taste, burning lips and dysphagia. Violent vomiting may ensue and may eventually lead to hematemesis. These gastrointestinal symptoms are the result of intestinal injury caused by dilatation of splanchnic vessels leading to mucosal vesiculation. These vesicles rupture causing bleeding, diarrhoea, and protein wasting. Gastrointestinal symptoms often result in dehydration and electrolyte imbalance, and may lead to the development of hypotension and hypoxia (Brayer et al., 1997). After the initial gastrointestinal problems, multiorgan failures may occur, followed by death. Survivors of acute arsenic poisoning have been shown to develop hepatomegaly, melanosis, bone marrow suppression, hemolysis, and polyneuropathy resulting from damage to the peripheral nervous system.

Fatal arsenic poisonings have been reported after oral exposure to estimated single doses of 2 g (Levin-Scherz et al.,), 8 g (Benramdane et al., 1999) and 21 g (Civantos et al., 1995) Non-fatal outcomes (usually following treatment) have been documented after oral single doses of 1-4 g (Fincher & Koerker, 1987; Fesmire et al., 1988; Moore et al., 1994) and up to 8-16g (Mathieu et al., 1992; Bartolome et al, 1999). In children non-fatal but nevertheless serious acute effects have been observed after exposure to as little as 0.7 mg of As_2O_3 (Cullen et al., 1995). Incidents in which continuous or repeated exposure to high levels of arsenic over a short period of time have also been described. Following consumption of water containing 108 mg As/L for one week, two

of nine persons died, four developed encephalopathy and eight showed gastrointestinal symptoms (Armstrong et al., 1984). In some cases, survivors of acute arsenic exposures are left with long-term or permanent health problems. Damage to the nervous system has been described in two cases involving subjects exposed to relatively high doses of arsenic (Murphy et al., 1981; Goebels et al., 1990). In both cases, despite some improvement in nervous system functions, neurological symptoms persisted for 2-3 years following exposure.

3.3.2 Chronic arsenic exposure

Chronic exposure to lower levels of arsenic has long since been linked to adverse health effects in human populations. The earliest reports date back to the latter part of the 19th century when the onset of skin effects (including pigmentation changes, hyperkerotosis and skin cancers) were linked to the consumption of arsenic in medicines and drinking water (WHO, 2001). In the early 1900s, numerous reports of skin disorders in Argentina, Chile, Mexico and Taiwan, which were attributed to arsenic exposure via drinking water, were published (Zaldivar, 1974). In the 1940s the discovery of a case of lung cancer, believed to be the result of exposure to arsenical dust in a British factory, sparked a series of more detailed investigations into the matter. These in turn revealed unexpectedly high lung cancer rates in a number of different occupational exposure situations (WHO, 2001).

Of the earliest reported cases of chronic arsenic poisoning, that of Blackfoot disease (BFD) or Wu Chiao Ping as it is locally known, is perhaps the most notorious. This peripheral vascular disease, which leads to progressive gangrenes of the legs, has been recognised in parts of Taiwan since the 1920s. During the 1950s its prevalence increased markedly, and since the late 1950s it has been the subject of intensive study.

3.3.2.1 Vascular diseases

Exposure to arsenic has been linked to various vascular diseases affecting both the large and small blood vessels. Much of the early work on arsenic and vascular disease focused on effects in small vessels (i.e. BFD and other peripheral vascular diseases), while later research has been directed primarily at effects in larger vessels (cardiovascular and cerebrovascular diseases). The findings of key studies in this area of research are summarised in Table 3.5 but for convenience the discussion which follows is divided into subsections on the peripheral vascular diseases and the cardio- and cerebrovascular diseases. Some work has also been done on the possible link between arsenic exposure and hypertension (a known vascular disease risk-factor); a brief sub-section on this topic is also included here.

Table 3.5 Effects of arsenic on vascular system (source: WHO, 2001)

Authors, study design	Study Population	Source and level of arsenic exposure	Health effects, metric of exposure and and measure of association				Comments
Chen et al (1988b) case-referent	241 BFD patients and 759 age-sex-residence matched controls	Well water arsenic concentration = 1140 µg/L, with progressive decrease since 1956	Exp. time yrs	Peripheral vascular disease OR			OR adjusted for nutritional factors, family history of BFD, education, and evidence of skin lesions
			<1	1.0			
			1-29	3.0			
			>30	3.4 p<0.001 for trend			
Chen et al (1988b) cohort	789 BFD patients	Well water arsenic concentration = 1140 µg/L, with progressive decrease since 1956	End point	$SMR_{national}$	SMR_{local}		No adjustment for potential confounders
			Periph. vasc. Disease	1243***	351***		
			Cardio-vasc. Disease	209***	160**		
			Cerebrovasc. Accid.	118 NS	107 NS		
			*** p < 0.001; ** p<0.01				
Wu et al(1989) ecological	Mortality and population data for 1973-1986 in 42 villages in Taiwan	Well water arsenic concentration = 1140 µg/L, with progressive decrease since 1956	Age adjusted mortality rates per 100,000 As exposure				No increase in cerebrovascular accidents in either males or females at any exposure dose. Used published Taiwan data from 1964 to 1966; The Natelson method was used (Tseng et al, 1968; Kuo, 1964).
				< 0.30	0.30-0.59	≥0.60ppm	
			All vascular diseases				
			Males	364	421	573	
			females	278	371	386	
			peripheral vascular diseases				
			males	23	58	60	
			females	18	48	35	
			cardiovascular diseases				
			males	126	154	260	
			females	1	153	145	
Chen et al (1995) cross-sectional	382 men and 516 women residing in villages in BFD-endemic area	Well water arsenic concentration = 1140 µg/L, with progressive decrease since 1956	Hypertension				Exposure determined from residential history and village median well water arsenic concentration, based on the analysis of Kuo (1968; 126 samples from 29 villages, Natelson method). ORs adjusted for age, sex, disease status of diabetes, proteinuria, body mass index, fasting serum triglyceride levels
			Cum expos. mg x L^{-1}yr	OR			
			0	1.0			
			0.1 - 6.3	0.8 (0.2 – 3.2)			
			6.4 - 10.8	2.3 (0.8 – 6.8)			
			10.9 - 14.7	3.4 (1.2 – 9.2)			
			14.8 - 18.5	3.8 (1.4 – 10.3)			
			>18.5	2.9 (1.1 – 7.3)			
			unknown	1.5 (0.6 – 4.2)			

Table 3.5 Effects of arsenic on vascular system, continued

Authors, study design	Study Population	Source and level of arsenic exposure	Health effects, metric of exposure and and measure of association				Comments
Tseng et al (1996) cross-sectional	582 residents of BFD-endemic area	Drinking water As range 1 to 1097 µg/L, 50% between 300 and 700 µg/L	Exposure category mg/l years 0 1 - 19 > 20	Periph. vasc. dis. OR (CI 95%) 1 3.1 (0.9 – 10.4) 4.8 (1.4 – 16.7)			142 water samples from 114 well analysed for As Used ratio of ankle and brachial systolic arterial pressure as indicator of PVD. Measurement by Doppler ultrasound. Those with ABI of >1.20 excluded due to possible misclassification of peripheral vascular disease. Adjusted for age, sex, body mass index, cigarette smoking, diabetes mellitus, hypertension, plasma lipids
Chen et al (1996) ecological	Residents of 60 villages in arsenic endemic area in Taiwan. 1,355,915 person years	Well water arsenic concentration = 1140 µg/L, with progressive decrease since 1956	Cumulative mortality from birth to age 79 from ischemic heart disease (1973-1986) Exposure category As mg/L < 0.10 0.10-0.34 0.35-0.59 ≥0.60	 cumulative mortality % 3.4 3.5 4.7 6.6			Exposure determined from village median well water arsenic concentration, based on the analysis of Kuo (1968; 126 samples from 29 villages).
Chen et al (1996) cohort	263 BFD patients and 2293 referents from the 60 villages above	Same as above	Expo category $mg \cdot l^{-1} \cdot yrs$ 0 <10 10.0-19.9 20 +	Relative risk of isch. heart disease (CI) 1.00 2.2 (0.46-10.2) 3.3 (0.83-13.4) 4.9 (1.4-17.7)			Exposure determined from village median well water arsenic concentration, based on the analysis of Kuo (1968; 126 samples from 29 villages). Small number of deaths. Cox proportional hazard model adjusted for age, sex, smoking, body mass index, serum cholesterol, serum triglyceride level, hypertension, diabetes mellitus black foot disease. Relative risk of BFD patients vs non-BFD, 2.48 (1.1.4-5.4)
Hsueh et al., 1998 case-referent	74 cases of ISHD and 193 referents from the population of the Chen et al, 1995 study	Well water arsenic concentration = 1140 µg/L, with progressive decrease since 1956	Duration of drinking As containing water, yr >13 13-29 ≥ 30	IHD	OR 1.0 2.6 2.9	(CI) (1.0 - 6.4) (1.0 - 8.3)	Exposure determined from village median well water arsenic concentration, based on the analysis of Kuo (1968; 126 samples from 29 villages). OR Age- and sex adjusted No significant association with cumulative arsenic exposure

Table 3.5 Effects of arsenic on vascular system, continued

Authors, study design	Study Population	Source and level of arsenic exposure	Health effects, metric of exposure and and measure of association			Comments
Tsai et al (1999) Ecological	4 townships in BFD-endemic area, mortality in 1971-1994, compared to local and national rates	Well water arsenic concentration = 1140 µg/L, with progressive decrease since 1956	Mortality compared to local rates			National statistics were used to calculated expected deaths. 99% of causes of deaths based on diagnosis of a physician. Overlaps with earlier studies in the BFD-endemic area.
				SMR	CI	
			Hypertension	73	62 - 85	
			Isch. Heart dis.	175	159 - 192	
			Cerebrovasc. dis	114	108 - 121	
			Vasc. Dis.	356	291 - 430	
Chiou et al (1997) cross sectional	8102 males and females from the Lanyang Basin on the northeast coast of Taiwan	Arsenic in drinking water	Exposure category µg/L	Cerebrovascular disease OR (CV)	Cerebral infarction OR (CV)	OR adjusted for age, sex, smoking, alcohol intake, hypertension and diabetes. Exposure category determined by median arsenic concentratoin of well water.
			<0.1	1.0		
			0.1-50	2.5 (1.5-4.5)	3.4 (1.6-7.3)	
			50-299.9	2.8 (1.6-5.0)	4.5 (2.0-9.9)	
			≥300	3.6 (1.8-7.1)	6.9 (2.9-16.4)	
Engel & Smith (1994) Ecological	Mortality study from 30 US counties 1968-84	Arsenic in drinking water	Diseases of arteries, arterioles and capillaries			No effects were observed for all circulatory diseases, ischaemic heart disease or cerebral vascular disease. Expected numbers of deaths generated using US mortality rates. Arsenic concentrations were from public water supply records.
			Expos. category	SMRs (CI)		
			µg/L	Males	Females	
			5-10	110 (110-120)	110 (110-120)	
			10-20	110 (100-110)	110 (100-120)	
			>20	160 (150-180)	190 (170-210)	

Table 3.5 Effects of arsenic on vascular system, continued

Authors, study design	Study Population	Source and level of arsenic exposure	Health effects, metric of exposure and and measure of association					Comments
Lewis et al (1999) cohort	4058 members of The Church of Jesus Christ of Latter Day Saints in Millard Co., Utah	Range of exposure from 3.5 µg/L to 620 µg/L; median exposures range from 14 to 166 µg/L depending on location.		Males SMR	(CI)	Females SMR	(CI)	for 2073 cohort members, "most" had at least 20 years history of exposure in their respective towns. The balance of the cohort (n = 1985) were included if they had spent any lenght of time in the arsenic-affected community. Existing and historic arsenic concentrations used. Death rates for the state of Utah for the years 1960 to 1992 were used to generate the expected deaths. No indication of exposure-response relationship for any of the vascular health effects. Exposure for the highest exposure group likely to be overestimated because of introduction of low-arsenic water into one community, which was not considered in the analysis
			Cerebrovasc. Dis.	79	(62-99)	87	(71-106)	
			All heart dis.	80	(73-88)	81	(72-91)	
			Isch. heart dis.	76	(67-85)	64	(53-76)	
			Dis. of arter. & capill.	93	(61-135)	86	(52-132)	
			Arteriosclerosis	124	(69-204)	118	(68-188)	
			Aortic aneurysm	76	(35-144)	48	(6-173)	
			Hypert. heart dis.	220	(136-336)	173	(111-258)	
			Other heart dis.	94	(71-122)	143	(111-180)	
Rahman et al (1999a) cross-sectional	1595 people from 4 villages in Bangladesh. 1481 exposed to arsenic and 114 non exposed controls	Arsenic in drinking water. For 39, 36, 18, and 7%, the exposure was <0.5, 0.5 - 1, and >1 mg/L, and unknown, resp.	Expo category mg/L yrs	PR* for hypertension (CI)				Used existing arsenic water measurements (measured by flow-injection hydride generation AAS). Hypertension defined as >140 mmHg systolic BP together with >90 mmHg diastolic BP Study limited to the 1595 individuals out of 1794 eligible, who were at home at the time of the interview. 114 persons were considered unexposed and were used as the reference group. *PR = Mantel-Haenszel prevalence ratio adjusted for age, sex and BMI
			0	0.8 (0.3 – 1.7)				
			< 5	1.5 (0.7 – 2.9)				
			5 - 10	2.2 (1.1 – 4.4)				
			>10	3.0 (1.5 – 5.8)				
Cuzick et al, 1992 cohort	478 patients treated with Fowler's solution for 2 weeks - 12 years in 1946-60 and followed until 1990	Cumulative dose <500 mg , 500-999 mg, 1000-1999mg; ≥2000 mg	Mortality from vascular diseases	SMR	CI			The SMR's for the whole group. No dose-response relationship observed, but the numbers were small.
			Cardiovacular disease	91	74 – 110			
			Ischemic disease	85	60 – 110			
			Cerebrovascular disease	72	40-110			

Table 3.5 Effects of arsenic on vascular system, continued

Authors, study design	Study Population	Source and level of arsenic exposure	Health effects, metric of exposure and and measure of association			Comments
Enterline et al (1995) cohort	2802 men who worked in the smelter for ≥ 1 yr during 1940 -64, vital status followed 1941-1986	Ambient air in a smelter	Cum. exp. $mg \cdot m^{-3} \cdot yr$	Isch. Heart dis SMR	Cases	Exposure assessed from industrial hygiene data (available from 1938) and extrapolation from urinary arsenic concentrations
			< 0.75	108	55	
			0.75 - 2.0	103	67	
			4.0	107	74	
			8.0	122	87	
			20	128	91	
			≥ 45	132	46	
				90	8	
Hertz-Picciotto et al, 2000 Cohort	2802 men who worked in the smelter for ≥ 1 yr during 1940-64, vital status followed 1940-1976 (same cohort as in Enterline et al., 1995, but a shorter follow-up time)	Ambient air in a smelter	Cum. exp. $mg \cdot m^{-3} \cdot yr$	Isch. Heart dis RR	CI	20-year lag and work status imcluded in the model No effects found for cerebrovascular disease.
			< 0.75	1.0		
			0.75 –1.999	0.9	0.64-1.3	
			2.0-3.999	1.1	0.78-1.6	
			4.0-7.999	1.4	0.98-2.0	
			8.0-19.999	1.7	1.2-2.5	
			>20	1.5	0.95-2.5	
Lubin et al (2000) cohort	8104 white males employed for ≥ 1 yr before 1957. Vital status followed 1938 - 1987.	Ambient air in a smelter	Arteriosclerosis and coronary heart disease SMR 105 (CI 99-110; Cerebrovascular disease SMR 103 CI (93-115)			
Järup et al, 1989 cohort	3916 men who worked ≥ 3 mo in the smelter in 1928-1967. Vital status followed until 1981	Ambient air in a smelter. Categories for cumulative exposure < 0.25, 0.25 - 15, 15-100 and ≥ 100 mg m^3 yr	Ischaemic heart disease SMR 107 (CI 97-117); Cerebrovascular disease SMR 106 (CI 88-126)			In an earlier report (Axelson et al, 1978), a two-fold increase in mortality from cardiovascular disease
Tokudome & Kuratsune (1976); cohort	839 copper smelter workers	Ambient air in a smelter	7 Deaths from heart diseases vs 14.9 expected			
Armstrong et al (1979); cohort	1974 gold miners	Air-borne exposure to arsenic, radon, silica	Ischaemic heart disease SMR 103 (173 expected cases)			

Authors, study design	Study Population	Source and level of arsenic exposure	Health effects, metric of exposure and and measure of association	Comments
Simonato et al (1994); cohort	1330 gold mine and refinery workers	Air-borne exposure to arsenic, radon and silica	SMR for "diseases of the circulatory system" 54 (CI 39-73)	

Table 3.5 Effects of arsenic on vascular system, continued

Authors, study design	Study Population	Source and level of arsenic exposure	Health effects, metric of exposure and and measure of association	Comments
Sobel et al (1988); cohort	611 workers of a pesticide plant	Inhalation exposure to arsenic	SMR for all circulatory diseases 80 (CI 65- 98)	
Jensen & Hansen 1998) cross-sectional	32 arsenic exposed workers and 26 non-exposed referents	Average urinary As 35.9 for the exposed and 14.5 µmol/mol creatinine for the referents	Average systolic blood pressure 128 among the exposed, and 120 among the referents, p = 0.023	The exposed group included taxidermists, garden fence makers, week-end cottage constructors, wood impregnators, electric pole impregnators, new house constructors

Peripheral vascular diseases

As mentioned above, arsenic has been linked to development of the peripheral artery disease, Blackfoot disease (BFD) that is endemic in parts of Taiwan. The condition is characterized by an insidious onset of coldness and numbness in the feet, followed by ulceration, black discoloration and subsequently dry gangrene of the affected parts.

Studies from Taiwan have clearly demonstrated that exposure to arsenic via drinking water is associated with BFD, with significant exposure-response relationships relating both the duration and level of exposure to observed effects (WHO, 2001). For example, in a cohort of 789 BFD-patients followed for 15 years, Chen et al. (1988) have reported that there was a significant increase in the number of deaths from peripheral vascular diseases (and from cardiovascular diseases) relative to death rates in both the general Taiwanese population and among residents of the BFD-endemic area. The same authors have also demonstrated that in case-control study of 241 BFD-patients, there was a significant exposure-response relationship between the risk of BFD mortality and length of duration of residence in the area of arsenic-contaminated artesian well water.

An increased risk of peripheral vascular disease (PVD) was also found in a study of subjects residing in 42 villages located in the BFD-endemic area of south western Taiwan (Wu et al., 1989). Age-adjusted mortality rates for peripheral vascular diseases increased with increasing median concentrations of arsenic well water of < 0.30 mg/L, 0.30-0.59 mg/L and > 60 mg/L in a dose-response relationship. More recently, Tseng et al. (1996) have attempted to establish a link between long-term arsenic exposure and PVD morbidity using Doppler ultrasound techniques to detect the presence of disease. Again, the risk of PVD was found to increase with increasing cumulative exposure to arsenic; the effect was evident also among people whose exposure to arsenic had significantly decreased.

The extreme form and high prevalence of BFD found in Taiwan has not been observed in other regions. It is probable therefore, that other factors, such as malnutrition or concurrent exposures, are playing a role in the pathopyhysiology of the disease (WHO, 2001). There is, however, good evidence from several studies performed in other countries that exposure to arsenic causes other forms of PVD. For example, Swedish copper smelter workers (n=47) who had been exposed to arsenic (for a mean of 23 years), had a high prevalence of “white fingers” or Raynaud’s phenomenon compared with 48 controls (Lagerkvist et al., 1988). As the condition did not disappear during the summer, when workers took their long holiday, it was considered to be related to arsenic exposure.

Cardio- and cerebrovascular diseases

Studies linking exposure to arsenic and mortality from cardiovascular diseases are also summarized in Table 3.5. Whereas studies in Taiwan involving BDF-patients have shown significant associations, including exposure-response relationships between arsenic concentrations in well waters and death rates from cardiovascular disease (Chen et al., 1988; Wu et al., 1989; Chen et al., 1996; Tsai et al., 1999), drinking water studies conducted in other world regions, albeit at lower exposure levels, have been less conclusive (WHO, 2001). For instance, Engel and Smith (1994) carried out an ecologic mortality study in which mortality due to cardiovascular diseases in 30 US counties was compared to the expected numbers of deaths generated by US mortality rates. The results indicated excess mortality rates for diseases of the arteries and anomalies of the circulatory system. The standard mortality ratios (SMRs) for these diseases were elevated for areas with an arsenic concentration of greater than 20 ug/L, but wereclose to 1.0 in the two lower concentration categories (5-10 ug/L and 10-20 ug/L) for both sexes. SMRs for aneurysms and arteriosclerosis were also elevated for arsenic concentrations greater than 20 ug/L. The SMRs for congenital anomalies of the heart and for congenital anomalies of the circulatory system were elevated in females at arsenic concentrations of greater than 20 ug/L only **(**Engel & Smith, 1994).

A subsequent mortality study by Lewis et al. (1999) examined several mortality outcomes among a cohort of individuals from Millard County, Utah, USA. The cohort was assembled using historic membership records dating from the early 1900s through to the mid-1940s from the Church of Jesus Christ of Latter-Day Saints (Lewis et al., 1998b). SMRs were calculated separately for males and females using death rates from the State of Utah to generate the expected numbers for selected causes of death coded from the death certificates. Results indicate a significant excess of deaths for cardiovascular diseases (including hypertensive heart disease) among males (SMR=2.20) and among females (SMR=1.73), and all other heart disease among females (SMR=1.43) (Lewis et al., 1998a; 1999). When SMRs were analysed according to low (<1000 ppb-ug/L), medium (1000-4999 pbb-ug/L), and high arsenic exposure index values (5000 to >5000 ppb-ug/L), the increases of hypertensive heart diseases were not sequential (i.e. there wasno dose-response relationship) from low to high exposed groups (SMRs=2.37, 1.91, 2.29 respectively, for low, medium, and high groups). A non-significant excess of deaths from arteriosclerosis was also noted (Lewis et al., 1999).

