5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 Environmental levels

Arsenic is a natural component of the earth's crust, and found in all environmental media. Concentrations in air in remote locations range from < 1 to 3 ng/m^3, but concentrations in cities may range up to 100 ng/m^3. Concentrations in water are usually < 10 µg/litre, although higher concentrations can occur near natural mineral deposits or anthropogenic sources. Natural levels in soils usually range from 1 to 40 mg/kg, but pesticide application or waste disposal can produce much higher values.

5.1.1 Air

Levels of arsenic in ambient air are summarized in Table 3. Examples are given of mean total arsenic concentrations in remote and rural areas ranging from 0.02 to 4 ng/m^3. Levels of arsenic in outdoor air near to urban and industrial sources are summarized in Table 4. Examples are given of mean total arsenic concentrations in urban areas ranging from 3 to 200 ng/m^3; much higher concentrations (> 1000 ng/m^3) have been measured in the vicinity of industrial sources. Arsenic in ambient air is usually a mixture of arsenite and arsenate, with organic species being of negligible importance except in areas of substantial methylated arsenic pesticide application or biotic activity. Schroeder et al. (1987) reviewed worldwide arsenic concentrations associated with particulate matter. They identified arsenic levels ranging from 0.007 to 1.9 ng/m^3 for remote areas, 1 to 28 ng/m^3 for rural areas and 2 to 2320 ng/m^3 in urban areas. The highest arsenic levels detected in the atmosphere were near non-ferrous-metal smelters.

Typical background levels for arsenic are now 0.2–1.5 ng/m^3 for rural areas, 0.5–3 ng/m^3 for urban areas and < 50 ng/m^3 for industrial sites (DG Environment, 2000).

Table 3. Concentrations of As in ambient air[a]

Location	Sampling period	Particle size and/or species	Concentration (ng/m^3)[b]	Reference
Antarctica	NS		0.019	Brimblecombe (1979)
Antarctic Ocean	1988–1989	As_i	0.05 (0.01–0.2)	Nakamura et al. (1990)
	1988–1989	As_o	0.002 (single sample)	Nakamura et al. (1990)
North Pacific Ocean	1981–1987	As_i	0.1 (0.01–0.95)	Nakamura et al. (1990)
	1981–1987	As_o	0.008 (0.001–0.03)	Nakamura et al. (1990)
North Atlantic Ocean	1989	As_i	0.1 (0.01–0.45)	Nakamura et al. (1990)
	1989	As_o	0.007 (0.001–0.3)	Nakamura et al. (1990)
Baltic Sea	1985		1.1 (0.3–3.7)	Häsänen et al. (1990)
Mid-Atlantic coast, USA	1985–1986		1.05	Scudlark & Church (1