In contrast, there is only limited evidence for an association between arsenic exposure and cerebrovascular diseases. A few Taiwanese studies have shown an elevated risk of death from cerebrovascular disease with increasing arsenic exposure, most notably that of Chiou et al. (1997). Other studies in this region have, however, not produced similar findings (Wu et al., 1989); elevations in mortality rates due to cerebrovascular diseases, if present at all, are only small

compared with those for cardiovascular disease (Tasi et al., 1999). Furthermore, studies from other countries provide only very limited support for the Taiwanese findings (WHO, 2001).

Studies involving occupationally-exposed subjects have also been used to explore the relationship between arsenic exposure and vascular diseases. Again, the weight of evidence points to a fairly strong association between arsenic exposure and cardiovascular diseases, but only a weak link with cerebrovascular diseases. Most of the studies of this type are concerned with miners and metal smelter workers where the inhalation of arsenic-polluted air is the main route of exposure (see Table 3.5). In the Tacoma cohort Enterline et al. (1995) reported a significant excess of ischaemic heart disease (428 deaths, $p< 0.01$), with a weak dose-response relationship. In an updated analysis of the same cohort, evidence of an association was stronger and a clear-cut dose-response relationship observed (Hertz-Picciotto et al., 2000). This is in marked contrast to an earlier study, when no excess in heart disease was found (Enterline and Marsh, 1982).

Mortality during 1939-1977 from diseases of the heart was elevated among the members of the Montana cohort (SMR 1.30 based on 1366 observed and 1051.5 expected cases, $p < 0.01$) (Lee-Feldstein, 1983). In a subsequent study among workers at the same smelter, no significant increase in mortality from arteriosclerosis/coronary heart disease or from cerebrovascular disease was observed (Lubin et al., 2000). Although the first report on the Rönnskär cohort reported a two-fold increase in the mortality from cardiovascular disease (Axelson et al., 1978), a later update found no relationship (Järup et al., 1989). In the Japanese smelter cohort (Tokudome & Kuratsune, 1976), there was a deficit in the mortality from heart diseases. No elevated mortality from cardiovascular disease mortality was observed among French or Australian gold miners, or US pesticide production workers (Simonato et al., 1994; Sobel et al., 1988; Armstrong et al., 1979).

Hypertension

Evidence for an association between long-term exposure to arsenic and the prevalence of hypertension is limited to only a few studies, two environmental and one occupational. Nevertheless, all three studies found elevations in blood pressure with arsenic exposure. Chen et al. (1995) studied a total of 382 men and 516 women residing in villages in the BFD-endemic regions of Taiwan. Arsenic-exposed residents had a 1.5-fold increase in age- and sex-adjusted prevalence of hypertension compared with residents in non-endemic areas. This study concluded that long-term arsenic exposure may induce hypertension in humans **(**Chen et al., 1995).

The prevalence of hypertension among residents in Bangladesh, with and without arsenic exposure, has been evaluated recently by Rahman et al. (1999). A total of 1,481 subjects exposed to arsenic contaminated drinking water and 114 unexposed subjects were analysed for their

time-weighted mean arsenic levels. There was a significant dose-response relationship between arsenic exposure and increased blood pressure ($p<0.01$). Potential limitations of the study include lack of information on other trace elements in the water, not all eligible participants were identified and that direct measurement of exposure rather than recall of exposure is preferred.

In a group of 40 Danish workers exposed to arsenic in different trades (average urinary arsenic level 22.3 umol/mol creatinine; twice that of the referents), blood pressure was slightly elevated among the exposed group, reaching statistical significance for the systolic but not for the diastolic value (Jensen & Hansen, 1998).

3.3.2.2 Cancer

The earliest indications that exposure to arsenic and cancer were related date back to the late 1930s and early 1940s. In the seminal investigation of 1948, a remarkably elevated relative cancer mortality rate from lung and skin cancer was observed amongst workers at a sheep-dip factory that manufactured sodium arsenite (Hill & Faning, 1948). Subsequently, Roth (1958) reported that autopsies of 47 winegrowers, who had showed signs of arsenic intoxication, revealed that 13 of the subjects had altogether 40 skin cancers and 19 had lung cancer. Case series indicated that the lung cancer mortality was unexpectedly high among Rhodesian gold miners; exposure to arsenic was considered an etiological factor (Osburn, 1957, 1969). Original suspicions that ingested arsenic could cause lung cancer were provided by a study in the Argentine province of Cordoba, where mortality records for all deaths occurring between 1949 and 1959 in areas with high arsenic level in drinking water (weighted average approximately 600 ug/L) were compared with cause-specific mortality rates from the entire province. Thirty five percent of all cancer deaths were related to respiratory organs (Bergoglio, 1964).

Detailed investigations into elevated cancer risks amongst copper smelter workers exposed to arsenic in the air were initiated in the 1960s; these studies were primarily concerned with the development of respiratory cancers, in particular lung cancers. Over the past 20-30 years, research effort has also focused on the likely relationship between various types of cancers and exposure to arsenic through the consumption of drinking water. Much of this type of work has centred on populations in the BFD-endemic parts of Taiwan, but there are reports of elevated cancer risks at multiple sites (notably lung, skin, bladder, kidney and liver) from other parts of the world including Japan, Chile and Argentina where subsets of the population are exposed to arsenic-contaminated drinking water. A considerable body of scientific research work has accumulated on the subject and several comprehensive reviews have been published in recent years (WHO, 1981, 2001; IARC, 1973, 1980, 1987).

Cancers of the lung, bladder and kidney

Exposures via drinking water

As mentioned above, the link between cancers of the lung, bladder and kidney and arsenic exposure in drinking water has been most thoroughly studied in Taiwan. Here, studies of differing design have consistently shown high mortality risks from lung, bladder and kidney cancers among populations exposed to arsenic via drinking water. Moreover, where exposure-response relationships have been investigated, the risk of cancer for these sites increases with increasing exposure.

The findings of selected epidemiological studies based on the Taiwanese populations are briefly outlined below; additional details are provided in **Table 3.6.** Chen and co-workers (Chen et al. 1985) published one of the first mortality studies; they investigated cancer mortalities in 84 communities in four townships located in the south-western coastal region of Taiwan (a known BFD-endemic area) and found a statistically significant excess of bladder, kidney, skin, lung and liver cancer deaths for both males and females, compared to the Taiwanese population as a whole. Areas with a greater Blackfoot disease generally had more of an excess of cancer mortality than did areas with lower Blackfoot disease prevalence (Chen et al., 1985).

Table 3.6 Studies on cancer following oral exposure to arsenic (via drinking water, unless otherwise stated; excludes skin cancers)

Source: WHO, 2001

Table 3.6 Studies on cancer following oral exposure (via drinking water, unless otherwise stated). For cancer of the skin, see Table 3.7

Authors, study design	Study Population	Source and level of arsenic exposure	Health effects, metric of exposure and and measure of association				Comments
Chen et al (1985) Ecological	BFD-endemic area of Taiwan; mortality 1968-1982	Drinking water up to 1.14 mg/L, decreasing with take into use of reservoir water starting in 1956		SMR (CI), Males	Females		Small intestine, oesophagus, rectum, stomach, naso-pharynx, leukaemia, thyroid were not significantly elevated in males or females. Population of Taiwan as the reference
			Bladder:	1100 (933-1267)	2009 (1702-2316)		
			Kidney:	772 (537-1007)	1119 (938-1400)		
			Liver:	170 (151-189)	229 (192-266)		
			Colon:	160 (117-203)	168 (126-210)		
			Lung:	320 (286-354)	413 (360-466)		
Chen et al (1986) case-referent	69 bladder, 76 lung, 65 liver cancer decedents in Taiwan in 1980-1982. 65 live controls matched by age and sex.	<40 years of use of artesian water in black foot disease endemic area up to 1.14 mg/L	OR for years of use of arsenic contaminated water:				Deceased cancer cases. OR's adjusted for age, sex, cigarette smoking, tea drinking, vegetarian habit, vegetable consumption frequency and fermented bean consuption frequency, when the factor was significant at p<0.1. Referents from the same area
			Site	none	1-20	21-40	>40
			Bladder	1.0	1.3	1.7	4.1 (p<0.01)
			lung	1.0	1.1	1.5	3.0 (p<0.01)
			liver	1.0	0.9	1.1	2.0 (p<0.1)
Chen et al (1988b) Cohort	Cohort of 789 Blackfoot disease patients (15 years and 7278 person years of follow-up).	Drinking water concentrations 350-1140 μg/L	SMR	National ref rate		local ref rate	10.6% lost to follow-up
			Bladder	3880	(p<0.001)	255 (p<0.01)	
			Kidney	1953	(NS)	160 (NS)	
			Prostate	1729	(NS)	268 (NS)	
			Lung	1049	(p<0.001)	284 (p<0.01)	
			Liver	466	(p<0.001)	248 (p<0.01)	
			Colon	381	(p<0.05)	230 (NS)	
			Esophagus	305	(NS)	222 (NS)	
			Stomach	194	(NS)	202 (NS)	

Table 3.6 Studies on cancer following oral exposure (via drinking water, unless otherwise stated). For cancer of the skin, see Table 3.7

Authors, study design	Study Population	Source and level of arsenic exposure	Health effects, metric of exposure and and measure of association				Comments
Wu et al (1989) Ecological	Mortality and population data from 1973-1986 in 42 villages in Taiwan.	Used data from the 1964-1966 survey of 155 wells in 42 villages and used village medians in the analysis	Age-adjusted mortality rates per 10^5 in males by well As conc.				Observed numbers of deaths smaller than in the Chen et al 1992 study, although the person-years are identical.
			Males	< 300	300 - 599	≥600 µg/L p	No significant association for leukemia or cancer of nasopharynx, oesophagus, stomach, colon or uterine cervix
			Bladder	22.6	61.0	92.7 < 0.001	
			Kidney	8.4	18.9	25.3 < 0.05	
			Lung	49.2	100.7	104.8 < 0.001	
			Liver	47.8	67.6	86.7 < 0.05	
			Prostate	1.0	9.0	9.2 < 0.05	
			Females				
			Bladder	25.6	57.0	111.3 < 0.001	
			Kidney	3.4	19.4	58.0 < 0.001	
			Lung	36.7	60.8	122.2 < 0.001	
			Liver	21.4	24.2	31.8 NS	
Chen & Wang (1990) Ecological	Mortality from malignant neoplasms in 1972-83 in 314 precincts and townships in Taiwan	74% or precincts had <5% wells with ≥ 50µg/L As, 15% has 5-14% and 12% had ≥15% such wells. Village mean used in analysis.	Statistically significant association between arsenic level in well water and mortality from the cancer of the lung, liver, kidney, bladder, skin, prostate, and nasopharynx after adjustment for indices of urbanisation and industrialisation				Nearly all cancer deaths among the arsenic exposed included in the Chen et al (1985) study No numerical risk estimates given.
Chiang et al (1993), ecological	Incident bladder cancer cases 1981-5 identified from tumour registry in 4 BFD-endemic and 2 neighbouring counties vs whole Taiwan	Arsenic-contaminated water in the BFD-endemic area in Taiwan	Average annual age-adjusted incidence of bladder cancer per 100 000 in the 4 counties 23.5, in the neighbouring counties, 4.45 and 2.29 in the whole of Taiwan				Tumour registry not validated
Chiou et al (1995) Cohort	263 blackfoot disease patients and 2293 residents in Taiwan. Follow-up of 7 years.	Cumulative As exposure for drinking water from village median well As concentration as determined in the 1964-6 survey	Cum expos mg/L-yr	SMR (CI) Bladder Cancer	Lung cancer:		Adjusted for age, sex, smoking, black foot disease Deaths not overlapping with older studies in Taiwan. Cases of BFD and referents largely from different villages
			0	100	100		
			0.1-19.9	160 (44 – 560)	274 (69 – 1100)		
			20+	360* (110 – 1220)	401 (100 – 1612)		

Table 3.6 Studies on cancer following oral exposure (via drinking water, unless otherwise stated). For cancer of the skin, see Table 3.7

Authors, study design	Study Population	Source and level of arsenic exposure	Health effects, metric of exposure and and measure of association	Comments
Guo et al (1997) Ecological	243 Taiwanese townships – approximately 11.4 million residents. Incident cases of urothelial and kidney cancer 1980-87	Arsenic measured in over 80,000 wells from 1974-1976 in 78% of townships average As content was nondetectable, in 91, below 50 and in 99.5%, below 640 μg/L	Estimated rate difference per 10^5 for 1% increase in the proportion of wells in the highest exposure category (640 μg/L): Males / Females Transitional cancer/bladder 0.57 / 0.33 Transitional cell/kidney 0.03 / 0.14 Transitional cell/ureter 0.11 / 0.10 All urethral cancer 0.056 / 0.027	Used mercuric bromide method to analyse arsenic. Smoking not included in the models as not good predictor for any cancer in this study. Tumor registry not validated
Tsai et al (1999) Ecological	4 townships in BFD-endemic area in Taiwan, mortality in 1971-1994, compared to local and national rates	Drinking water up to 1.14 mg/L, decreasing with take into use of reservoir water starting in 1956	Cancer SMRs for females and males combined, compared to local rates All malignant 219 (211-228) Oesophagus 167 (130-212); Lung 310 (288-334) Stomach 136 (117-146); Bone 246 (177-334) Small intestine 210 (120-354); Prostate 252 (186-334) Colon 149 (120-183); Bladder 892 (796-996) Liver 183 (169-198); Kidney 676 (546-827) Nasal 300 (214-409); Lymphoma 163 (123-211) Laryngeal 178 (120-255); Leucaemia 134 (104-170)	Age- and sex-specific mortality rates based on population data from Miniistry of Interior, deaths from computer data base on deaths. 99% of causes of deaths based on diagnosis of a physician. All cancers confirmed by pathological examination. Overlaps with earlier Taiwan studies.
Morales et al, 2000 Ecological	Mortality and population data from 1973-1986 in 42 villages in Taiwan.	Drinking water concentrations 350-1140 μg/L	SMRs men and women, Well water As (μg/l) / Bladder cancer / Lung cancer <50 1002 156 50-100 415 143 100-200 1047 243 200-300 766 308 300-400 744 197 400-500 2968 365 500-600 1490 332 600+ 3270 514	Used data from the 1964-1966 survey of 155 wells in 42 villages and used village medians in the analysis

Table 3.6 Studies on cancer following oral exposure (via drinking water, unless otherwise stated). For cancer of the skin, see Table 3.7

Authors, study design	Study Population	Source and level of arsenic exposure	Health effects, metric of exposure and and measure of association				Comments
Hopenhayn-Rich et al (1996a, 1998) Ecological	Residents in Cordoba vs rest of Argentina	In the high exposure group, in two selected towns, 42/61 and 49/57 measurements ≥ 40 µg/L. Highest measured concentration 533 µg/L	SMRs (95% CI) by exposure group: Males				No smoking data, but no difference in COPD, used as surrogate, between exposure groups Cancer of liver, stomach or skin not significantly related to arsenic exposure
				low	intermed.	high	
			Bladder	80 (66-096)	128 (105-153)	214 (178–253)	
			Lung	92 (85-098)	154 (144-164)	177 (163–190)	
			Kidney	87 (66-110	133 (102-168)	157 (117– 205)	
					Females		
			Bladder	122 (86-167	139 (93-199)	182 (119 – 264)	
			Lung	124 (106-142)	134 (112-158)	216 (183 – 252)	
			Kidney	100 (71-137)	136 (94-189)	181 (119 – 264)	
Rivara et al (1997 Ecological	Region 2 (high exposure) Northern Chile compared to Region 8 (low exposure). Region 2 is arsenic endemic area Mortality 1952-1990	Drinking water arsenic concentration in 1950 – 1992 ND to 860 µg/L in different locations in Region 2. Average concentration < 200 before 1958, >500 1959-1977, < 100 thereafter	Cancer mortality		rate ratio	CI	Air levels of arsenic were measured in some locations and concentration s up to 2.7 µg/m^3 were observed at Chuquichamata, a copper smelter area in Region 2.
			All cancer:		1.2	1.17 - 1.21	
			Lung		5.6	5.3 - 6.3	
			Bladder		6.7	5.9 – 7.7	
			Kidney		2.7	2.4 – 3.1	
			Larynx		3.2	2.7 – 4.0	
			Liver		1.1	1.0 – 1.2	
Smith et al (1998) Ecological	Region 2 Chile (1989-1993) compared to the rest of Chile.	Drinking water Avg. 43-568 µg/L (1950-1994) Exposure decreased over time: 569 µg/L (1955-69) to 43 µg/L (1990-94)	SMR (CI)	Males	Females		Routinely collected arsenic concentration measurements. Population is partially overlapping Rivara (1997)
			Bladder cancer:	600 (480-740)	820 (630-1050)		
			Lung cancer :	380 (350-410)	301 (270-370)		
			Kidney cancer :	160 (110-210)	270 (190-380)		
			Liver cancer :	110 (80-150)	110 (80-150)		
Ferreccio et al (1998, 2000) Case-control	Three Regions in Northern Chile. 151 lung cancer cases in 1994-6, histologically confirmed. 2 referents per case	Drinking water levels measured in 1950-1996 by water companies	Mean lifetime exposure mg/L		OR (CI)		Some gaps in exposure measures in some years Patients with skin lesions had higher risk of lung cancer. Adjusted for age, sex and smoking status, occupational history.
			0 - 0.01		1		
			0.01 - 0.029		1.7 (0.5 – 5.1)		
			0.03 - 0.049		3.9 (1.2 – 13.4)		
			0.05 - 0.199		5.5 (2.2 – 13.5)		
			0.2 - 0.40		9.0 (3.6 – 22)		

Authors, study design	Study Population	Source and level of arsenic exposure	Health effects, metric of exposure and and measure of association			Comments
Tsuda et al (1989, 1995) Cohort	Residents of Niigata, Japan (n = 467).	Drinking water contaminated with As from a factory in 1955-9. Water analysed for arsenic in 1959	SMR for ≥ 1 mg/L compared to 0 mg/L			97.2% of residents in 1959 followed for vital status 1959-1992. RR controlled for smoking and age: Gender was correlated with smoking.
			All causes of death	174	110 - 274	
			All cancer	482	209 - 1114	
			Lung cancer	1972	434 - 895000	
			Mortality from "urinary" cancer significanlty elevated, SMR 627 (CI 171 - 1839).			

Table 3.6 Studies on cancer following oral exposure (via drinking water, unless otherwise stated). For cancer of the skin, see Table 3.7

Authors, study design	Study Population	Source and level of arsenic exposure	Health effects, metric of exposure and and measure of association	Comments
Bates et al (1995) Case-control	117 newly diagnosed histologically confirmed cases of bladder cancer in Utah, US and 266 population referents	Drinking water; Cumulative dose categories: <19 mg; 19-<33 mg; 33-<53 mg; ≥53 mg	OR for bladder cancer, adj. for sex, age, smoking, exposure to chlorinated water, history of bladder infection, high risk occupation, education level, urbanisation, in different cumulative exposure groups: 1.00 ; 1.6 (0.8 – 3.2); 1.0 (0.4 – 2.0); 1.4 (0.7 – 2.9)	Among ever smokers with As expousre 10-19 years earlier, an association between OR of quartiles of total proportion or arsenic contining drinking water of total daily fluid intake.
Buchet & Lison (1998) Ecological	Belgium, residents in areas with various exposures to arsenic.	Exposure from air (0.3 µg/m^3 annual mean); and water (20-50 µg.As/L). Daily geometric mean U-As 35 µg in the most exposed group (smelter area), 7-12 µg/d in the less exposed	Cancer of lung, kidney, bladder and leukemia studied. Increased RR, 1.3 (1.14 – 1.43) observed for lung cancer in males in smelter area compared to a lesser-exposed group.	Directly standardized rate ratios (SRRs) were used. The authors explained the increase lung cancer risk by occupational exposure. Other "arsenic-linked" diagnosis was analyzed showing no elevated risks.
Hinwood et al (1999) ecological	Cancer incidence in 22 areas in Victoria, Australia, in 1982-91. Population size in 1986, 152 246	Soil/water arsenic elevated in some parts, medians for low water As areas 1 - 2 µg/L, and between 13 and 1077 for high water-As areas (median of medians, 80 µg/L)	SIR were below 120, and the confidence interval included unity for cancers of nasal cavity, lung, bladder, stomach, colon, rectum, Hodgkin's lymphoma, non-Hodgkin's lymphoma, multiple myeloma, acute and chronic lymphatic leukaemia, and acute myeloid leukaemia. The SIR for prostate cancer was 114 (CI 105-123, melanoma 136 (124-148), breast 110 (103-148), and for chronic myeloid leukaemia 154 (113-210. For liver cancer, the SIR was 53 (CI 34-82).	No information on coverage or frequency of water arsenic sampling. Postal codes that were used for calculating expected cases, represent large geographic areas and may lead to random misclassification. Rain water reservoirs at least at present are an important alternative source of drinking water again leading to exposure misclassification

Table 3.6 Studies on cancer following oral exposure (via drinking water, unless otherwise stated). For cancer of the skin, see Table 3.7

Authors, study design	Study Population	Source and level of arsenic exposure	Health effects, metric of exposure and and measure of association			Comments
Lewis et al (1999) Cohort	Mormons in Millard County, Utah, USAs	Median range: 14 µg/L - 166µg/L	SMR (CI)	Males	Females	Historic arsenic concentrations in drinking water used.
			All causes	91 (86 - 96)	96 (92 - 104)	
			Non-malign. resp.	68 (54 - 85	93 (70 - 120)	Death rates for the state of Utah for the years 1960 to 1992 were used to generate the expected deaths.
			All cancer	82 (70 - 95)	73 (61 - 87)	
			Large intestine	50 (28 - 99)	74 (40 - 124)	
			Biliary tract &liver	85 (18 - 248)	142 (57 - 293)	Decreased SMR for lung and bladder cancer and all cancers may be due to lower prevalence of smoking among cohort members than in the reference population of the State of Utah.
			Respiratory System	57 (38 - 82)	44 (16 - 95)	
			Prostate	145 (107 - 191)		
			Kidney	175 (80 - 332)	160 (44 - 411)	
			Bladder & other urinary organs	42 (8 - 122)	81 (10 - 293)	Exposure for the highest exposure group likely to be overestimated because of introduction of low-arsenic water into one community, which was not considered in the analysis
Kurttio et al (1999) Case-referent	61 bladder and 49 kidney cancer cases and 275 referents not serviced by municipal drinking water supply, Finland	5% of reference group had arsenic in drinking water >5 µg/L and 1% (11/275) had consumed > 10 µg/L. Arsenic in drinking water <0.05 to maximum 64 µg/L. Detection limit 0.05 µg/L	Age-, sex- and smoking-adjusted risk ratios for bladder cancer when exposure 3-9 years prior to diagnosis			No association between cumulative arsenic exposure and bladder cancer. No association between well water arsenic and kidney cancer
			As in water µg/L	RR	CI	
			< 0.1	1.0		
			0.1-0.5	1.5	0.8 - 3.1	
			≥ 0.5	2.4	1.1 - 5.4	

Authors, study design	Study Population	Source and level of arsenic exposure	Health effects, metric of exposure and association		and measure of	Comments
Cuzick, et al (1992) cohort	478 patients treated with Fowler's solution for 2 weeks - 12 years in 1946-60 and followed until 1990	Exposure from treatment with Fowler's solution. Cumulative dose <500 mg , 500-999 mg, 1000-1999mg; ≥2000 mg	Mortality from cancer in the entire cohort			No dose response observed
				SMR	CI	
			All cancer	95	17 – 130	
			Bladder	307	101 – 730	
			Liver	123	40 – 470	
			Hematopoietic system	38	1 – 200	
			Digestive organs	119	70 – 190	
			Stomach	99	30 – 170)	
			Respiratory System	100	50 – 170	
			Skin	244	8 – 1400	

Chen and co-workers also performed a case-referent study on malignant neoplasms in the same population (Chen et al., 1986). The cases comprised persons who had died of bladder, lung or liver cancer, the diagnosis having been confirmed by biopsy or other techniques. The results demonstrated an increasing risk of cancers of the lung, bladder and liver with increasing duration of exposure. The trend remained significant for cancers of the lung and bladder after adjustments for age, sex, cigarette smoking, tea drinking, vegetarian habits and vegetable consumption, and fermented bean consumption (all potential confounders) had been made (Chen et al., 1986).

Cancer mortality statistics of residents from 42 villages in five townships in the BFD-endemic part of Taiwan (i.e. a smaller, but partly overlapping population sample relative to that considered by Chen et al. (1985, 1986)) have been analysed by Wu et al. (1989). The mortality data spanned the period 1973-1986; well water arsenic concentrations had been monitored in the early 1960s and were used to classify the villages into three categories based on median well water concentrations, < 300 ug/L, 300-590 ug/L and > 600 ug/L. Again, the age-adjusted mortality rates for lung, liver, kidney, bladder (and skin) cancer showed a significant dose-response increase in relation to drinking water arsenic concentration in both men and women (Wu et al., 1989).

An island-wide ecologic study of cancer mortality was conducted by Chen & Wang (1990) using data on deaths from cancer in 1972-83 and on arsenic concentrations in well water from 1974-76. The average township well water arsenic concentration was taken as the indicator of arsenic exposure. The relationship between arsenic exposure and mortality from cancer at 21 different sites was analysed by multiple linear regression, the results of which (after adjusting for levels of industrialisation and urbanisation) indicated that the magnitude of the increase in risk associated with arsenic concentration in well water was similar for both males and females for nasal cavity, lung, skin, bladder, and kidney cancers. Mortality from liver cancer was three times higher for men than for women. In addition, a positive association between well water arsenic and mortality from prostate cancer was observed (Chen et al., 1990).

The incidence of bladder cancer has been investigated by (Chiang et al., 1993) who found a higher annual incidence of bladder cancer (23.53 per 100,000 persons) in the BFD-endemic area compared with the average incidence in Taiwan as a whole (2.29 per 100,000 persons). The ratio of male to female bladder cancer in the BFD-endemic area and the neighbouring area was 1.24 and 1.09, which was lower than that in all of Taiwan (2.75) and compared with elsewhere around the world. The lack of disparity of bladder cancer rates between males and females supports the view that a common environmental factor shared by both sexes in the endemic area is responsible (Chiang et al., 1993). Another study found increased incidence rates for bladder cancers and transitional kidney cell cancers when incidence rates at high and low exposures to arsenic were compared (Guo et al., 1997).

Deaths from cancer occurring between 1986-1993 in a study population of 263 BFD-patients and 2,293 healthy subjects, not previously included in the Taiwanese studies, were analysed as part of a cohort study by Chiou et al. (1995). A statistically significant positive association between arsenic exposure (i.e estimated cumulative arsenic exposure from drinking artesian well water in $mg/yr/L^{-1}$) and cancer of the lung and bladder was found to exist even after adjustment for age, sex, cigarette smoking and Blackfoot disease status.

The work of Tsai and colleagues (Tsai et al., 1998) indicates that reductions in drinking water arsenic concentrations may have contributed to a decrease in the incidence rates of various cancers. Analysis of age-adjusted mortality rates for cancers of the lung, liver, bladder and skin combined in 4 townships in Taiwan, where there had been a fall in arsenic concentrations in drinking water since the 1970s, showed a gradual decrease in the risk of cancer in males aged > 40 years. In women the lowest risk was found to be in the most recent time periods studied (i.e. since 1988) irrespective of age, while for men < 40 years of age little change was observed.

Reports of increased cancer risk from exposure to exposure to arsenic in drinking water are not confined to Taiwan; studies from Argentina, Chile Japan and Finland have also demonstrated positive associations. For example, a small historical cohort study carried out between 1959-1992 in the Niiagata Prefecture, Japan, followed 454 subjects exposed to arsenic-contaminated well water; the contamination arose as a result the discharge of wastewater effluents from a factory producing arsenic trisulfide (King's yellow). This study found that subjects exposed to arsenic in well water of greater than 1 mg/L had a significant number of excess deaths from lung cancer (SMR=15.69, number observed = 8) and urinary tract cancer (SMR=31.18, number observed = 3) while subjects exposed to moderate or low concentrations of arsenic of 0.05-0.99 mg/L and less than 0.05 mg/L respectively showed a nonsignificant excess for lung cancer at the 0.05-0.99 mg/L level. Significantly elevated SMRs were also found for liver and uterine cancers with SMRs of 7.17, and 13.47 for exposures >1 mg/L (2 deaths were observed for each of these causes). A strong association was also observed between arsenic-induced lesions identified in 1959 and subsequent mortality from lung cancer (Tsuda et al., 1995).

A similar study was carried out in Northern Chile; cancer mortality data for Region II (an area where arsenic concentrations in drinking water had been high; range <100 ug/L to 570 ug/L) covering the period between 1989 and 1993 region were compared with age-adjusted mortality rates for the rest of Chile. Mortality rates for both lung and bladder cancers were elevated in Region II; SMRs for bladder cancer were 6.0 (95% CI= 4.8-7.4) for men and 8.2 (95% CI=6.3-10.5) for women. The SMRs for lung cancer were 3.8 (95% CI = 3.50-4.10) for men and SMR=3.1 (CI = 2.70-3.70) for women in this region, and smoking did not appear to be a major confounding factor (Smith et al., 1998). In a more recent Chilean study, based on a set of 151 lung

cancer patients (and 417 referents), lung cancer risk was found to increase in a dose-response relationship over five exposure categories. The increased risk was statistically significant at concentrations of 30-50 ug/L and above (Ferreccio et al., 1998, 2000).

Increased mortality from lung and bladder cancers was also found to be linked to increased drinking water arsenic concentrations in the eastern region of the Cordoba province in Argentina (Hopenhayn-Rich et al., 1996). Mortality data from 26 counties in the Cordoba province for the period 1986-1991 were compared with estimated mortality data for the whole of Argentina. The counties were divided into three exposure groups - low, medium and high - depending on their drinking water arsenic concentration (limited number of available measurements) and on the number of reports of arsenical skin diseases). The mortality from lung, kidney and bladder cancer was lowest in the counties with the presumed lowest drinking water concentration, intermediate in the medium exposure counties and greatest in the high-exposure counties (average concentration in the high-exposure group=178 ug/L in drinking water). Despite the different genetic composition and the high protein diet of the study population, the findings generally support results from studies in Taiwan (Hopenhayn-Rich et al., 1996; 1998).

A study of the risk of bladder and kidney cancer in a cohort of people from Finland that had been using drilled well water as drinking water over a period of 13 years (1967-1980) has recently been published (Kurttio et al. 1999). The study population comprised a group of 61 bladder cancer cases, 49 kidney cancer cases and 275 control subjects; exposure history was reconstructed from questionnaire data on residence and from measurements of arsenic in the well water made in 1996 (range < 0.05 – 64 ug/L; median 0.14 ug/L). No association was made for kidney cancer. However, in the case of bladder cancer, there was an increased risk associated with an increased arsenic intake during the third to ninth year prior to the cancer diagnosis, which reached statistical significance in the high-dose group (i.e. well arsenic > 0.5 - 64ug/L). Bladder cancer risk ratios for longer latency periods of 10 years or more were not elevated.

Not all studies of populations exposed to arsenic via drinking water have conclusively shown positive findings for increased, lung, bladder and kidney cancer (see **Table 3.6**). Several mortality studies from the USA, for example, have not shown positive associations between ingested arsenic and lung cancer. An ecological study based on records of average drinking water arsenic concentration at the county level found no significant excess county lung cancer mortality (Engel & Smith, 1994). The case-referent study conducted by Bates et al. (1995) as part of the US National Bladder Cancer Study involving communities in Utah showed no significant increase in bladder cancer risk with increasing exposure to arsenic in drinking water in non-smokers. However, among smokers, there is some evidence to suggest that bladder cancer risk may be associated with arsenic intake (two indices of arsenic exposure were used, but only one of the two

gave a positive result). The drinking water arsenic concentrations were relatively low, 0.5 – 160 ug/L with an average of 5.0 ug/L.

A recent analysis by Lewis et al. (1998b, 1999) of cancer incidence among Mormons in Utah found no evidence of excess deaths for lung or bladder cancer among males or females. However, the study indicated a slightly elevated, but not statistically significant mortality from kidney cancer in both males and females (SMR = 1.75 and 1.60, respectively). Significant excess mortality from nephritis and nephrosis, a noncancerous condition of the kidneys, for males (SMR=1.72) and females (SMR=1.21, non-significant) leaves the possibility that the kidney is a target organ of arsenic for noncancerous conditions (Lewis et al., 1998b).

Studies in Belgium and Australia have also failed to find conclusive evidence of a link between arsenic exposure in drinking water and cancers of the lung, bladder and kidney. Buchet & Lison (1998) reported that mortality ratios did not support an association of cancer with drinking water exposures in a population living in the vicinity of a conglomeration of non-ferrous smelters. Arsenic concentrations were again relatively low, the area of highest exposure having measured concentrations in the range 20-50 ug/L. Similarly in Victoria, Australia Hinwood et al. (1999) SIRs were below 120 (with the confidence interval including unity) for most cancers, including lung and bladder.

In addition to drinking water, the ingestion of Fowler's solution (potassium arsenite) by individuals has also been associated with elevated cancer mortality. An excess of skin cancer and a significant excess of bladder cancer mortality have been observed in a cohort of patients exposed to Fowler's solution (Cuzick et al., 1992).

Exposures via inhalation

Studies on populations occupationally exposed to arsenic, such as non-ferrous metal smelter workers, pesticide manufacturers and miners, have consistently demonstrated an excess lung cancer risk among those exposed. Dose-response relationships have been investigated in those populations were there is sufficient information on the levels of exposure. The most important studies of this type are based on data obtained from three copper smelters, in Tacoma (Washington, USA), Anaconda (Montana, USA) and Rönnskär (Sweden). In all three cohorts, a statistically significant increase in lung cancer risk with increasing exposure has been demonstrated.

Results of studies from the Tacoma copper smelter have been published in a series of papers (Pinto & Bennett, 1963; Pinto et al., 1977, 1978; Enterline & Marsh, 1980, 1982; Enterline et al., 1987a, 1995). The most recent considers mortality rates among 2,802 men, all of whom had

worked at the smelter for at least one year during the period 1940-1964 (Enterline et al., 1995). An increase in lung cancer risk with increasing cumulative arsenic exposure was observed (SMR of 316 in the highest exposure category). When the SMR is plotted against cumulative arsenic exposure on an arithmetic exposure scale, relatively larger increments in respiratory cancer risk are observed at low exposure levels, i.e., the dose-response curve is concave downward (Figure 3.2).

Figure 3.2 Respiratory cancer risk in three copper smelter cohorts
Source: Enterline et al., 1995 (PENDING)

Elevated lung cancer risks among workers in the Anaconda copper smelter have also been well documented in the literature (Lee and Fraumeni, 1969; Lee-Feldstein, 1983, 1986, 1989; Lubin et al., 1981; Welch et al., 1982; Brown and Chu, 1983a,b). The study population of the most recent cohort study (Lubin et al., 2000) consists of 8,014 white males, who were alive on 1 January 1938 and who had been employed at the smelter at least 12 months prior to 1957. Vital status was followed from 1938 to 1987. In the "heavy" arsenic exposure work areas the estimated mean airborne arsenic concentration was 11.3 mg/m^3, and for the "medium" and "light" exposure areas it was 0.6 and 0.3 mg/m^3, respectively. For each worker, the cumulative exposure was estimated from his time of working in different work areas. Of the total 4,930 known deaths amongst the study population, 446 were due to lung cancer (SMR = 155). A trend of increasing risk with increasing estimated exposure was seen; the risk increased linearly with length of employment in each exposure category.

The elevated lung cancer incidence among workers of the Rönnskär smelter in northern Sweden was originally reported in a population-based case-referent study in St Örjan parish in 1978 (Axelson et al., 1978). Thereafter, studies using both cohort and case-referent approaches have been published (Wall, 1980; Pershagen et al., 1981, 1987; Järup et al., 1989; Sandström et al., 1989; Järup & Pershagen, 1991; Sandström & Wall, 1993). The study population comprises 3916 male smelter workers, who had worked for at least 3 months in the smelter between 1928 and 1967. Using air concentrations estimated by the factory industrial hygienists, each work site has been characterised by an exposure level during three consecutive time periods, and the workers' cumulative exposure derived from his working history in these different work sites. Information on mortality was compiled from death certificates, and mortality rates due to lung cancer compared with local rates. A dose-dependent increase in lung cancer mortality was observed, and a statistically significantly increased risk was observed even in the lowest exposure category, that is < 0.25 mg/m^3/yr. However, in a nested case-referent study on the interaction between smoking and arsenic exposure little increased risk of lung cancer due to arsenic exposure was observed among smokers or non-smokers in exposure categories below 15 mg/m^3/yr (Järup & Pershagen,

1991). In most subcohorts, and in the total cohort, the mortality increased with increasing average intensity of exposure, but no clear-cut trend was observed for the duration of exposure. Exposure to sulphur dioxide was also assessed. The lung cancer risk was elevated in all sulphur dioxide-exposed groups, but there was no dose-response relationship between cancer risk and the estimated cumulative sulphur dioxide exposure.

Collectively, these three studies demonstrate a statistically significant excess risk of lung cancer at arsenic exposure levels of approximately > 75 mg/m^3/yr. The risk seems to increase more rapidly with dose at low cumulative dose levels than at higher exposures. It is interesting to note that the general form of the dose-response is rather similar in the three studies; however, the relative risks differ substantially between the Swedish study on one hand, and the American studies on the other (Figure 3.2). Although these groups of workers will have been exposed to other chemicals in addition to arsenic, it is considered unlikely that some other common factor could explain the findings. The role of tobacco smoking has been considered in several studies and was not generally found to be the cause of the increased lung cancer. It was, however, found to be interactive with arsenic in increasing the risk of lung cancer (WHO, 2001).

Increased lung cancer risks have also been observed in workers employed at pesticide manufacturing plants (Ott et al., 1974; Sobel et al., 1988; Mabuchi et al., 1979, 1980) and amongst tin miners in the UK and China (Hodgson & Jones, 1990; Qiao et al., 1997) and gold miners in France (Simonato et al., 1994), Canada (Kusiak et al., 1991, 1993) and Australia (Armstrong et al., 1979). Furthermore, several studies have reported an increased mortality from lung cancer in populations residing in areas close to arsenic-emitting industries, including for example, non-ferrous metal smelter complexes (Blot & Fraumeni, 1975; Brown, et al., 1984; Pershagen, 1985) and factories producing arsenical pesticides (Matanoski et al., 1981).

In contrast to the situation for lung cancers, kidney or bladder cancer risks are not consistently elevated in studies among people occupationally exposed to arsenic. Although early autopsy series (Roth, 1955, 1957a; b) on wine growers have linked exposure to arsenic to hepatic angiosarcoma, later studies have failed to provide conclusive evidence for such a link. Among 168 persons diagnosed with hepatic angiosarcoma in the USA, occupational exposure to arsenic could be demonstrated in only four cases and exposure to Fowler's solution in only six (Falk et al., 1981a,b). There was no significant association of arsenic exposure with kidney cancer in the Tacoma smelter cohort (Enterline et al., 1995) or in the 1938-1977 follow-up of the Anaconda cohort (Lubin et al., 1981). In addition, no increase in kidney cancer was observed in the French gold miner cohort (Simonato et al., 1994), in the US pesticide producer cohort (Sobel et al., 1988) or "urogenital organs" in the Swedish cohort (Sandström et al., 1989). This difference between the occupational and environmental studies may reflect lower systemic concentrations of arsenic after inhalation exposure (WHO, 2001).

Skin cancer and precancerous lesions of the skin

Several early case reports have suggested that arsenic from medicinal use, drinking water and occupational exposure may be related to skin diseases, including cancer (Hill & Fanning, 1948; Zaldivar, 1974). Exposure to arsenic via drinking water has since been shown to be associated with an increased risk of skin cancer and other skin diseases.

Skin cancer often arises from a keratotic change, the developed forms of which are classified as Bowen's disease; keratosis in turn may be preceded by disturbances in the skin pigmentation (hyper- and/or hypopigmentation). Arsenical skin cancers are usually squamous or basal in histologic type and arise primarily on unexposed areas of the body, including the palms and feet (Scotto et al., 1996). It has been hypothesized that arsenic combines with sulphydryl groups in body tissues and interferes with pyruvate-oxidase activity (see section 3.2.1.6), both mechanisms that are associated with cancers of the skin (Leonard & Lauwerys, 1980).

The cutaneous effects of ingested arsenic have been most intensively studied in environmentally exposed populations in Taiwan, South America, India, Mexico and the USA; a representative selection of these studies are summarized below and in **Table 3.7** .

Table 3.7 Effects of arsenic exposure on the skin (Source: WHO, 2001)

Authors study design	Study Population	Source and level of arsenic exposure	Health effects, metric of exposure and and measure of association	Comments
Tseng et al (1968), Tseng (1977) cross-sectional	40,421 males and females in 37 villages in arsenic southwest Taiwan high exposure area and 7500 in low exposure area	142 water samples from 114 well analysed for As. Variation 1 to 1097 µg/L, 50% between 300 and 700 µg/L	Prevalence (10^{-3}) of hyperpigmentation 183.5, of keratosis 71.0 in high exposure area, 0 for both in low exposure (1-17µg/L) area As conc. µg/L — Prevalence of skin cancer (10^{-3}) <300: 4 (M) 1.3 (F) 300-600: 14.4 (M) 6.3 (F) >600: 31.0 (M) 12.1 (F) unknown: 16.3(M) 4.7 (F)	Reference cited for arsenic analysis. The exposure-response effect was seen across age and gender
Chen et al (1985) ecological	Arsenic exposed areas of Taiwan	Drinking water up to 1.14 mg/L decreasing with take into use of reservoir water starting in 1956	SMR values from 1973-1986 mortality in arsenic exposed area of SW Taiwan: Skin: 534 (379-689)(M) 652 (469-835)(F)	Population of Taiwan as the reference
Chen et al (1988b) cohort	Cohort of 789 Blackfoot disease patients (7278 person years of observation)	Drinking water concentrations 350-1140 µg/L	SMR 2846 ($p<0.01$) Taiwan Reference pop. SMR 451 ($p<0.05$) Local Reference pop.	10.6% lost on follow-p
Chen & Wang (1990) ecological	Mortality from malignant neoplasms in 1972-83 in 314 precincts and townships in Taiwan	74% or precincts had <5% wells with ≥ 50µg/L As, 15% has 5-14% and 12% had ≥15% such wells. Village mean used in analysis.	statistically significant association between arsenic level in well water and mortality from skin cancer after adjustment for indices of urbanisation and industrialisation	
Wu et al, (1989) ecological	Mortality and population data from 1973-1986 in 42 villages in Taiwan.	Used published Taiwan data from 1964-1966 and village medians in the analysis	Age-adjusted mortality rates per 10^5 by well As concentration. Well As: < 300 — 300 - 599 — ≥600 µg/L — p Males: 2.03 — 14.01 — 32.41 — < 0.001 Females: 1.73 — 14.75 — 18.66 — < 0.05	Observed numbers of deaths smaller than in the Chen et al 1992 study, although the person-years are identical

Table 3.7 Effects of arsenic exposure on the skin (continued)

Authors study design	Study Population	Source and level of arsenic exposure	Health effects, metric of exposure and and measure of association	Comments
Hsueh et al (1995) cross-sectional	1571 residents >30 years of age from high arsenic exposure areas of Taiwan	Median As in well water 0.70 - 0.93 mg/L in early 1960's	Cum expos. Prevalence OR ≤ 4 mg/L-yrs 1.0 5-24 mg/L-yrs 6.7 (1.1 – 59) ≥ 25 mg/L-yrs 13.8 (1.1 – 77)	Drinking water arsenic concentration estimates based on the study done in 1960's (Kuo 1964), using the Natelson metod. 68.8% perticipation rate, for approx 25% cumulative exposure history not known. Exposure-response between duration of consumption of sweet potato and prevalence of skin cancer. OR's adjusted for age and sex, duration of consumption of sweet potato, working in rice fields and hepatitis B – surface antigen.
Guo et al (1998) Ecological	243 Taiwanese townships – approximately 11.4 million residents. Incident cases of urothelial and kidney cancer 1980-87	Arsenic measured in over 80,000 wells from 1974-1976 in 78% of townships average As content was nondetectable, in 91, below 50 and in 99.5%, below 640 µg/L	No relationship between skin cancer incidence and the mean township well water arsenic concentration. A positive association between skin cancer and percentage of wells in the highest concentration category (> 640 µg/L) and a negative association between skin cancer and percentage of wells in the lowest concentratin category.	Used data from the 1970's survey on arsenic in well water, using mercuric bromide method to analyse arsenic. Smoking not included in the models as not good predictor for any cancer in this study. Potential bias from source of case ascertainment, ie tumor registry not validated
Tsai et al (1999) Ecological	4 townships in BFD-endemic area in Taiwan, mortality in 1971-1994, compared to local and national rates	Drinking water up to 1.14 mg/L, decreasing with take into use of reservoir water starting in 1956	Skin cancer SMR for females and males combined, compared to local rates SMR CI 483 374 - 615 (Local rates) 597 462 - 760 (National rates)	Age- and sex-specific mortality rates based on population data from Miniistry of Interior, deaths from computer data base on deaths. 99% of causes of deaths based on diagnosis of a physician. All cancers confimred by pathological examination. Overlaps with earlier Taiwan studies.

Table 3.7 Effects of arsenic exposure on the skin (continued)

Authors study design	Study Population	Source and level of arsenic exposure	Health effects, metric of exposure and and measure of association	Comments
Hopenhayn-Rich et al (1998) ecological	Residents in Cordoba vs rest of Argentina	In the high exposure group, in two selected towns, 42/61 and 49/57 measurements ≥ 40 µg/L. Highest measured concentration 533 µg/L	Exposure SMR (CI) males females low 204 (138-289) 85 (42-151) medium 149 (83-245) 82 (32-168) high 149 (71-273) 278 (161-444)	
Rivara et al (1997) ecological	Region 2 (higher exposure) Northern Chile compared to Region 8 (low exposure). Region 2 is arsenic endemic area	Drinking water Arsenic concentration varied during 1950 – 1992 ranging from ND to 860 µg/L through the time period in different locations in Region 2.	Mortality Rate Ratio (CI) Region II vs Region VIII 4.3 (2.3 – 5.1)	Air levels of arsenic were measured in some locations ad were considerably elevated at Chuquicamata copper smelter in Region 2.
Smith et al (1998) ecological	Region II Chile (1989-1993) compared to the rest of Chile.	Drinking water Avg. 43-568 µg/L (1950-1994) Exposure decreased over time: 569 µg/L (1955-69) to 43 µg/L (1990-94)	SMR (CI) Males 770 (470 – 1190) Females 320 (130 – 660)	Measurements taken by water company. Population is partially overlapping Rivara (1997)
Cebrian et al (1983) cross sectional	One third of households in two towns in North Mexico, one with arsenic contaminated drinking water, and the other without	Average water As 400 (SD 114) µg/L for the exposed, based on 20 samples in 1975-8. For the referents, mean (SD), 5 (7) µg/L	Prevalence of hypopigmentation, hyperpigmentation, palmoplantar keratosis, papular keratosis and cancer 17.6, 12.2, 11.2, 5.1 and 1.4% among the exposed, and 2.2, 1.9, 0.3, 0.0, 0.0 % among the referents	Prevalence rates not age-standardized, but among the referents, the proportion of >60 year-olds greater than among the exposed.

Table 3.7 Effects of arsenic exposure on the skin (continued)

Authors study design	Study Population	Source and level of arsenic exposure	Health effects, metric of exposure and and measure of association	Comments

Mazumder et al (1998) cross-sectional	7683 inhabitants in 25 villages in West-Bengal in 1995-6. Exposure to arsenic started most likely in the late 1960s	For 45%, drinking water As was <50 µg/L, for 69% <200 µg/L, for 88% < 500 µg/L and for 99.8% <800 µg/L	Prevalence of keratosis and hyperpigmentation			
			As-conc µg/L	Keratosis Males	Females	Hyperpigmenta Males	Females
			< 50	0.2	0	0.4	0.3
			50 - 99	1.5	0.4	3.2	0.8
			100-149	1.6	1.2	11.0	5.7
			150-199	4.7	2.3	7.8	5.1
			200-349	4.9	2.0	13.1	6.5
			350-499	9.0	2.7	15.7	9.5
			500-799	8.9	3.1	13.8	5.3
			≥ 800	10.7	8.3	22.7	11.5
Tondel et al (1999) cross sectional	1481 subjects in 4 villages in Bangladesh	Well water As concentration at the time of the study, 10 - 2040 µg/L	Well water As concentration-dependent increas the prevalence of skin lesions (hyper- or hypopigmentation, or keratosis)				
			As-conc µg/L	Skin lesion prevalence, % Males	Females		
			< 150	18.6	17.9		
			151 - 350	21.9	20.5		
			351-550	32.9	32.1		
			551-1000	36.8	34.0		
			≥ 1000	37.0	24.9		

A series of studies from BFD-endemic parts of Taiwan have clearly demonstrated the existence of an exposure-response relationship between the magnitude of arsenic exposure and incidence of skin cancer and other manifestations including keratosis and hyperpigmentation. Tseng et al. (1968) found that ascending rates for skin cancer, keratosis and hyperpigmentation corresponded with increasing arsenic content of well water in a study population comprising 40,000 “exposed” and 7,500 “comparison” individuals; a dose-response relationship for arsenic concentration and black foot disease prevalence was also reported. The studies of Chen et al. (1985; 1988), Chen & Wang (1990), Wu et al. (1989) and Tasi et al (1999), which found evidence of links between mortality from cancers of the lung and bladder and arsenic exposure (see previous section), all report similar associations for cancers of the skin. Given that the fatality rates of non-melanoma skin cancers are low relative to other cancers, it is likely that mortality studies of this type markedly underestimate the incidence of the disease.

Hsueh et al. (1995) conducted a detailed investigation of the relationship between skin cancer and arsenic exposure in three Taiwanese villages. Out of a study population of 1,081 inhabitants, who were interviewed about their drinking water consumption patterns and personal histories in 1988-89, 66 were diagnosed as having skin cancer. The age- and sex-adjusted prevalence odds ratio of skin cancer was related to all the chosen indicators of arsenic exposure, i.e. village well-water mean concentration (based on analyses made in the early 1960s), duration of living in the BFD-endemic area, duration of drinking artesian well water and cumulative arsenic exposure.

Evidence for the link between skin cancers and arsenic is further supported by the results of studies conducted in other world regions. The work of Hopenhayn-Rich et al. (1998) in Argentina and Smith et al (1998) in Chile, mentioned previously in the context of lung and bladder cancers, both demonstrated positive associations between mortality from skin cancer and arsenic exposure (although in Argentina the positive association was confined to women). In a more recent analysis, Smith et al. (2000) documented skin changes in 6 out of 44 well-nourished subjects from a village in northern Chile supplied by water containing up to 800 ug/L of arsenic. Arsenic exposure in this village is reported to have been present for thousands of years, suggesting that there has been no adaptation to arsenic exposure by the population.

The prevalence of skin lesions was reported to be significantly elevated in two towns in Mexico (where the average concentration of arsenic in water samples was 0.41 mg/L) relative to a “control” town (average concentration 0.005 mg/L) (Cebrian et al., 1983). In the “exposed” town there were 52 cases (or 17.6%) of hypopigmentation, 36 (12.2%) cases of hyperpigmentation, 33 cases (11.2%) of palmoplantar keratosis, 15 cases (5.1%) of papular keratosis and 4 cases (1.4%) of ulcerative zones (cancers). In the “control” town the prevalence rates were significantly lower: 7 cases of hypopigmentaion, 6 cases of hyperpigmentation, 1 case of palmoplantar keratosis, no

cases of papular keratosis and no cases of ulcerative zones (cancers). The prevalence of all skin lesions was found to increase with age. Non-specific symptoms such as nausea, epigastric pain, abdominal pain, diarrhoea, headache and oedema were found to be more prevalent in the exposed town and more common in those with lesions.

Recent studies from West Bengal, India and Bangladesh in populations with a history of exposure to arsenic-contaminated drinking water, have documented similar findings. In West Bengal, a survey of 7,683 participants from “high” and “low” exposure areas, found that the age-adjusted prevalence of keratosis rose from zero in the lowest exposure level (< 50 ug/L) to 8.3 per 100 women drinking water containing > 800 ug/L. For men, the age-adjusted prevalence rates rose from 0.2 per 100 in the lowest exposure category to 10.7 per 100 in the high exposure group. Similar results were reported for hyperpigmentation prevalence. Comparison by dose per body weight revealed that men had roughly 2-3 times the prevalence of both keratosis and hyperpigmentation compared to women for the same apparent ingested dose. Subjects below 80% of their body weight for their age and sex had a 1.6-fold increase in the prevalence of keratoses, suggesting that malnutrition may play a role in increasing susceptibility. However, no such difference was observed for hyperpigmentation (Mazumder et al., 1998).

In Bangladesh, Tondel et al. (1999) examined a total of 1,481 subjects (aged 30 or over) residing in four villages were arsenic concentrations in drinking water ranged from 10 to 2,040 ug/L. Almost one third (430) were found to have skin lesions (i.e. pigmentation changes or keratois). A statistically significant exposure-response relationship was also demonstrated; the age-adjusted prevalence rate of skin lesions increased from 18.6 per 100 in the lowest exposure group (< 150 ug/L), to 37.0 per 100 in the highest exposure category (> 1000 ug/L) for males and from 17.9 to 24.9 per 100 in females. Again, when the exposure was considered by dose (in ug/L per kg body weight) there was an increase in the age-adjusted prevalence rates of skin lesions for males and females across dose groups.

In contrast, studies carried out in the USA have not shown any excess of skin disorders. For example, Morton and colleagues (1976) examined the incidence rates of skin cancer in Lane County, Oregon and found that neither basal cell or squamous cell carcinoma were positively associated with the arsenic levels ranging from 0 to 2,150 ug/L (average = 8.6 µg/L).

A recent analysis by Valberg et al. (1998) reviewed data obtained from a series of studies of skin cancer in US populations. Populations included were from Fallon, Nevada (105 individuals at 100 ug/L, 0.091 predicted arsenic skin cancers), Fairbanks, Alaska (49 individuals at 401 ug/L, 0.072 predicted arsenic skin cancers; and 30 individuals at 76 ug/L, 0.012 predicted arsenic skin cancers) and Millard County, Utah (145 individuals at 208 ug/L, 0.630 predicted arsenic skin cancers). Using the US EPA (1988) cancer slope factor for ingested arsenic to predict the

incidence of skin cancer in these populations, the total number of predicted arsenic skin cancers from all four areas is not quite one case. The data from Millard County, Utah alone also indicated that the risk of no additional skin cancer was more likely by a factor of nearly two. The relatively small sample sizes and the low arsenic exposures mean that these US results do not necessarily contradict previous reports of positive correlations from other countries.

Exposure to arsenic via other exposure routes have also been linked to dermal effects. Although an early study linked excess skin cancer mortalities to occupational arsenic exposure (Fierz, 1965), more recent occupational studies involving arsenic exposure do not support this finding (WHO, 2001). Isolated reports of other dermal effects have, however, been found in the literature. For example, Goncalo et al. (1980), concluded that arsenite (As_2O_3) can induce an irritative contact dermatitis following occupational exposure. Three glass workers suffered cutaneous lesions, including pruritic maculopapules, pustules and folliculitis, that were localized primarily in exposed and moist areas. Patch tests of the powders the workers were exposed to were positive, and there was a weak positive response to a 5% concentration of As_2O_3 in petrolatum. A change in work practices by the workers alleviated the skin conditions. Barbaud et al. (1995) reported on a case of contact hypersensitivity to arsenic in a crystal factory employee, who had no previous history of skin disorders. A patch test was done with various diluted compounds and sodium arsenate was the only chemical that tested positive. The skin disorder healed after treatment and reassignment to another position.

Cancer at other sites

Several studies in Taiwan have suggested that arsenic may be related to cancers of the oesophagus, stomach, small intestine, colon, nose, larynx, bone and prostate, as well as lymphoma and leukaemia. In several studies, an elevated mortality from liver cancer was associated with high exposures to arsenic via drinking water (Chen et al., 1986; Chen & Wang, 1990). Increased rates of prostate cancer with increasing exposure to arsenic have been noted (Chen et al.1985).

Links between arsenic exposure and cancer at sites other than skin, lung, bladder and kidney have not been investigated in any great detail in countries outside of Taiwan. Of the studies available, results are generally mixed. In one of two studies in Chile (Smith et al., 1998), mortality from liver cancer was positively associated with drinking water arsenic exposure. The study by Hopenhayn-Rich et al. (1996) in Argentina, however, found no such relationship. One study in the USA (Lewis et al. 1999) and another in Australia, neither of which showed a clear cut increase in the risk of lung, bladder or kidney cancer, found evidence of a moderately elevated mortality of cancer of the prostate.

Similarly, occupational studies of arsenic exposure have not revealed any consistent relationship between cancer incidence at sites other than the lung. A significant relationship was observed between arsenic exposure and the incidence of cancers of a large category of "digestive organs " in a Swedish cohort (Sandström et al., 1989). In the Montana cohort, a small, non-exposure related excess of digestive tract cancers was observed (Lee-Feldstein, 1983).

There was a statistically significant association between arsenic exposure and cancer of the buccal cavity and pharynx in the Tacoma cohort (Enterline et al., 1995), but not in the Anaconda cohort in 1964-1977 (Lubin et al., 1981) or in the US pesticide producer cohort (Sobel et al., 1988). Similarly, no excess of stomach cancer was observed in the Japanese smelter cohort (Tokudome & Kuratsune, 1976). However, in UK tin miners, two deaths from stomach cancer were observed (0.2 expected, SMR 890, $p<0.05$; Hodgson & Jones, 1990). In the Tacoma cohort, there was an increase in the cancer of large intestine ($p < 0.01$) but not a significant excess of rectal or bone cancer (Enterline et al., 1995). An excess of rectal cancer was observed in the French gold miner cohort (Simonato et al., 1994) and of cancer of the large intestine (except rectum) in the Japanese smelter cohort (Tokudome & Kuratsune, 1976).

Supporting evidence from experimental studies in animals

A number of animal carcinogenicity studies on arsenic have been carried out, the results of which are reviewed by IARC (1973, 1980, 1987) and most recently by WHO (2001). Results are inconclusive owing to the fact that the majority of such studies are considered to suffer from limitations of one sort or another, either high dose levels, relatively short exposure times and small sample sizes. Furthermore, some studies have been conducted using strains of animals that are believed to have a high background number of tumours.

These comments notwithstanding, a recent study involving mice exposed to arsenic in drinking water at a relevant level of exposure (i.e. at concentrations similar to those commonly found in BFD-endemic parts of Taiwan) has provided what some researchers consider to be the first clear evidence of a treatment-related increase in the number of tumours (Ng et al., 1998, 1999). Sodium arsenate in drinking water was given to 90 female C57BL/6J mice, 140 metallothionein knock-out transgenic mice and 120 control mice (60 in each group) over a period of up to 26 months. (C57BL/6J mice have a very low incidence of spontaneous tumours, whereas metallothionein knock-out transgenic mice are expected to be more susceptible to arsenic toxicity on account of absence of the metallothionein protein which has an affinity for metals.

The average arsenic intake by the mice was 2-2.5 ug per day and mice that survived for 2 years consumed approximately 1.5 –1.8 mg As. 81% of the C57BL/6J and 74% of the knock-out mice survived the arsenic treatment, compared with 98% in the controls groups. One or more tumours were detected in 41% of the C57BL/6J mice and 26% in the knock-out mice; tumours were found

in the gastrointestinal tract, lung, liver, spleen, skin and reproductive organs. Pathological and histopathological examination confirmed the ovary, lung and skin tumour findings (Ng, 1999). No macroscopic tumours were observed in the control groups.

Other animal experimental studies have shown that inorganic arsenic can produce chromosomal aberrations in vitro, affect methylation and repair of DNA, induce cell proliferation, transform cells and promote tumours. However, inorganic arsenic was not seen to induce genetic point mutations in either bacteria or mammalian cells (WHO, 2001).

3.3.2.3 Genotoxicity and related end points

Genotoxicity studies in relation to arsenic exposure have included exposed and unexposed individuals from several populations, and have based their analyses on various tissues, including blood, buccal and bladder cells as well as sections from tumour sections or Bowen's disease. Studies of this type usually take the form on one of three distinct groupings according to the focus of investigation:

a) p53 mutations in tumour samples,
b) SCE, chromosome aberrations (CA) and RI in cultured lymphocytes, and
c) MN in exfoliated bladder and buccal cells (possible target tissues from direct exposure to arsenic from drinking water).

A brief description, plus a summary of the key findings, of all three types of study can be found in **Table 3.8**.

Table 3.8 Genotoxicity of arsenic in exposed humans (Source: WHO, 2001)

Author, study design	**Study Population, end-points measured**	Source and level of arsenic exposure	Health effects, metric of exposure and and measure of association	**Comments**
Warner et al (1994), cross sectional	18 exposed and 18 referents in Nevada MN in bladder and buccal cells	High exposure: well water As concentration >500 (average 1312) µg/L. Referents, average 16 µg/L	Bladder cells MN/100 cells (SE) Freq. ratio (CI) Males Exposed Referents 5.00 (1.50) 2.14 (0.46) 2.34 (1.27, 4.29) Females 1.82 (0.53) 1.28 (0.31) 1.43 (0.76, 2.65) Both acentric and whole chromosomes increased. No effect on MN in buccal cells.	Referents age- and smoking-matched
Moore et al (1996); cross-sectional	Same as Warner et al (1994) Absence/presence of centromeres by FISH in bladder cells	High exposure: well water As concentration >500 (average 1312) µg/L. Referents, average 16 µg/L	MN+ (%) MN-(%) Expos. Ref P Exp. Ref p Males 0.190 0.102 0.08 0.167 0.081 0.07 Females 0.078 0.072 0.31 0.057 0.041 0.48 MN+/- = aberrations with/without centromere	
Moore et al (1997a) cross sectional	70 Chilean males with high water arsenic exposure and 50 referents Bladder cell MN using FISH for centromeres	High exposure: 600 µg/L As, referents 15 µg/L. Average U-As levels 616 and 66 µg/L, respectively	U-As µg/L MN+ * CI MN-* CI <54 1.0 1.0 54 - 137 2.3 1.0-5.0 4.7 1.7-13.2 137 - 415 2.0 0.9-4.5 7.5 2.8-20.3 415 - 729 3.1 1.4-6.6 5.2 1.9-14.6 >729 0.9 0.4-2.2 1.0 0.3-3.3 *prevalence ratio	Exposure stratified by quintiles.
Moore et al (1997b) intervention	34 men from the the exposed group in the previous (Moore et al 1997a) study Bladder cell MN	Water with 45 µg/L As supplied to participants for 8 weeks. U-As decreased from 742 to 225 µg/L	MN frequency decreased from 2.6 to 1.8/1000 (prevalence ratio 0.7, p<0.05). For those whose U-As was <700 µg/L at the beginning of the intervention, the decrease was from 3.5 to 1.5 (prevalence ratio 0.4, p=0.002).	
Ostrosky-Wegman et al (1991) cross-sectional	13 exposed and 15 less exposed habitants in North Mexico; CA, SCE, HPRT mutations in lymphocytes	Average drinking water As concentration for the exposed 390 µg/L, 19-60 µg/L for the referents	CA% (SD) SCE (SD) Vf (SD)* High esp. 2.55 (1.73) 9.10 (2.7) 2.42 (2.26) Low exp. 3.00 (2.82) 8.80 (1.6) 5.03 (2.99) All nonsignificant; *: HPRT mutations	Complex chromosomal aberrations (dicentrics, rings, translocations) increased among the more heavily exposed (0.73% vs. 0.16%)

Table 3.8 Genotoxicity of arsenic in exposed humans, continued

Author, study design	Study Population, end-points measured	Source and level of arsenic exposure	Health effects, metric of exposure and and measure of association	Comments
Gonsebatt et al (1994) cross-sectional	33 exposed and 30 referents in Lagunera region, Mexico Labeling index, mitotic index, replication index in lymphocytes	Water arsenic in average 412 µg/L for the exposed and 37 µg/L for the referents	Labeling index controls 3.37 (SE 0.61), exposed without skin lesions: 3.95 (0.56), exposed with skin lesions 2.42 (0.49; $p<0.05$). Mitotic index at 72 h for controls 3.78 (SE 0.34), for exposed 6.34 (0.45; $p < 0.01$); no difference at 48 or 72 h Replication index lower in exposed females at 48, 60 and 72h; no difference among males.	
Gonsebatt et al (1997) cross sectional	35 exposed volunteers and 35 referents in Lagunera region, Mexico CA in lymphocytes, MN in buccal and bladder cells	Water arsenic in average 410 µg/L for the exposed and 30 µg/L for the referents	CA (SE) / MN_{buccal} (SE) / $MN_{bladder}$ (SE) Refer 2.96 (0.54) / 0.56 (0.13) / 0.48 (0.10) Exposed 7.12 (1.00)* / 2.21 (0.47)* / 2.22 (0.99)* Skin les. 7.38 (1.46 / 3.28 (0.96)* / 4.64 (2.59)* § buccal; §§ bladder cells. * $p<0.05$	Statistical comparisons included other variables, such as smoking, age and gender.
Lerda et al (1994) cross sectional	282 nonsmoking exposed inhabitants and 155 referents from neighbouring province in Argentina. Lmphocyte SCE	Water arsenic for the exposed province ≥130 µg/L, for the reference area, =20 µg/L. Duration of exposure ≥20 years	Lymphocyte SCE/cell among exposed 10.46 (SD 1.02) and among referents (7.49 SD 0.97, $p< 0.001$). Correlation between urinary arsenic and SCE: R^2 0.64 for females and 0.33 for males	The exposed considerably younger than referents (mean ages, 38.9 vs. 56.7 years). Age or sex not considered in the analysis.
Dulout et al (1996) cross sectional	12 exposed women and 10 exposed children & 10 referent women and 12 referent children in Argentina MN & SCE in lymphocytes; FISH for aberration type	Drinking water As 0.2 - 0.5 mg/l for the exposed. U-As median 260 µg/L for exposed women and 310 for exposed children, and 8 and 13 µg/L for the nonexposed	MN/1000 (SE) / SCE/cell (SD) Exp. children 35 (46) / 4.4 (1.1) Exp. women 41 (4.9) / 5.7 (1.3) Ref. children 5.6 (1.6) / 4.6 (1.2) Ref. women 8.5 (3.4) / 5.5 (1.3) No differences in chromosomal translocations; aneuploidy more frequent (0.21 vs 0 %) among the exposed	MN frequency unusually low among the referents. Arsenic metabolite pattern different from that reported earlier for Caucasian populations

Table 3.8 Genotoxicity of arsenic in exposed humans, continued

Author, study design	Study Population, end-points measured	Source and level of arsenic exposure	Health effects, metric of exposure and and measure of association			Comments
Mäki-Paakkanen et al (1998) cross sectional	32 current and 10 ex-users of arsenic-containing well water plus 8 referents in Finland; lymphocyte CA	Median well water arsenic concentration 410 µg/l for the exposed (all > 1 µg/L) and < 1µg/L for the referents		CA incl gaps (SD);p	CA excl gaps (SD);p	
			current users	6.9 (3.4)	3.5 (2.5)	
			Ex-users	4.2 (1.9)	1.9 (1.3)	
			Referents	8.6 (3.6); 0.02	3.6 (1.7); 0.1	
			Cum dose mg/lifetime*			
			≤ 1.894	6.0 (2.9)	2.8 (4.3)	
			> 1.894	8.6 (4.3); 0.02	4.5 (3.0); 0.02	
			As in urine µg/L*			
			≤ 206	6.1 (3.0)	2.8 (1.8)	
			>206	8.9 (4.4); 0.02	4.8 (3.0); 0.008	
			*Cut-off point 75th percentile. P-values from analysis of variance			
Kuo et al (1997) cross-sectional	26 individuals with Bowen's disease with known drinking water arsenic exposure and 22 non-exposed BfD patients from the BFD endemic area. p53 overexpression and proliferation in the tumour	Well water arsenic concentration = 1140 µg/L, with progressive decrease since 1956	>10% immunohistochemical staining for p53 protein in tumours from 11/26 exposed and 2/22 non-exposed (p=0.01). No difference in cell proliferative activity			
Hsu et al (1997) cross-sectional	15 cases of Bowen disease and 34 referents from the BFD endemic area	Well water arsenic concentration = 1140 µg/L, with progressive decrease since 1956		SCE/cell (SE); p	HFC % (SE); p	Referents matched for age, sex and residence
			Patients	8.42 (51)	17.89 (2.83)	
			Referents	6.94 (0.37) ; <0.05	8.59 (1.66) < 0.05	
Liou et al (1996) cross sectional	22 patients with cancer, 10 with BFD, 8 with cancer and BFD, 26 healthy individuals from the BFD endemic area, and 23 healthy non-exposed referents.	Well water arsenic concentration = 1140 µg/L, with progressive decrease since 1956	SCE frequencies not different among different groups. Mitomycin-induced SCE frequencies higher among individuals from the BFD area than among referents not exposed ot arsenic.			

Table 3.8 Genotoxicity of arsenic in exposed humans, continued

Author, study design	Study Population, end-points measured	Source and level of arsenic exposure	Health effects, metric of exposure and and measure of association				Comments
Liou et al (1999) prospective	686 residents of the Taiwan BFD endemic area, out of whom 31 developed cancer during a 4-year-follow up period; SCE and CA in lymphocytes	Well water arsenic concentration = 1140 µg/L, with progressive decrease since 1956		Cases	Referents	p	For 9 of the 31 CA could not be analysed = final analysis done on 22 cases and 22 referents
			SCE/cell (SD)	6.73 (1.53)	6.22 (1.11)	0.36	
			CA (chromosome-type)	2.6 (1.7)	0.9 (1.0)	0.01	
			CA (chromatid-type)	3.3 (1.8)	3.4 (2.0)	NS	
			CA Total	6.1 (2.4)	4.4 (2.6)	0.018	
Shibata et al (1994) cross sectional	13 Cases (age, 37-74 years) of urothelial cancer from BFD-endemic area in Taiwan	Well water arsenic concentration = 1140 µg/L, with progressive decrease since 1956	8/13 cases had a mutation in exxons 5-8 of the P-53 gene. 9/10 point mutations were transitions.				The authors conclude that the mutation pattern observed is not different from those observed in transitional cell tumours in patients without arsenic exposure
Hsieh et al (1994) cross sectional	26 skin biopsies from 16 Bowen's disease patients from the BFD endemic area r*as* and p53 mutations	Well water arsenic concentration = 1140 µg/L, with progressive decrease since 1956	No mutations observed in exons 5-8 in p53, or in codons 12, 13 or 61 H-, K- or N-ras oncogenes				No information on personal exposure level or duration of the study subjects, nor any personal characteristics such as age, sex or smoking.
Hsu et al (1999) cross sectional	23 patients with Bowen's disease, 7 with basal cell carcinoma, and 9 with squamous cell carcinoma from the BFD endemic area	Well water arsenic concentration = 1140 µg/L, with progressive decrease since 1956	9/23 (39%) of Bowen's disease patients, 23/7 (29%) of BCC cases, and 5/9 (56%) of SCC cases had mutations in the P53 gene.				The authors concluded that the p53 gene mutation rates, sites and types in arsenic-related skin cancer are significantly different from those in UV-induced skin cancer (from earlier studies).

Despite some negative findings, the weight of evidence indicates that arsenic can cause clastogenic damage in a variety of cell types, with differing end points, in exposed individuals. Clastogenic effects have also been observed in cells from cancer patients (WHO, 2001). In the case of point mutations the results are largely negative. No HPRT gene mutation was seen in the single available study in lymphocytes (Ostrosky-Wegman et al., 1991). Mutations of ras genes and p53 mutations were rarely found in the cells taken from patients with cancer or Bowen's disease from the BFD-endemic parts of Taiwan. One study did, however, report increased p53 expression in Bowen's disease patients (Kuo et al., 1997).

3.3.2.4 Diabetes mellitus

Diabetes mellitus has also been linked with drinking water arsenic exposure. Lai et al. (1994) assessed the relationship between ingested inorganic arsenic and prevalence of diabetes mellitus in 891 adults residing in southern Taiwan. Their study found that residents in the BFD-endemic areas had a two-fold increase in the prevalence of diabetes mellitus (after adjustment for age and sex) when compared to residents in Taipei and the entire Taiwan population. The authors also described a dose-response relationship between the level of arsenic in water and the prevalence of diabetes after adjusting for age, sex, body mass index and activity level. Positive associations were also demonstrated in two further studies from Taiwan. An excess mortality from diabetes among the arsenic exposed population in four townships, relative to local and national rates, has been reported by Tsai et al. (1999). The incidence of diabetes mellitus in a cohort of inhabitants of the Taiwan BFD area was related to the cumulative exposure to arsenic in drinking water (Tseng et al., 2000).

A positive association with diabetes has also been found in Bangladesh. Rahman et al. (1998) used the presence of keratosis as an indicator of arsenic exposure and showed elevated risks for diabetes in those exposed to arsenic in their drinking water (prevalence ratio= 5.9). On the other hand, in the Utah mortality study, Lewis et al. (1999) failed to find a significant excess in the number of deaths from diabetes in males and females exposed to elevated levels of arsenic in drinking water. However, in the US diabetes is a condition with a low-case fatality rate, so an association with diabetes mellitus may not be observed. More work is needed prior to deciding whether there is an association in the US between diabetes and drinking water arsenic.

Two occupational studies have found an association between arsenic exposure and diabetes mellitus. In both cases, however, the results were of borderline significance. Based on a case-referent analysis involving glass workers, Rahman et al. (1996) found a slightly elevated risk for diabetes among those glasswork employees considered to be exposed to inhaled forms of

arsenic. In a smaller (12 exposed cases) case- referent study (Rahman & Axelson, 1995) in the Rönnskär cohort (Axelson et al., 1978), a slightly elevated risk of diabetes mellitus associated with arsenic exposure was also observed.

3.3.2.5 Neurological effects

It is generally accepted that acute arsenic poisoning causes neurological effects in humans, especially in the peripheral nervous system (see section on acute effects).To date, however, little work has been done on the possibility that lower-level, long-term exposure to arsenic may also lead to neurological effects. Of the limited number of available studies on this topic, several have described the onset of various neurological symptoms in subjects exposed to arsenic. Hindmarsh et al. (1977), for example, reported a positive association between electromyography (EMG) abnormalities and arsenic levels in drinking water and hair samples in residents of Waverley, Nova Scotia, Canada. Among those using water with more than 1 mg/L arsenic, the frequency of ENG abnormalities was 50%.

Workers at a copper smelting plant exposed to arsenic trioxide were examined for peripheral neuropathy (Feldman et al., 1979). A total of 70 factory workers and 41 non-arsenic workers were evaluated. The data suggested an association between exposure to arsenic and a higher number of peripheral neuropathological disorders (sensory and motor neuropathy) and electrophysiological abnormalities (reduced nerve conduction velocity and amplitude measurements) among the exposed workers. Not all studies have found evidence of positive associations; in a cross-sectional study of 211 residents of Fairbanks, Alaska Harrington et al. (1978) could find no evidence of neurotoxicity amongst the exposed population.

On balance therefore, the evidence for a link between exposure to arsenic and neurological effects remains weak. Although a handful of studies have suggested that changes in nerve function may occur following exposure to arsenic, such studies are typically limited by their small sample populations, differing end-points and methods of measurement and probable coexposure to other known neurotoxins (WHO, 2001).

3.3.2.6 Reproductive effects

In addition to the health effects already mentioned, arsenic has also been linked to adverse reproductive outcomes. A number of studies have attempted to investigate this possible connection, the results of which suggest increased foetal, neonatal and postnatal mortalities, and elevations in low birth weights, spontaneous abortions, stillbirths, pre-eclampsia and congenital malformations.

A series of ecological studies involving workers and their families living in the vicinity of the Ronnskar copper smelter in Sweden, for example, have reported an increase in the prevalence of low birthweight infants (Nordstrom et al., 1978a; 1979a), higher rates of spontaneous abortions (Nordstrom et al., 1978b; 1979b) and elevations in congenital malformations (Nordstrom et al., 1979b) among female employees and in women living close to the smelter relative to women living further afield. According to Tabocova & Hunter (1994) the frequency of pregnancy complications, mortality rates at birth and low birth weights were significantly higher in 49 maternal-infant pairs living near a Bulgarian copper smelter, relative to country-wide rates. Placental arsenic levels were also found to be higher for the smelter area than for the non-smelter area. In both cases, however, a lack of rigorous treatment of the potential role of confounding risk factors, such as coexposures (lead, copper, cadmium), maternal age, lifestyle/socioeconomic status and smoking habits, have cast doubts over the validity of these findings (WHO, 2001).

Other studies involving arsenic exposure via drinking water have produced conflicting results. Zierler et al. (1988) found no evidence of an increased frequency of congenital heart disease in infants born to women consuming drinking water containing arsenic levels between 0.8-22 ug/L. A 1.4-fold increase in spontaneous abortions and a 2.8-fold increase in still births were, however, observed in a group of “exposed” individuals (arsenic concentrations in water samples > 100 ug/L, N = 25,648) compared with a “low” exposure group (unspecified low arsenic concentration in water samples, N = 20,836) from the south eastern part of Hungary (Borzsonyi et al., 1992).

In sum, there does not appear to be consistent evidence linking any one particular reproductive outcome to arsenic exposure, and at the present time it is generally accepted that there is insufficient evidence to support the notion that arsenic causes reproductive effects in humans.

3.4 EVALUATION OF HUMAN HEALTH RISKS

3.4.1 ENVIRONMENTAL LEVELS AND HUMAN EXPOSURES

Arsenic concentrations in all environmental media are reasonably well documented. Concentrations in air range from a few ng/m3 in remote and rural areas, up to 1,000 ng/m3 and above in the vicinity of industrial sources. Concentrations in rivers and lakes are generally below 10 ug/L, but can reach 5 mg/L near industrial sources. Similarily, ground water concentrations are typically 1-2 ug/L, but can exceed 3 mg/L in geologically-rich arsenic areas. Levels in soils average around 5 mg/kg, with a range of 1 to 40 mg/kg. Background concentrations in freshwater and terrestrial biota rarely exceed 1 mg/kg, but in areas near anthropogenic sources or in areas of geothermal activity markedly higher levels have been observed, in some cases up to 3000 mg/kg.

Whereas the majority of measurements of arsenic concentrations are for total arsenic, accurate estimates of human health risks require the determination of the relative proportions of organic and inorganic arsenicals in air, soil, food and drinking water. It has been established that the arsenic present in water, soil and absorbed on air particulates is predominantly inorganic. In contrast, there is a significant amount of organic arsenic in foodstuffs especially in fish and shellfish. Preliminary data indicate that the proportion of inorganic species in foods varies between 75% in meat, poultry and dairy products and < 1 % in fish/shellfish. More work on the speciation of various arsenicals in foods is needed.

For most non-occupationally exposed adults, ingestion of arsenic in food is the main route of arsenic exposure. In areas where concentrations of arsenic in drinking water exceed 100 ug/L, this source is significant and, in some cases, may even be the principle contributor to the daily intake of arsenic. Depending upon the bioavailability, soil may be a potentially significant source of arsenic intake in children, particularly in areas near industrial and hazardous waste sites.

Daily intake of total arsenic by adults varies widely across the globe, primarily because of differences in the amount of fish and shellfish consumed in the diet. Best estimates indicate that daily intake of total arsenic due to the ingestion of food and beverages generally lies in the range 20-300 µg/day. According to a limited data set, about 25% of the arsenic found in food is present in inorganic forms (assuming a typical “western-style diet”); however, this proportion is significantly reduced (< 10%) in diets having a high fish/shell fish component. In non-polluted areas, inhalation of airborne particulates contributes a further 1 ug As/day to the total intake of non-smokers, and up to 10ug As/day in a heavy smoker. Total daily intakes may be significantly higher in all age groups living in the vicinity of industrial point sources, hazardous waste facilities, or in regions with high inorganic arsenic concentrations in groundwater. It is believed that there are millions of people potentially at risk due to the consumption of arsenic-contaminated drinking water in several world regions including West Bengal, Bangladesh, Inner Mongolia and the Xinjiang province in China.

In addition to exposure to arsenic in ambient air, water and food, some workers may be exposed to airborne arsenic and arsenic-containing dusts within the workplace. Actual levels of exposure depend on the specific tasks performed, the type of arsenical compound encountered, and the adequacy of workplace hygiene practices. In workplaces with up-to-date occupational hygiene practices and well-maintained pollution control equipment, levels of arsenic are likely to be below 10 ug/m^3. In some cases, however, workroom atmospheric arsenic concentrations could be as high as several mg/m^3.

3.4.2 CRITICAL ISSUES RELATING EXPOSURE TO DOSE

The assessment of toxic effects of arsenic is complicated by the fact that arsenic can exist in more than one valence state and as both inorganic and organic compounds. For acute and sub-acute toxicity of arsenic, it has been established that the inorganic forms of arsenic are more toxic than the organic, and that the trivalent arsenicals (arsenite) are more toxic than the pentavalent forms (arsenate). Accurate determination of the chemical speciation of arsenic is thus an important concern in studies involving assessment of arsenic toxicity.

Arsenic is relatively unusual amongst metals and metalloids in that it exhibits large interspecies differences in its metabolism. As a result of this, there is no obvious “best”animal model which can be used to assist in the study of the kinetics and metabolism of arsenic in humans. Fortunately, there is a considerable amount of available information from human studies, and thus human arsenic metabolism is reasonably well understood.

For most people exposure to arsenic occurs via the ingestion pathway. Subsequent absorption will depend upon the bioavailability of the ingested arsenic, which in turn will vary according to the form of arsenic and on the matrix (i.e. food, water, soil) in which it is ingested. In drinking water, arsenic occurs mainly as inorganic, bioavailable forms. Arsenic in food occurs as both inorganic and organic forms, most of which appears to be bioavailable. The bioavailability of arsenic from mine tailings and soils on the other hand varies widely from a few percent to about 70%. Such differences indicate that risk assessment of arsenic at contaminated sites should be site specific.

Respiratory absorption of arsenic is a two-stage process involving first, the deposition of inhaled particles onto airway and lung surfaces, followed by the absorption of arsenic from deposited particles. The rate of absorption of inhaled arsenic is thus not only highly dependent on the solubility of the arsenicals, but also on the size of the inhaled particles.

A combination of human and animal studies confirms that both the pentavalent and trivalent soluble inorganic arsenic compounds are readily absorbed from the respiratory and gastrointestinal tracts of humans. Absorption of the organic forms is also thought to occur readily, although there are few studies which substantiate this.

During the metabolic process of arsenic, reduction of pentavalent arsenic species to trivalent arsenic takes places prior to the sequential methylation to the MMA and DMA metabolites. Methylation facilitates the excretion of inorganic arsenic from the body as the end-products, MMA and DMA, are readily excreted in the urine. In "healthy" humans, the urinary excretion of unchanged inorganic arsenic (Asi) concentrations are usually less than 20% of the total metabolites concentrations (i.e. Asi +MMA + DMA). Ingested organoarsenicals (MMA, DMA

and arsenobetaine) are much less extensively metabolised and more rapidly eliminated in the urine.

There are major qualitative and quantitative interspecies differences in the extent of methylation to the extent that some species do not appear to methylate arsenic at all. In human urine, the percentage of MMA is higher than that of any other animal species, while the percentage of DMA is similar to that excreted by the rat. In contrast, the highest concentrations of DMA are found in the mouse and rabbit. Large interindividual variation in arsenic methylation is also a feature of arsenic metabolism. Factors such as dose, age, gender and smoking habits account for only part of the variation seen between individuals. It is speculated that much of the observed variation might be explained by genetic differences in the activity of methylating enzymes and related co-factors; furthermore, the existence of polymorphism has been hypothesised. There are some indications that arsenic methylation may be inhibited at high acute exposures.

Levels of arsenic in blood, hair nails and urine are used as biomarkers of arsenic exposure. Blood arsenic is useful only as an indicator of acute poisoning or stable chronic high-level exposure. Arsenic in hair and nails can be good indicators of past exposure, provided care is taken to avoid external contamination. Speciated arsenic in urine, expressed as either inorganic arsenic or inorganic arsenic + MMA + DMA, provides the best estimate of a recently absorbed dose of arsenic. In order to reflect exposure to inorganic arsenic, however, consumption of fish and shellfish should be avoided for 2-3 days prior to urine sampling.

3.4.3 RISK EVALUATION

Acute and chronic arsenic exposure can result in a wide variety of adverse health outcomes. Acute arsenic poisoning occurs usually as an acute gastrointestinal syndrome. Indirect effects caused by arsenic include renal failure, bone marrow suppression, hemolysis, respiratory failure and polyneuropathy. Deaths have been reported from ingestion of arsenic doses of approximately 1 g. Ingestion by a child of 1 mg arsenic trioxide has resulted in non-fatal but nevertheless severe adverse effects.

Arsenic is unusual in that sufficient human epidemiological data of acceptable scientific quality are available for the assessment of health risks associated with the long-term exposure to arsenic. Long-term exposure to arsenic in drinking water is causally related to increased risks of cancer in the skin, lungs, bladder and kidney, as well as other skin changes such as hyperkeratosis and pigmentation changes. These effects have been clearly demonstrated in a number of epidemiological studies of differing design. High risks and exposure-dose relationships have been observed for each of these end-points.

Determining the lowest arsenic concentration in drinking water at which an increased risk of cancers of the skin, lung, kidney and bladder is likely to occur is not easy. This is partly due to the fact that the exposure categories used in the majority of epidemiological studies have historically been rather broad (e.g. < 300ug/L, 300-600 ug/L and >600 ug/L).

According to a recent report, based on data from the BFD-endemic part of Taiwan, there is an increased risk of lung and bladder cancer mortality in persons consuming drinking water containing arsenic concentrations at < 50 ug/L. Evidence from Chile suggests an increased risk of lung cancer at concentrations in the range 30-50 ug/L and above. A case-control from Finland indicates that there is an elevated risk of bladder cancer at drinking water concentrations of > 0.5 to 64 ug/L (but only when exposure occurred 3-9 years prior to diagnosis). Based on an analysis of data from Argentina, elevated risks from cancers of the lung, bladder and kidney were observed in a group of "highly" exposed individuals exposed to concentrations of arsenic in drinking water which averaged 178 ug/L. However, bladder, kidney and lung were significantly elevated in the "intermediate" exposure group for which concentrations were not available. It is probable therefore that the lowest exposure at which elevated cancer risks could be observed would have been considerably lower than 178 ug/L. In the case of skin cancer, the lowest arsenic drinking water concentration at which an increased risk of skin cancer was observed is 300 ug/L; this is based on the results of a Taiwanese study which used very broad exposure categories. It is likely that the concentration associated with increased skin cancer risk is lower than this. According to a study from West Bengal, elevated risks of arsenic-associated skin lesions (hyperpigmentation and/or keratosis) are associated with drinking water concentrations of < 50 ug/L.

On the basis of the above, it is concluded that increased risks of lung and bladder cancers, and of arsenic-induced skin lesions, are likely to occur following the ingestion of drinking water containing arsenic at concentration of < 50 ug/L (WHO, 2001).

Studies involving occupationally-exposed populations have also demonstrated a causal link between arsenic exposure and lung cancer. Exposure-response relationships and high risks have again been observed. Increased risks have been observed at cumulative exposure levels in excess of 0.75 mg/3.year (e.g. 15 years of exposure to a workroom air concentrations of 50 ug/m3). It has been shown that tobacco smoking is interactive with arsenic in increasing arsenic risk.

In the past, arsenic has been classified as a carcinogen on the strength of evidence from human epidemiological studies. Although several animal carcinogenicity studies have been conducted, they have been inconclusive. In a recent study, however, in which female mice were exposed to arsenic in drinking water at concentrations commonly found in BFD-endemic areas, a high incidence of tumours were found in lungs (17.5%) and the intestinal tract (14.4%). Supporting evidence for the carcinogenicity of arsenic has been obtained from other laboratory studies.

Inorganic arsenic has not been seen to induce point mutations in bacteria or in mammalian cells, but it can produce chromosomal aberrations in vitro, transform cells and promote tumours. Arsenic has caused clastogenic damage in different types of cells from exposed humans and in human-derived *in vitro* test systems.

In addition to cancer of the lung, skin, bladder and kidney, long-term exposure to arsenic has also been linked to a number of other health effects. Chronic exposure via drinking water has been shown to cause peripheral vascular diseases. Whether arsenic alone is sufficient to cause the severe form of this disease, Blackfoot disease, is not known. Genotoxic effects are also evident.

Cancer at sites other than the lung, bladder kidney and skin, hypertension, ischemic heart disease, cerebrovascular disease and diabetes-mellitus have all been associated with long-term exposure to arsenic. Neurological effects and reproductive effects have also been reported in exposed populations. However, conclusions regarding the causality of the relationship between arsenic exposure and these other effects are less clear-cut. The evidence is strongest for hypertension and cardiovascular diseases, suggestive for diabetes and reproductive diseases and weakest for cerebrovascular diseases, long-term neurological effects and cancer at sites other than the skin, lung, bladder and kidney.

REFERENCES

Abdelghani AA, Anderson, AC, Jaghabir, M, & Mather, F (1986) Arsenic levels in blood, urine, and hair of workers applying monosodium methanearsonate (MSMA). Arch Environ Health, 41:163-169.

Agahian, B, Lee, JS, Nelson, JH, & Johns, RE (1990) Arsenic levels in fingernails as a biological indicator of exposure to arsenic. Am Ind Hyg Assoc J, 51:646-651.

Andreae MO (1980) Arsenic in rain and the atmospheric mass balance of arsenic. Journal of Geophysical Research, 85(C8):440-452.

Andreae MO & Andreae TW (1989) Dissolved arsenic species in the Schelde Estuary and watershed, Belgium. Estuar Coast Mar Sci, 29: 421-433.

ANZFA (1994) The 1994 Australian market basket survey- A total diet survey of pesticides and contaminants. Canberra, Australian New Zealand Food Authority.

Arbouine, MW, & Wilson, HK (1992) The effect of seafood consumption on the assessment of occupational exposure to arsenic by urinary arsenic speciation. J Trace Elem Electrolytes Health Dis, 6:153-160.

Armienta, MA, Rodriguez, R, & Cruz, O (1997) Arsenic content in hair of people exposed to natural arsenic in polluted groundwater at Zimapan, Mexico. Bull Environ Contam Toxicol, 59:583-589.

Armstrong BK, McNulty JC, Levitt LJ, Williams KA, & Hobbs MST (1979) Mortality in gold and coal miners in Western Australia with special reference ot lung cancer. Br J Ind Med, 36: 199-205.

ATSDR (1993) Toxicological profile for arsenic. Atlanta, Georgia, Agency for Toxic Substances and Disease Registry, U.S. Department of Health & Human Services. TP-92/02).

Axelson O, Dahlgren E, Jansson CD, & Rehnlund SO (1978) Arsenic exposure and mortality: a case-referent study from a Swedish copper smelter. Br J Ind Med, 35: 8-15.

Barbaud A, Mougeolle JM, & Schmutz JL (1995) Contact hypersensitivity to arsenic in a crystal factory worker. Contact Dermatitis, 33: 272-273.

Bates M, Smith A, & Hopenhayn-Rich C (1991) Arsenic ingestion and internal cancers: a review. Amer J Epidemiol, 135: 462-76.

Bates MN, Smith AH, & Cantor KP (1995) Case-control study of bladder cancer and arsenic in drinking water. Amer J Epidemiol, 141: 523-530.

Beavington F & Cawse PA (1978) Comparative studies of trace elements in air particulate in northern Nigeria. Sci Total Environ, 10: 239-244.

Beckman L (1982) Occupational and environmental risks in and around a smelter in Northern Sweden. IX. Fetal mortality among wives of smelter workers. Hereditas, 97: 1-7.

Benson, LM, Porter, EK, Peterson, PJ (1981) Arsenic accumulation, tolerance and geotypic variation in plants on arsenical mine wastes in SW England. Journal of Plant Nutrition, 3(1/4): 655-666.

Bergoglio RM (1964) Mortalidad por cancer en zonas de aguas arsenicales de la Provincia de Cordoba, Republica Argentina. Pren med argent, 51: 994-998.

Beyer WN & Cromartie EJ (1987) A survey of Pb, Cu, Zn, Cd, Cr, As, and Se in earthworms and soil from diverse sites. Environ Monit Assess, 8(1): 27-36.

Binder, S, Forney, D, Kaye, W, & Paschal, D (1987) Arsenic exposure in children living near a copper smelter. Bull Environ Contam Toxicol, 39:114-121.

Blot W & Fraumeni JF, Jr. (1975) Arsenical air pollution and lung cancer. The Lancet, 2: 142-144.

Bollinger, CT, van Zijl, P, & Louw, JA (1992) Multiple organ failure with the adult respiratory distress syndrome in homicidal arsenic poisoning. Respiration, 59:57-61.

Borgono JM, Vincent P, Venturino H (1977) Arsenic in the drinking water of the city of Antofagasta: Epidemiological and clinical study before and after installation of a treatment plant. Environ Health Perspect, 19: 103-105.

Borum Dr and Abernathy, CO (1994) Human oral exposure to inorganic arsenic. In: Chappell WR, Abernathy CO & Cothern CR (Eds). Arsenic Exposure and Health. Science & Technology Letters, Northwood, UK. 21-29.

Borzsonyi M, Bereczky A, Rudnai P, Csanady M, & Horvath A (1992) Epidemiological studies on human subjects exposed to arsenic in drinking water in Southeast Hungary. Arch Toxicol, 66: 77-78.

Bowen HJM (1979) Elemental chemistry of the elements. London, Academic Press.
Brayer AF, Callahan CM, & Wax PM (1997) Acute arsenic poisoning from ingestion of "snakes". Pediatric Emergency Care, 13(6): 394-396.
Brimblecombe P (1979) Atmospheric arsenic. Nature, 280: 104-105.
Brouwer OF, Okenhout W, Edelbroek PM, de Kom JFM, de Wolff FA, & Peters ACB (1992) Increased neurotoxicity of arsenic in methylenetetrahydrofolate reductase deficiency. Clin Neurol Neurosurg 94:307-310.
Brown CC & Chu KC (1983a) Implications of the multistage theory of carcinogenesis applied to occupational arsenic exposure. J Natl Cancer Inst, 70: 455-463.
Brown CC & Chu KC (1983b) A new method for the analysis of cohort studies: implications of the multistage theory of carcinogenesis aplied to occupational arsenic exposure. Environ Health Perspect, 50: 293-308.
Brown IR & Rush SJ (1984) Induction of a 'stress' protein in intact mammalian organs after the intravenous administration of sodium arsenite. Biochem Biophys Res Commun 120:150-155.
Brown JL, Kitchin KT, & George M (1997) Dimethylarsinic acid treatment alters six different rat biochemical parameters: relevance to arsenic carcinogenesis. Teratogenesis Carcinog Mutagen 17:71-84.
Brown, RM, Newton, D, Pickford, CJ, & Sherlock, JC (1990) Human metabolism of arsenobetaine ingested with fish. Human Exp Toxicol, 9:41-46.
Buchet J & Lison D (1998) Mortality by cancer in groups of the Belgian population with a moderately increased intake of arsenic. Int Arch Environ Health, 71: 125-130.
Buchet, JP, Geubel, A, Pauwels, S, Mahieu, P, & Lauwerys, R (1984) The influence of liver disease on the methylation of arsenite in humans. Arch Toxicol, 55:151-154.
Buchet, JP, Lauwerys, R, & Roels, H (1981a) Comparison of the urinary excretion of arsenic metabolites after a single oral dose of sodium arsenite, monomethylarsonate, or dimethylarsinate in man. Int Arch Occup Environ Health, 48:71-79.
Buchet, JP, Lauwerys, R, & Roels, H (1981b) Urinary excretion of inorganic arsenic and its metabolites after repeated ingestion of sodium metaarsenite by volunteers. Int Arch Occup Environ Health, 48:111-118.
Buchet, JP, Lison, D, Ruggeri, M, Foa, V, & Elia, G (1996) Assessment of exposure to inorganic arsenic, a human carcinogen, due to the consumption of seafood. Arch Toxicol, 70:773-778.
Buchet, JP, Pauwels, J, & Lauwerys, R (1994) Assessment of exposure to inorganic arsenic following ingestion of marine organisms by volunteers. Environ Res, 66:44-51.
Buchet, JP, Roels, H, Lauwerys, R, Bruaux, P, Thoreau-Claeys, F, Lafontaine, A, & Verduyn, G (1980) Repeated surveillance of exposure to cadmium, manganese, and arsenic in school-age children living in rural, urban, and nonferrous smelter areas in Belgium. Environ Res, 22:95-108.
Buiatti E, Kriebel D, Geddes M, Santucci M, & Pucci N (1985) A case control study of lung cancer in Florence, Italy. I. Occupational risk factors. J Epidemiol Community Health, 39: 244-250.
Carlson-Lynch, H, Beck, BD, & Boardman, PD (1994) Arsenic risk assessment. Environ Health Perspect, 102:354-356.
Cebrian ME, Albores A, Aguilar M, & Blakely E (1983) Chronic arsenic poisoning in the North of Mexico. Human Toxicol, 2: 121-133.
Chan TYK (1994) The prevalence use and harmful potential of some chinese herbal medicines in babies and children. Vet Human Toxicol 36: 238-240.
Chatterjee A & Mukherjee A (1999) Hydrogeological investigation of ground water arsenic contamination in South Calcutta. Sci Total Environ, 225: 249-262.
Chatterjee A, Das D, Mandal BK, Chowdhury TR, Samanta G & Chakraborti D (1995) Arsenic in ground water in six districts of West Bengal, India: the biggest arsenic calamity in the world. Part 1. Arsenic species in drinking water and urine of the affected people. Analyst, 120: 643-650.
Chatterjee, A., Das, D. & Chakraborti, D. (1993) A study of ground water contamination by arsenic in the residential area of Behala, Calcutta due to industrial pollution. Environ. Pollut., 80: 57-65.

Chen C-J & Wang C-J (1990) Ecological correlation between arsenic level in well water and age-adjusted mortality from malignant neoplasms. Cancer Res, 50: 5470-5474.
Chen C-J, Chiou H-Y, Chiang M-H, Lin L-J, & Tai T-Y (1996) Dose-response relationship between ischemic heart disease mortality and long-term arsenic exposure. Arterioscler Thromb Vasc Biol, 16(4): 504-510.
Chen C-J, Chuang Y-C, Lin T-M, & Wu H-Y (1985) Malignant neoplasms among residents of a blackfoot disease endemic area in Taiwan: high-arsenic artesian well water and cancers. Cancer Res, 45: 5895-5899.
Chen C-J, Chuang Y-C, You S-L, Lin T-M, & Wu H-Y (1986) A retrospective study on malignant neoplasms of bladder, lung and liver in blackfoot disease endemic area in Taiwan. Br J Cancer, 53: 399-405.
Chen C-J, Hsueh Y-M, Lai M-S, Shyu M-P, Chen S-Y, Wu M-M, Kuo T-L, & Tai T-Y (1995) Increased prevalence of hypertension and long-term arsenic exposure. Hypertension, 25: 53-60.
Chen C-J, Wu M-M, Lee S-S, Wang J-D, Cheng S-H, & Wu H-Y (1988) Atherogenicity and carcinogenicity of high-arsenic artesian well water. Multiple risk-factors and related malignant neoplasms of blackfoot disease. Arteriosclerosis, 8: 452-460.
Chen SL, Dzeng SR & Yang MH (1994) Arsenic species in groundwaters of the blackfoot disease area, Taiwan. Environ Sci Technol, 28: 877-881.
Chen, GS, Asai T, Suzuki Y, Nishioka K, & Nishiyama S (1990) A possible pathogenesis for Blackfoot disease. J Dermatol 17:599-608.
Chiang H-S, Guo H-R, Hong C-L, Lin S-M, & Lee E-F (1993) The incidence of bladder cancer in the blackfoot disease endemic area in Taiwan. Br J Urology, 71: 274-8.
Chiou H-Y, Hsueh Y-M, Liaw K-F, Horng S-F, Chiang M-H, Pu Y-S, Lin J S-N, Huang C-H, & Chen C-J (1995) Incidence of internal cancers and ingested inorganic arsenic: a seven-year follow-up study in Taiwan. Cancer Res, 55:1296-1300.
Chiou H-Y, Huang W-I, Su C-L, Chang S-F, Hsu Y-H, & Chen C-J (1997) Dose-response relationship between prevalence of cerebrovascular disease and ingested inorganic arsenic. Stroke, 28: 1717-1723.
Chiou, P W-S, Chen, K-L, & Yu, B (1997) Effects of roxarsone on performance, toxicity, tissue accumulation and residue of eggs and excreta in laying hens. J Sci Food Agric, 74:229-236.
Choucair AK & Ajox ET (1988) Hair and nails in arsenical neuropathy. Annals of Neuroology, 23:628-629.
Choudry TR, Mandal BK, Samanta G, Basu GK, Chowdhury PP, Chanda CR, Karan NK, Lodh D, Dhar D, Saha KC and Chakraborti D (1997) Arsenic in groundwater in six districts fo West Bengal, India: the biggest arsenic calamity in the world. Status report up to August 1995. In: Abernathy CO, Calderon RL, and Chappell (eds). Arsenic: Exposure and Health Effects. London, Chapman & Hall. 93-112.
Civantos DP, Lopez Rodriguez A, Aguado-Borruey JM, & Julia Narvaez JA (1995) Fulminant malignant arrhythmia and multiorgan failure in acute arsenic poisoning. Chest, 108(6): 1774-1775.
Collecchi, P, Esposito, M, Brera, S, Mora, E, Mazzucotelli, A, & Oddone, M (1985) The distribution of arsenic and cobalt in patients with laryngeal carcinoma. J Appl Toxicol, 6:287-289.
Concha G, Nermell B & Vahter M (1998) Metabolism of inorganic arsenic in children with chronic high arsenic exposure in Northern Argentina. Environ Health Perspec, 106: 355-359.
Concha G, Vogler G, Nermell B & Vahter M (1998a) Low-level arsenic excretion in breast milk of native Andean women exposed to high levels of arsenic in the drinking water. Int. Arch. Occup. Environ. Health, 71: 42-46.[presently listed in press][EHP ref should be 1998b]
Concha, G, Nermell, B, & Vahter, M (1998a) Exposure to inorganic arsenic metabolites during early human development. Toxicolog Sci, 44(2)185-190.
Crearley JE (1973) Arsenic contamination of Finfeather and Municipal Lakes in the City of Bryan. Texas Water Quality Board, Austin, Texas. 21pp
Crecelius EA, Bothner MH & Carpenter R (1975) Geochemistries of arsenic, antimony, mercury, and related elements in sediments of Puget Sound. Environ Sci Technol, 9(4): 325-333.

Cullen NM, Wolf LR, & St. Clair D (1995) Pediatric arsenic ingestion. Am J Emerg Med, 13: 432-435.
Cullen, WR, & Reimer, KJ (1989) Arsenic speciation in the environment. Chem Rev, 89:713-764.
Cuzick J, Sasieni P, & Evans S (1992) Ingested arsenic, keratoses, and bladder cancer. Amer J Epidemiol, 136: 417-421.
Dabeka RW, McKenzie AD, Lacroix GMA, Cleroux C, Bowe S, Graham RA & Conacher HBS (1993) Survey of arsenic in total diet food composites and estimation of the dietary intake of arsenic by Canadian adults and children. JAOAC Int, 76: 14-25.
Dang, HS, Jaiswal, DD, & Somasundaram, S (1983) Distribution of arsenic in humans tissues and milk. Sci Total Environ, 29:171-175.
Das D, Chatterjee A, Mandal BK, Samanta G and Chakraborti D (1995) Arsenic in ground water in six districts of West Bengal, India: the biggest arsenic calamity in the world. Part 2. Arsenic concentrations in drinking water, hair, nails, urine, skin-scale and liver tissue (biopsy) of the affected people. Analyst, 120: 917-924.
Davidson CI, Goold WD, Mathison TP, Wiersma GB, Brown KW & Reilly MT (1985) Airborne trace elements in Great Smoky Mountains, Olympic, and Glacier National Parks. Environ Sci Technol, 19(1): 27-35.
Del Razo LM, Arellano MA & Cebrián ME (1990) The oxidation states of arsenic in well-water from a chronic arsenicism area of northern Mexico. Environ Pollut, 64(2): 143-153.
DFG (1994) Deutsche Forschungsgemeinschaft- List of MAK and BAT values 1994. Commission for the Investigation of Health Hazards of Chemical Compounds in the work Area. Report No.30. Weinheim,Germany. 165 p
Dhar RK, Biswas BK, Samanta G, Mandal BK, Chakraborti D, Roy S, Fafar A, Islam A, Ara G, Kabir S, Khan AW, Ahmed SA and Hadi SA (1997) Groundwater arsenic calamity in Bangladesh. Current Science, 73(1): 48-59.
DG Environment (2000) Ambient air pollution by As, Cd and Ni compounds. Position paper, final version October 2000. Working Group on Arsenic, Cadmium and Nickel Compounds. DG Environment. European Commission. In press.
Diaz-Barriga F, Santos MA, Mejia JD, Batres L, Yanez L, Carrizales L, Vera E, Del Razo LM and Cebrian ME (1993) Arsenic and cadmium exposure in children living near asmelter complex in San Luis Pososi, Mexico. Environmental Research, 62:242-250.
Dulout FN, Grill CA, Seoane AI, Maderna CR, Nilsson R, Vahter M, Darroudi F, & Natarajan AT (1996) Chromosomal aberrations in peripheral blood lymphocytes from native Andean women and children from Northwestern Argentina exposed to arsenic in drinking water. Mutat Res, 370: 151-158.
Ellenhorn, MJ (1997) Arsenic, In: Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning, 2nd ed. Williams & Wilkins, Baltimore, pp. 1538-1542.
Edmonds JS and Francesconi KA (1993) Arsenic in seafoods: human helath aspects and regulations. Marine Pollution Bulletin, 26(12):665-674.
Engel R & Smith A (1994) Arsenic in drinking water and mortality from vascular disease: an ecologic analysis in 30 counties in the United States. Arch Environ Health, 49: 418-427.
Enterline P, Henderson VL, & Marsh GM (1987) Exposure to arsenic and respiratory cancer: a reanalysis. Am J Epidemiol, 125: 929-938.
Enterline PE & Marsh GM (1980) Mortality studies of smelter workers. Am J Ind Med, 1: 251-259.
Enterline PE & Marsh GM (1982) Cancer among workers exposed to arsenic and other substances in a copper smelter. Am J Epidemiol, 116: 895-911.
Enterline PE, Day R, & Marsh GM (1995) Cancers related to exposure to arsenic at a copper smelter. Occup Environ Med, 52: 28-32.
Enterline PE, Henderson VL, & Marsh GM (1987a) Exposure to arsenic and respiratory cancer. A reanalysis. Am J Epidemiol, 125: 929-938.
Falk H, Caldwell GG, Ishak KG, Thomas LB, & Popper H (1981a) Arsenic-related hepatic angiosarcoma. Am J Ind Med, 2: 43-50.
Falk H, Herbert J, Crowley S, Ishak KG, Thomas LB, Popper H, & Caldwell GG (1981b) Epidemiology of hepatic angiosarcoma in the United States: 1964-1974. Environ Health Perspect, 41: 107-113.

Farmer JG & Johnson LR (1990) Assessment of occupational exposure to inorganic arsenic based on urinary concentration and speciation of arsenic. Br J Ind Med 47: 342-348.

Faust SD, Winka A, Belton T & Tucker R (1983) Assessment of the chemical and biological significance of arsenical compounds in a heavily contaminated watershed. Part II. Analysis and distribution of several arsenical species. J Environ Sci Health, A18(3): 389-411.

Faust SD, Winka AJ & Belton T (1987a) An assessment of chemical and biological significance of arsenical species in the Maurice River drainage basin (N.J.). Part I. Distribution in water and river and lake sediments. J Environ Sci Health, 22A(3): 209-237.

Fávaro DIT, Maihara VA, Armelin MJA, Vasconcellos MBA & Cozzolino SM (1994) Determination of As, Cd,Cr, Cu, Hg, Sb and Se concentrations by radiochemical neutron activation analysis in different Brazilian regional diets. J. Radioanalytical and Nuclear Chemistry, Articles, 181: 385-394.

Feldman RG, Niles CA, Kelly-Hayes M, Sax DS, Dixon WJ, Thompson DJ, & Landau E (1979) Peripheral neuropathy in arsenic smelter workers. Neurology, 29: 939-944.

Ferreccio C, Gonzalez C, Solari J & Noder C (1996) [Bronchopulmonary cancer in workers exposed to arsenic: a case control study]. Rev Med Chil 124: 119-123 (in Spanish).

Ferreccio C, Gonzalez C, Solari J, & Noder C (1995) Cáncer broncopulmonar entre trabajadores expuestos a arsénico: un estudio de cases y controles (Lung cancer in workers exposed to arsenic. A case control study). Rev Med Chile, 124: 119-123.

Freeman, HC, Uthe, JF, Fleming, RB, Odense, PH, Ackman, RG, Landry, G, & Musial, C (1979) Clearance of arsenic ingested by man from arsenic contaminated fish. Bull Environ Contam Toxicol, 22:224-229.

Frost F, Harter L, Milham S, Royce R, Smith AH, Hartley J, & Enterline P (1987) Lung cancer among women residing close to an arsenic emitting copper smelter. Arch Environ Health, 42: 148-152.

Garland, M, Morris, JS, Rosner, BA, Stampfer, MJ, Spate, VL, Baskett, CJ, Willett, WC, & Hunter, DJ (1993) Toenail trace element levels as biomarkers: reproducibility over a 6-year period. Cancer Epidemiol Biomarkers Prev, 2:493-497.

Gerhardsson L & Nordberg G (1993) Lung cancer in smelter workers-interactions of metals as indicated by tissue levels. Scand J Work Environ Health, 19 Suppl: 90-94.

Gerhardsson, L, Dahlgren, E, Eriksson, A, Lagerkvist, BEA, Lundstrom, J, & Nordberg, GF (1988) Fatal arsenic poisoning - a case report. Scand J Work Environ Health, 14:130-133.

Geubel, AP, Mairlot, MC, Buchet, JP, Dive, C, & Lauwerys, R (1988) Abnormal methylation capacity in human liver cirrhosis. Int J Clin Pharm Res, VIII:117-122.

Ginsburg, JM, & Lotspeich, WD (1963) Interrelations of arsenate and phosphate in the dog kidney. Am J Physiol, 205:707-714.

Goebel HH, Schmidt PF, Bohl J, Tettenborn B, Kramer G, & Gutmann L (1990) Polyneuropathy due to acute arsenic intoxication: biopsy studies. J Neuropathol Exp Neurol, 49: 137-149.

Goessler, W, Schlagenhaufen, C, Duehnelt, D, Greschonig, H, & Irgolic, KJ (1997) Can humans metabolize arsenic compounds to arsenobetaine? Appl Organomet Chem, 11:327-335.

Goncalo S, Silva MS, Goncalo M, & Baptista AP (1980) Occupational contact dermatitis to arsenic trioxide. In: Fosch PJ & Dooms-Goossens A eds. Current topics in Contact Dermatitis. New York, Springer Verlag 333-336.

Gonzalez, MJ, Aguilar, MV, & Para, MCC (1995) Gastrointestinal absorption of inorganic arsenic (V): the effect of concentration and interactions with phosphate and dichromate. Vet Human Toxicol, 37:131-136.

Grandjean P, Weihe P, Needham LL, Burse VW, Patterson DG, Sampson EJ, Jorgensen PJ, & Vahter M (1995) Relation of a seafood diet to mercury, selenium, arsenic, and polychlorinated biphenyl and other organochlorine concentrations in human milk. Environ Res, 71:29-38.

Gresser, MJ (1981) ADP-arsenate, formation by submitochondrial particles under phosphorylating conditions. J Biol Chem, 256:5981-5983.

Gunderson EL (1995) FDA total diet study-1986-1991-dietary intakes of pesticides, selected elements, and other chemicals. JAOAC Int, &*: 1353-1363.

Guo H-R, Chiang H-S, Hu H, Lipsitz SR, & Monson RR (1994) Arsenic in drinking water and urinary cancers: a preliminary report. In: Chappell WR, Abernathy CO, Cothern CR eds. Arsenic Exposure and Health. Northwood, United Kingdom, Science and Technology Letters, pp 119-128.

Hakala, E, & Pyy, L (1995) Assessment of exposure to inorganic arsenic by determining the arsenic species excreted in urine. Toxicol Lett, 77:249-258.

Harrington JM, Middaugh JP, Morse DL and Housworth (1978) A suvey of a population exposed to high concentrations of arsenic in well water in Fairbanks, Alaska. American Journal of Epidemiology, Nov, 108(5):377-385.

Hertz-Picciotto I & Smith A (1993) Observations on the dose-response curve for arsenic exposure and lung cancer. Scand J Work Environ Health, 19: 217-26.

Hill AB & Faning EL (1948) Studies on the incidence of cancer in a factory handling inorganic compounds of arsenic: mortality experience in the factory. Br J Ind Med, 5: 1-6.

Hindmarsh J, McLetchie OR, Heffernan LPM, Hayne OA, Ellenberger HA, McCurdy RF, & Thiebaux HJ (1977) Electromyographic abnormalities in chronic environmental arsenicalism. Clin Chem and Chem Toxicol of Metals, 1: 287-293.

Hodgson JT & Jones RD (1990) Mortality of a cohort of tin miners 1941-86. Br J Ind Med, 47: 665-676.

Hopenhayn-Rich C, Biggs ML, & Smith AH (1998) Lung and kidney cancer mortality associated with arsenic in drinking water in Cordoba, Argentina. Int J Epidemiol, 27: 561-569.

Hopenhayn-Rich C, Biggs ML, Fuchs A, Bergoglio R, Tello EE, Nicolli H, & Smith A (1996) Bladder cancer mortality associated with arsenic in drinking water in Argentina. Epidemiol, 7: 117-124.

Hopenhayn-Rich, C, Biggs, ML, C, Smith, AH, Kalman, DA, & Moore, LE (1996a) Methylation study of a population environmentally exposed to arsenic in drinking water. Environ Health Perspect, 104:620-628.

Hopenhayn-Rich, C, Biggs, ML, Kalman, DA, Moore, LE, & Smith, AH (1996b) Arsenic methylation patterns before and after changing from high to lower concentrations of arsenic in drinking water. Environ Health Perspect, 104:1200-1207.

Hopenhayn-Rich, C, Smith, AH, & Goeden, HM (1993) Human studies do not support the methylation threshold hypothesis for the toxicity of inorganic arsenic. Environ Res, 60:161-177.

Hsu K-H, Froines JR, & Chen CJ (1997) Studies of arsenic ingestion from drink-water in northeastern Taiwan: chemical speciation and urinary metabolites. In Arsenic Exposure and Health Effects II, CO Abernathy, RL Calderon & WR Chappell, eds. New York: Chapman & Hall, pp. 190-209.

Hsueh Y-M, Cheng G-S, Wu M-M, Yu H-S, Kuo T-L, & Chen C-J (1995) Multiple risk factors associated with arsenic-induced skin cancer: effects of chronic liver disease and malnutritional status. Br J Cancer, 71: 109-114.

Hughes, MF, Mitchell, CT, Edwards, BC, & Rahman, MS (1995) In vitro percutaneous absorption of dimethylarsenic acid in mice. J Toxicol Environ Health, 45:101-112.

IARC (1980) Arsenic and arsenic compounds. In: IARC Monographs on the evaluation of carcinogenic risk of chemicals to humans. Some metals and metallic compounds. Vol 23. International Agency for Research on Cancer, Lyon, pp 39-142.

IARC (1993) Exposures in the glass manufacturing industry. In: IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 58: Berylium, cadmium, mercury and exposure in the glass manufacturing industry. pp 347-375.

Ihrig MM, Shalat SL, & Baynes C (1998) A hospital-based case-control study of stillbirths and environmental exposure to arsenic using an atmospheric dispersion model linked to a geographical information system. Epidemiol, 9: 290-294.

ILO (1991 Occupational exposure limits for airborne toxic substances, 3rd edition. Occupational Safety and Health Series. International Labour Office, Geneva, 455 pp.

IPCS (1994) International Programme on Chemical Safety. Environmental Health Criteria Volume 170, Assessing human health risks of chemicals: Derivation of guidance values for health-based exposure limits. Geneva, World Health organization, 73 pp.

Järup L & Pershagen G (1991) Arsenic exposure, smoking, and lung cancer in smelter workers--a case-control study. Am J Epidemiol, 134: 545-551.
Järup L, Pershagen G, & Wall S (1989) Cumulative arsenic exposure and lung cancer in smelter workers: a dose response study. Am J Ind Med, 15: 31-41.
Jensen GE & Hansen ML (1998) Occupational arsenic exposure and glycosylated haemoglobin. Analyst, 123: 77-80.
Jensen GE & Olsen ILB (1995) Occupational exposure toinorganic arsenic in wood workers and taxidermists-air sampling and biological monitoring. J. Environ. Science and health Part A: Environ Sci Engineering & Toxic and Haz Substance Control. 30: 921-938.
Jensen, GE, Christensen, JM, & Poulsen, OM (1991) Occupational and environmental exposure to arsenic - increase urinary arsenic in children. Sci Total Environ, 107:169-177.
Kagey, BT, Bumgarner, JE, & Creason, JP (1977) Arsenic levels in maternal-fetal tissue sets. In: Hemphill, DD, ed. Trace substance in environmental health XI. A symposium. Columbia, University of Missouri Press, pp. 252-256.
Kaise, T, & Fukui, S (1992) The chemical form and acute toxicity of arsenic compounds in marine organisms. Appl Organomet Chem, 6:155-160.
Kalman, DA, Hughes, J, van Belle, G, Burbacher, T, Dolgiano, D, Coble, K, Mottet, NK, & Polissar, L (1990) The effect of variable environmental arsenic contamination on urinary concentrations of arsenic species. Environ Health Perspect, 89:145-151.
Karagas, MR, Morris, JS, Weiss, JE, Spate, V, Baskett, C, & Greenberg, ER (1996) Toenail samples as an indicator of drinking water arsenic exposure. Cancer Epidemiol Biomarkers Prev, 5:849-852.
Kavanagh PJ, Farago ME, Thornton I & Braman RS (1997) Bioavailability of arsenic in soil and mine wastes of the Tamar valley, SW England. Chemical Speciation and Bioavailability, 9(3): 77-81.
Koons, RD, & Peters, CA (1994) Axial distribution of arsenic in individual human hairs by solid sampling graphite furnace AAS. J Anal Toxicol, 18:36-
Korte NE & Fernando Q (1991) A review of arsenic (III) in groundwater. CRC Crit Rev Environ Control, 21(1): 1-39.
Kurttio P, Komulainen H, Hakala E, Kahelin H & Pekkanen J (1998) Urinary excretion of arsenic species after exposure to arsenic present in drinking water. Arch Environ Contam Toxicol, 34: 297-305.
Kusiak RA, Ritchie AC, Muller J, & Springer J (1993) Mortality from lung cancer in Ontario uranium miners. Br J Ind Med, 50: 920-928.
Kusiak RA, Springer J, Ritchie AC, & Muller J (1991) Carcinoma of the lung inOntario gold miners: possible aetiological factors. Br J Ind Med, 48: 808-817.
Lagerkvist BEA, Linderholm H, & Nordberg G (1988) Arsenic and Raynaud's phenomenon. Int Arch Occup Environ Health 60:361-364.
Lai M-S, Hsueh Y-M, Chen C-J, Shyu M-P, Chen S-Y, Kuo T-L, Wu M-M, & Tai T-Y (1994) Ingested inorganic arsenic and prevalence of diabetes mellitus. Amer J Epidemiol, 139: 484-492.
Le, SXC, Cullen, WR, & Reimer, KJ (1994a) Speciation of arsenic compounds in some marine organisms. Environ Sci Technol, 28:1598-1604.
Le, SXC, Cullen, WR, & Reimer, KJ (1994b) Human urinary arsenic excretion after one-time ingestion of seaweed, crab and shrimp. Clin Chem, 40:617-624.
Lee AM & Fraumeni JF Jr (1969) Arsenic and respiratory cancer in man: an occupational study. J Natl Cancer Inst, 42: 1045-1052.
Lee-Feldstein A (1983) Arsenic and respiratory cancer in humans: Follow-up of copper smelter employees in Montana. J Natl Cancer Inst, 70: 601-609.
Lee-Feldstein A (1986) Cumulative exposure to arsenic and its relationship to respiratory cancer among copper smelter employees. J Occup Med, 28: 296-302.
Lee-Feldstein A (1989) A comparison of several measures of exposure to arsenic. Matched case-control study of copper smelter employees. Am J Epidemiol, 129: 112-124.
Leonard A & Lauwerys RR (1980) Carcinogenicity, teratogenicity, and mutagenicity of arsenic. Mutat Res, 75: 49-62.
Lewis DR & Calderon R (1998a) Drinking water arsenic and non-cancer health effects. Epidemiol, 9 (4 Supplement): S30.

Lewis DR, Calderon R, Southwick JW, Ouellet-Helstrom R, & Rench J (1998b) Drinking water arsenic in the U.S.: the Millard County, Utah mortality study. Submitted to Environmental Health Perspectives, October 1998.

Lewis DR, Southwick JW, Scanlan LP, Rench J, & Calderon RL (1998c) The feasibility of epidemiologic studies of waterborne arsenic. A mortality study in Millard County, Utah. J Environ Health, 60: 14-19.

Lin, T-H, Huang, Y-L, & Wang, M-Y (1998) Arsenic species in drinking water, hair, fingernails, and urine of patients with blackfoot disease. J Toxicol Environ Health, Part A, 53:85-93.

Lindgren, A, Vahter, M, & Dencker, L (1982) Autoradiographic studies on the distribution of arsenic in mice and hamsters administered ^{74}As-arsenite or -arsenate. Acta Pharmacol et Toxicol, 51:253-265.

Liu YT & Chen Z (1996) A retrospective lung cancer mortality study of people exposed to insoluble arsenic and radon. Lung Cancer 14(suppl 1): S137-S148.

Lubin JH, Pottern LM, Blot WJ, Tokudome S, Stone BJ, & Fraumeni JF Jr (1981) Respiratory cancer among copper smelter workers: recent mortality statistics. J Occup Med, 23: 779-784.

Lüchtrath H (1983) The consequences of chronic arsenic poisoning among Moselle wine growers. Pathoanatomical investigatyions of post-mortem examinations between 1960 and 1977. J Cancer Res Clin Oncol, 105: 173-182.

Lugo, G, Cassady, G, & Palmisano, P (1969) Acute maternal arsenic intoxication with neonatal death. Ann J Dis Child, 117:328-330.

Lunde, G (1977) Occurrence and transformation of arsenic in the marine environment. Environmental Health Perspectives, 19: 47-52.

Ma, M, & Le, SC (1998) Effect of arsenosugar ingestion on urinary arsenic speciation. Clin Chem, 44:539-550.

Mabuchi K, Lilienfeld AM, & Snell LM (1979) Lung cancer among pesticide workers exposed to inorganic arsenicals. Arch Environ Health, 34: 312-320.

Mabuchi K, Lilienfeld AM, & Snell LM (1980) Cancer and occupational exposure to arsenic: a study of pesticide workers. Prev Med, 9: 51-77.

MAFF (1997) Ministry of Agriculture, Fisheries and Food. Lead, arsenic and other metals in food. Food Surveillance Paper No 52. London, UK. Her Majesties Stationery Office.

Maher W & Butler E (1988) Arsenic in the marine environment. Appl Organomet Chem, 2: 191-214.

Maki-Paakkanen J, Kurttio P, Paldy A, Pekkanen J (1998) Association between the clastogenic effect in peripheral lymphocytes and human exposure to arsenic through drinking water. Environ Mol Mutagen 32 (4): 301-313.

Mandal BK, Chowdhury TR, Samanta G, Basu GK, Chowdhury PP, Chanda CR, Lodh D, Karan NK, Dhar RK, Tamili DK, Das D, Saha KC and Chakraborti D (1996) Arsenic in groundwater in seven districts of West Bengal, India – The biggest arsenic calamity in the world. Current Science, 70(11): 976-986.

Marafante, E, Bertolero, F, Edel, J, Pietra, R, & Sabbioni, E (1982) Intracellular interaction and biotransformation of arsenite in rats and rabbits. Sci Tot Environ, 24:27-39.

Marafante, E, Vahter, M, Norin, H, Envall, J, Sandstrom, M, Christakopoulos, A, & Ryhage, R (1987) Biotransformation of dimethylarsinic acid in mouse, hamster & man. J Appl Toxicol, 7:111-117.

Marcus, WL, & Rispin, AS (1988) Threshold carcinogenicity using arsenic as an example. In: Risk assessment and risk management of industrial chemicals (Cothern, CR, Mehlman, MA, & Marcus, WL, eds). Princeton, NJ: Princeton Scientific Publishing Co, pp. 138-158.

Matanoski G, Landau E, Tonascia J, Lazar C, Elliott EA, McEnroe W, & King K (1981) Cancer mortality in an industrial area of Baltimore. Environ Res, 25: 8-28.

Matisoff G, Khourey CJ, Hall JF, Varnes AW & Strain WH (1982) The nature and source of arsenic in Northeastern Ohio ground water. Ground Water, 20(4): 446-456.

Mayes, PA (1983) Harper's review of biochemistry, 19th ed, (Martin, DW, Mayes, PA & Rodwell, VW, eds), Lange Medical Publishers, Los Altos, CA, p. 165.

McLaughlin JK, Chen J-Q, Dosemeci M, Chen R-A, Rexing SH, Zhien W, Hearl FJ, McCawley MA & Blot WJ (1992) A nested case-control study of lung cancer among silica exposed workers in China. Brit J Ind Med, 49: 167-171.

Minkkinen P & Yliruokanen I (1978) The arsenic distribution in Finnish peat bogs. Kemia-Kemi, 7-8: 331-335.

Mohri T, Hisanaga A & Ishinishi N (1990) Arsenic intake and excretion by Japanese adults: A 7-day duplicat diet study. Fd Chem Toxic, 28: 521-529 .

Morris R (1995) Drinking water and cancer. Environ Health Perspect, 103: 225-232.

Morton W, Starr G, Pohl D, Stoner J, Wagner S, & Weswig P (1976) Skin cancer and water arsenic in Lane County, Oregon. Cancer, 37: 2523-2532.

Morton WE & Caron GA (1989) Encephalopathy: an uncommon manifestation of workplace arsenic poisoning? Am J Ind Med, 15: 1-5.

MSZW (2000) Nationale MAC-lijst 2000. Ministerie van Sociale Zaken en Werkgelegenheid. Den Haag, Sdu Uitgevers.

Murphy MJ, Lyon LW, & Taylor JW (1981) Subacute arsenic neuropathy: clinical and electrophysiological observations. J Neurol Neurosurg Psychiatry, 44: 896-900.

Narang, APS, & Datta, DV (1983) Brain arsenic concentrations in fulminant hepatitis. J Assoc Physicians - India, 31:518-519.

NAS (1977) Arsenic. Washington, D.C., National Academy of Sciences. 332.

Nelson WC, Lykins MH, Mackey J, Newill VA, Finklea JF, & Hammer DI (1973) Mortality among orchard workers exposed to lead arsenate spray: a cohort study. J Chronic Dis, 26: 105-118.

Ng JC & Moore MR (1996) Bioavailability of arsenic in soils from contaminated sites using a 96 hour rat blood model. In: The Health Risk Assessment and Management of Contaminated Sites, Contaminated Sites Monograph Series No. 5. Eds. A. Langley, B. Markey and H. Hill. Department of Health and Family Services and the Commonwealth Environment Protection Agency. 354-363.

Ng JC, Kratzmann SM, Qi L, Crawley H, Chiswell B & Moore MR (1998b) Speciation and absolute bioavailability: risk assessment of arsenic-contaminated sites in a residential suburb in Canberra. Analyst, 123: 889-892.

NHMRC (1996) National Health and Medical Research Council. Australian drinking water guidelines. Canberra, Commonwealth of Australia.

NHW/DOE (1993) National Health & Welfare/Department of the Environment. Arsenic and its compounds-Supporting Documentation, Canadian Environmental Protection Act Priority Substances List. Ottawa, 210 pp.

NRC (1999) United States Nation Research Council. Arsenic in drinking water. National Academy Press, Washington, DC. 310 pp

Nygren O, Nilsson CA & Lindahl R (1992) Occupational exposure to chromium, copper and arsenic during work with impregnated wood in joinery shops. Ann Occup Hyg, 36: 509-517.

Offergelt, JA, Roels, H, Buchet, JP, Boeckx, M, & Lauwerys, R (1992) Relation between airborne arsenic trioxide and urinary excretion of inorganic arsenic and its methylated metabolites. Br J Ind Med, 49:387-393.

Omura M, Hirata M, Tanaka A, Zhao M, Makitar Y, Inoue N, Gotoh K, Ishinishi N (1996a) Testicular toxicity evaluation of arsenic-containing binary compound semiconductors, gallium arsenide and indium arsenide, in hamsters. Toxicol Lett 89:123-129.

Omura M, Tanaka A, Hirata M, Zhao M, Makita Y, Inoue N, Gotoh K, & Ishinishi N (1996b) Testicular toxicity of gallium arsenide, indium arsenide, and arsenic oxide in rats by repetitive intratracheal instillation. Fundam Appl Toxicol 32:72-78.

Osburn HS (1957) Cancer of the lung in Gwanda. Centr Afr J Med, 3: 215-223.

Osburn HS (1969) Lung cancer in a mining district in Rhodesia. S Afr Med J, 43: 1307-1312.

OSHA (2000) http://www.osha-slc.gov/OshStd_data/1910_1018.html.

Ostrosky-Wegman P, Gonsebatt ME, Montero R, Vega L, Barba H, Espinosa J, Palao A, Cortinas C, Garcia-Vargas G, Del Razo LM, & Cebrian M (1991) Lymphocyte proliferation kinetics and genotoxic findings in a pilot study on individuals chronically exposed to arsenic in Mexico. Mutat Res, 250: 477-482.

Ott MG, Holder BB, & Gordon HL (1974) Respiratory cancer and occupational exposure to arsenicals. Arch Environ Health, 29: 250-255.
Page GW (1981) Comparison of groundwater and surface water for patterns and levels of contamination by toxic substances. Environ Sci Technol, 15(12): 1475-1481.
Paschal DRM, DiPietro ES, Phillips DL and Gunter EW (1989) Age dependence of metals in hair in a selected US population. EnvironmentalResearch, 48: 17-28.
Pedersen GA, Mortensen GK & Larsen EH (1994) Beverages as a source of toxic trace element intake. Fd Additives Contaminants. 11: 351-363.
Peirson DH, Cawse PA & Cambray RS (1974) Chemical uniformity of airborne particulate material, and a maritime effect. Nature, 251: 675-679.
Pershagen G (1985) Lung cancer mortality among men living near an arsenic-emitting smelter. Am J Epidemiol, 122: 684-694.
Pershagen G, Bergman F, Klominek J, Damber L, & Wall S (1987) Histological types of lung cancer among smelter workers exposed to arsenic. Br J Ind Med, 44: 454-458.
Pershagen G, Elinder CG, & Bolander AM (1977) Mortality in a region surrounding an arsenic emitting plant. Environ Health Perspect, 19: 133-137.
Pershagen G, Wall S, Taube A, & Linnman L (1981) On the interaction between occupational arsenic exposure and smoking and its relationship to lung cancer. Scand J Work Environ Health, 7: 302-309.
Phillips, DJH (1990) Arsenic in aquatic organisms: a reviewemphasising chemical speciation. Aquatic Toxicology, 16(3): 151-186.
Pinto SS & Bennett BM (1963) Effect of arsenic trioxide exposure on mortality. Arch Environ Health, 7: 583-591.
Pinto SS, Enterline PE, Henderson V, & Varner MO (1977) Mortality experience in relation to a measured arsenic trioxide exposure. Environ Health Perspect, 19: 127-130.
Pinto SS, Henderson V & Enterline PE (1978) Mortality experience of arsenic-exposed workers. Arch Environ Health 33: 325-331.
Pomroy, C, Charbonneau, SM, McCullough, RS, & Tam, GKH (1980) Human retention studies with ^{74}As. Toxicol Appl Pharmacol, 53:550-556.
Porter, EK & Peterson, PJ (1975) Arsenic accumulation by plants on mine waste (UK). Science of the Total Environment, 4: 365-371.
Qiao YL, Taylor PR, Yao SX, Erozan YS, Luo XC, Barrett MJ, Yan QY, Giffen CA, Huang SQ, Maher MM, Forman MR, & Tockman MS (1997) Risk factors and early detection of lung cancer in a cohort of Chinese tin miners. Ann Epidemiol, 7: 533-541.
Rahman M & Axelson O (1995) Diabetes mellitus and arsenic exposure: a second look at case-control data from a Swedish copper smelter. Occup Environ Med, 52: 773-774.
Rahman M, Tondel M, Ahmad SA, & Axelson O (1998) Diabetes mellitus associated with arsenic exposure in Bangladesh. Am J Epidemiol, 148: 198-203.
Rahman M, Wingren G, & Axelson O (1996) Diabetes mellitus among Swedish glass workers - an effect of arsenic exposure? Scand J Work Environ Health, 22: 146-149.
Rahman, MS, & Hughes, MF (1994) In vitro percutaneous absorption of monosodium methanarsonate and disodium methanearsonate in female B6C3F $_1$ mice. J Toxicol Environ Health, 41:421-433.
Raie, RM (1996) Regional variation in As, Cu, HG, and Se and interaction between them. Ecotoxicol Environ Safety, 35:248-252.
Robertson FN (1989) Arsenic in ground-water under oxidizing conditions, south-west United States. Environ Geochem Health, 11: 171-185.
Roels H, Buchet J-P, Truc J, Croquet F & Lawerys R (1982) The possible role of direct ingestion on the overall absorption of cadmium or arsenic in workers exposed to CdO and As_2O_3 dust. Am J Ind Med 3: 53-65.
Rom WN, Varley G, Lyon JL, & Shopkow S (1982) Lung cancer mortality among residents living near the El Paso smelter. Br J Ind Med, 39: 269-272.
Roth F (1955) Haemangioendothelioma of the liver after chronic arsenic intoxication. Zentralbl Allg Pathol, 93: 424-425.
Roth F (1957a) Arsenic-liver tumours (haemangioendothelioma). Z Krebsforsch, 61: 468-503.

Roth F (1957b) Über die Spätfolge des chronischen Arsenismus der Moselwinzer (Late consequencies of chronic arsenicism in Moselle vine-dressers). Dtsch Med Wochenschr, 82: 211-217.

Roth F (1958) Über den Bronchialkrebs arsengeschädigter Winzer (On bronchial carcinoma in arsenic-exposed vineyard workers). Virchows Arch A Pathol Anat Histopathol, 331: 119-137.

Sandström A & Wall S (1993) Cancer incidence among male salaried employees at a smeltery in northern Sweden. Acta Oncol, 32: 9-14.

Sandström AIM, Wall SGI, & Taube A (1989) Cancer incidence and mortality amon Swedish smelter workers. Br J Ind Med, 46: 82-89.

Sanok WJ, Ebel JG, Manzell KL, Gutenmann WH & Lisk DJ (1995) Residues of arsenic and lead in potato soils on Long Island. Chemosphere, 30(4): 803-806.

Sapunar-Postruznik J, Bazulic D & Kubala H (1996) Estimation of dietary intake of arsenic in the general population of the Republic of Croatia. Sci Total Environ, 191: 119-123.

Schaller KH, Schiele R & Valentin H (1982) [Questions on the action of arsenic in mixing, melting and charging in the lead crystal industry]. [Medical study at work of the action of impurities and hazardous substances in the ceramics and glass industry]. No. 31. [Professional Association of the Ceramics and Glass Industry], Würzburg. [in German].

Schrag S & Dixon R (1985) Occupational exposures associated with male reproductive dysfunction. Ann Rev Pharmacol Toxicol, 25: 567-592.

Schroeder WH, Dobson M, Kane DM & Johnson ND (1987) Toxic trace elements associated with airborne particulate matter: a review. J Air Pollut Control Assoc, 37(11): 1267-1285.

Schulz E (1967) Arsenic as a cause of skin cancer with notes on its occurrence in Pretoria. SA Med J, 2 Sept: 819-822.

Scotto J, Fears TR, Kraemer KH, & Fraumeni JF, Jr. (1996) Non-melanoma skin cancer. In: Schottenfeld J & Fraumeni JF eds. Cancer Epidemiology and Prevention, 2nd ed. New York, Oxford University Press, pp 1313-1330.

Scudlark JR & Church TM (1988) The atmospheric deposition of arsenic and association with acid precipitation. Atmos Environ, 22(5): 937-943.

Shah, PV, Fisher, HL, Sumler, MR, Monroe, RJ, Chernoff, N, & Hall, LL (1987) Comparison of the penetration of 14 pesticides through the skin of young and adult rats. J Toxicol Environ Health, 21:353-366.

Shotyk W (1996) Natural and anthropogenic enrichments of As, Cu, Pb, Sb, and Zn in ombrotrophic versus minerotrophic peat bog profiles, Jura Mountains, Switzerland. Water Air Soil Pollut, 90(3/4): 375-405.

Simonato L, Moulin JJ, Javelaud B, Ferro G, Wild P, Winkelmann R, & Saracci R (1994) A retrospective mortality study of workers exposed to arsenic in a gold mine and refinery in France. Am J Ind Med, 25: 625-633.

Smith A, Goycolea M, Haque R, & Biggs ML (1998) Marked increase in bladder and lung cancer mortality in a region of Northern Chile due to arsenic in drinking water. Amer J Epidemiol, 147: 660-669.

Smith A, Hopenhayn-Rich C, Bates M, Goeden H, Hertz-Picciotto I, Duggan H, Wood R, Kosnett M, & Smith M (1992) Cancer risks from arsenic in drinking water. Environ Health Perspect, 97: 259-267.

Smith RA, Alexander RB & Wolman MG (1987) Water-quality trends in the nation's rivers. Science, 235: 1607-1615.

Sobel W, Bond GG, Baldwin CL, & Ducommun DJ (1988) An update of respiratory cancer and occupational exposure to arsenicals. Am J Ind Med, 13: 263-270.

Sorahan T & Lancashire RJ (1997) Lung cancer mortality in a cohort of workers employed at a cadmium recovery plant in the United States: an analysis with detailed job histories. Occup Environ Med, 54: 194-201.

Stevens, JT, Hall, LL, Farmer, JD, DiPasquale, LC, Chernoff, N, & Durham, WF (1977) Disposition of cacodylic acid in rats after intravenous, intratracheal, or per oral administration. Environ Health Perspect, 19:151-157.

Stilwell DE & Gorny KD (1997) Contamination of soil with copper, chromium, and arsenic under decks built from pressure treated wood. Bull Environ Contam Toxicol, 58: 22-29.

Styblo M, & Thomas DJ (1995) In vitro inhibition of glutathione reductase by arsenotriglutathione. Biochem Pharmacol 49:971-977.

Styblo, M, Delnomdedieu, M, & Thomas, DJ (1996) Mono- and dimethylation of arsenic in rat liver cytosol in vitro. Chem-Biol Interact, 99:147-164.

Subra I, Hubert G, Aubert S, Héry M & Elcsbache JM (1999) Exposition professionnelle aux métaux lors de l=usinage des bois traités au cuivre, chrome, arsenic. INRS, Cahiers de notes documentaire - Hygiene et sécurité du travail - No. 175, Centre de recherche de l=IRNS, Nancy, France.

Tabacova S & Hunter ES. Pathogenic role of peroxidation in prenatal toxicity of arsenic. In: Zelikoff J, Bertin J, Burbacher T, Hunter S, Miller R, Silbergeld E, Tabacova S, & Rogers J (1995) Health risks associated with prenatal exposure. Experimental and Applied Toxicology, 25: 161-170.

Takamatsu T, Aoki H & Yoshida T (1982) Determination of arsenate, arsenite, monomethylarsonate, and dimethylarsinate in soil polluted with arsenic. Soil Sci, 133(4): 239-246.

Tam, GKH, Charbonneau, SM, Bryce, F, & Sandi, E (1982) Excretion of a single oral dose of fish-arsenic in man. Bull Environ Contam Toxicol, 28:669-673.

Tanaka T (1990) Arsenic in the natural environment. Part II: Arsenic concentrations in thermal waters from Japan. Appl Organomet Chem, 4: 197-203.

Taylor PR, Qiao Y-L, Schatzkin A, Yao S-X, Lubin J, Mao B-L, Rao J-Y, McAdams M, Xuan X-Z & Li J-Y (1989) Relation of arsenic exposure to lung cancer among tin miners in Yunnan Province, China. Br J Ind Med 46: 881-886.

Thiers H, Colomb D, Moulin G, & Colin L (1967) Le cancer cutané arsenical des viticulteurs du Beaujolais (Arsenical skin cancer among vine dressers in Beaujolais). Ann Dermatol Syphiligr, 94: 133-158.

Toa & Bolger 1998

Tokudome S & Kuratsune M (1976) A cohort study on mortality from cancer and other causes among workers at a metal refinery. Int J Cancer, 17: 310-317.

Tollestrup K, Daling JR, & Allard J (1995) Mortality in a cohort of orchard workers exposed to lead arsenate pesticide spray. Arch Environ Health, 50: 221-229.

Tremblay GH & Gobeil C (1990) Dissolved arsenic in the St Lawrence Estuary and the Saguenay Fjord, Canada. Mar Pollut Bull, 21(10): 465-469.

Trepka, MJ, Heinrich, J, Schulz, C, Krause, C, Popescu, M, Wjst, M, & Wichmann, H-E (1996) Arsenic burden among children in industrial areas of eastern Germany. Sci Total Environ, 180:95-105.

Tseng W-P (1977) Effects and dose-response relationship of skin cancer and blackfoot disease with arsenic. Environ Health Perspect, 19: 109-119.

Tseng W-P, Chu H-M, How S-W, Fong J-M, Lin C-S, & Yeh S (1968) Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. J Nat Cancer Inst, 40: 453-463.

Tsuda T, Babazono A, Yamamoto E, Kurumatani N, Mino Y, Ogawa T, Kishi Y, & Aoyama H (1995) Ingested arsenic and internal cancer: a historical cohort study followed for 33 years. Amer J Epidemiol, 141: 198-209.

Urieta I, Jalon M & Eguilero I (1996) Food surveillance in the Basque Country (Spain). II. Estimation of the dietary intake of organochlorine pesticides, heavy metals, arsenic, aflatoxin M1, iron and zinc through the total diet study, 1990/91. Food Addit Contam, 13: 29-52.

US EPA (1982) An exposure and risk assessment for arsenic. Washington, D.C., U.S. Environmental Protection Agency. EPA 440/4-85-005).

US EPA (1988) Special report on ingested arsenic: skin cancer and nutritional essentiality. Washington, DC, US Environmental Protection Agency Risk Assessment Forum (EPA/625/3-87/013).

US EPA (1993) US Environmental Protection Agency. Drinking water criteria document for arsenic. Office of Water, Washington, D.C., 236 pp.

Vaessen, HA and van Ooik, A (1989) Speciation of arsenic in Dutch total diets: methodology and results. Zeitsschrift fur Lebensmittel Untersuchung und Forschung, Sep 189(3): 232-235.

Vahter M (1999) Methylation of inorganic arsenic in different mammalian species and population groups. Science Progress, 82:69-88.

Vahter M, Couch, R, Nermell, B, & Nilsson, R (1995b) Lack of methylation of inorganic arsenic in the chimpanzee. Toxicol Appl Pharmacol, 133:262-268.
Vahter M, Concha G, Nermell b, Nilsson R, Dulout F and Natarajan AT (1995a) A unquie metabolism of inorganic arsenic in native Andean women. European Jouranl of Pharmacology (Environmental Toxicology and Pharmacology Section), 293:455-462.
Vahter, M, Friberg, L, Rahnster, B, Nygren, A, & Nolinder, P (1986) Airborne arsenic and urinary excretion of metabolites of inorganic arsenic among smelter workers. Int Arch Occup Environ Health, 57:79-91.
Vahter, M, Marafante, E, & Dencker, L (1984) Tissue distribution and retention of ^{74}As-dimethylarsinic acid in mice and rats. Arch Environ Contam Toxicol, 13:259-264.
Valberg PA, Beck BD, Boardman PD, & Cohen JT (1998) Likelihood ratio analysis of skin cancer prevalence associated with arsenic in drinking water in the USA. Environ Geochem Health, 20: 61-66.
Valentine, JL, Kang, HK, & Spivey, G (1979) Arsenic levels in human blood, urine, and hair in response to exposure via drinking water. Environ Res, 20:24-32.
Varsanyi I (1989) Arsenic in deep groundwater. In: Proceedings of the 6th International Symposium on water-rock interaction (WRI-6), Malvern. Ed. Miles DL. Publisher AA Balkema, Rotterdam/Brookfield. pp715-718.
Vianna NJ, Brady JA, & Cardamone AT (1981) Epidemiology of angiosarcoma of liver in New York State. N Y State J Med, 81: 895-899.
Vig BK, Figueroa ML, Cornforth MN, & Jenkins SH (1984) Chromosome studies in human subjects chronically exposed to arsenic in drinking water. Am J Ind Med 6:325-228.
Wagemann R, Snow NB, Rosenberg DM & Lutz A (1978) Arsenic in sediments, water, and aquatic biota from lakes in the vicinity of Yellowknife, Northwest Territories, Canada. Arch Environ Contam Toxicol, 7: 169-191.
Wall S (1980) Survival and mortality pettern among Swedish smleter workers. Int J Epidemiol, 9: 73-87.
Walsh LM & Keeney DR (1975) Behavior and phytotoxicity of inorganic arsenicals in soils. ACS Symp Ser, 7: 35-52.
Warner ML, Moore LE, Smith MT, Kalman DA, Fanning E, & Smith AH (1994) Increased micronuclei in exfoliated bladder cells of individuals who chronically ingest arsenic-contaminated water in Nevada. Cancer Epidemiol Biomarkers Prevent 3:583-590.
Warren, HV, Jorksy, SJ, & Gould, CE (1983) Quantitative analysis of zinc, copper, lead, molybdenum, bismuth, mercury and arsenic in brain and other tissues from multiple sclerosis and non-multiple sclerosis cases. Sci Total Environ, 29:163-169.
Weinshilboum, RM (1992) Methylation pharmacogenetics: thiopurine methyltransferase as a model system. Xenobiotica, 22:1055-1071.
Weiss W (1983) Respiratory cancer risk in relation to arsenic exposure and smoking. Arch Environ Health, 38: 189-191.
Welch AH, Lico MS & Hughes JL (1988) Arsenic in groundwater of the western United States. Ground Water, 26(3): 333-347.
Welch K, Higgins I, Oh M & Burcfiel C (1982) Arsenic exposure, smoking, and respiratory cancer in copper smelter workers. Arch Environ Health 37: 325-335.
Wester, RC, Maibach, HI, Sedik, L, Melendres, J, & Wade, M (1993) In vitro and in vivo percutaneous absorption and skin decontamination of arsenic from water and soil. Fundam Appl Toxicol, 20:336-340.
WHO (1981) Arsenic. Environmental Health Criteria 18 Geneva, World Health Organization. 174 pp.
WHO (2001) Arsenic and arsenic compounds. Environmental Health Criteria 22? (Second edition). Geneva, World Health Organization. In press.
Wicks MJ, Archer VE, Auerbach O, & Kuschner M (1981) Arsenic exposure in a copper smelter as related to histological type of lung cancer. Am J Ind Med, 2: 25-31.
Williams M, Fordyce F, Paijitprapapon A & Charoenchaisri P (1996) Arsenic contamination in surface drainage and groundwater in part of the southeastern Asian tin belt, Nakhon Si Thammarat Province, southern Thailand. Environ Geol, 27: 16-33.

Wolfsperger M, Hauser G, Gobler W and Schlagenhaufen C (1994) Heavy metals in human hair samples from Austria and Italy: influence of sex and smoking habits. Science of the Total Environment, 156:235-242.

Wong O, Whorton MD, Foliari DE & Lowengart R (1992) An ecologic study of skin cancer and environmental arsenic exposure. Int Arch Occup Environ Health, 64: 235-241.

Wu M-M, Kuo T-L, Hwang Y-H & Chen C-J (1989) Dose-response relation between arsenic concentration in well water and mortality from cancers and vascular disease. Am J Epidemiol, 130: 1123-1132.

Xu JL & Thornton I (1985) Arsenic in garden soils and vegetable crops in Cornwall, England: implications for human health. Environ Geochem Health, 7(4): 131-133.

Yager JW, Hicks JB & Fabianova E (1997) Airborne arsenic and urine excretion of arsenic metabolites during boiler cleaning operations in a Slovak coal-fired power plant. Environ. Health Perspec, 105: 836-842.

Yamauchi, H& Yamamura, Y (1984) Metabolism and excretion of orally ingested trimethylarsenic in man. Bull Environ Contam Toxicol, 32:682-687.

Yamauchi, H, & Yamamura, Y (1983) Concentration and chemical species of arsenic in human tissue. Bull Environ Contam Toxicol, 31:267-277.

Yamauchi, H, Kaise, T, Takahashi, K & Yamamura, Y (1990) Toxicity and metabolism of trimethylarsine in mice and hamster. Fundam Appl Toxicol, 14:399-407.

Yamauchi H, Yamato N and Yamamura Y (1988) Metabolism and excretion of orally and intraperitoneally administered methylarsenic in the hamster. Bulletin of Environmental Contamination & Toxicology, 40: 280-286.

Yamauchi, H, Takahashi, K, Mashiko, M, & Yamamura, Y (1989) Biological monitoring of arsenic exposure of gallium arsenide- and inorganic arsenic-exposed workers by determination of inorganic arsenic and its metabolites in urine and hair. Am Ind Hyg Assoc J, 50:606-612.

Yost LJ, Schoof RA & Aucoin R (1998) Intake of inorganic arsenic in the North American diet. Human Ecol Risk Assessment, 4: 137-152.

Zaldivar R (1974) Arsenic contamination of drinking water and foodstuffs causing endemic chronic poisoning. Beitr Path Bd, 151: 384-400.

Zaldivar R, Prunes L & Ghai G (1981) Arsenic dose in patients with cutaneous carcinomata and hepatic haemangio-endolthelioma after environmental and occupational exposure. Arc Toxicol, 47: 145-154.

Zhang X, Cornelis R, De Kimpe J, Mees L, & Lameire N (1997) Speciation of arsenic in serum, urine and dialysate of patients on continuous ambulatory peritoneal dialysis. Clin Chem, 43(2):406-408.

Zhang X, Cornelis R, De Kimpe J, Mees L, & Lameire N (1998) Study of arsenic-protein binding in serum of patients on continuous ambulatory peritoneal dialysis. Clin Chem, 44(1):141-147.

Zhang X, Cornelis R, De Kimpe J, Mees L, Vanderbiesen V, De Cubber A, & Vanholder R (1996) Speciation of arsenic in serum, urine and dialysate of patients on continuous ambulatory peritoneal dialysis. Clin Chem, 43(2):406-408.

Zhu B & Tabatabai MA (1995) An alkaline oxidation method for determination of total arsenic and selenium in sewage sludges. J Environ Qual, 24(4): 622-626.

Zhuang, GS, Wang, YS, Tan, MG, Zhi, M, Pan, WQ, & Cheng, YD (1990) Preliminary study of the distribution of the toxic elements As, Cd, and Hg in human hair and tissues by RNAA. Biol Trace Elem Res, 12:729-736.

Zierler S, Theodore M, Cohen A & Rothman K (1988) Chemical quality of maternal drinking water and congenital heart disease. Int J Epidemiol, 17: 589-594.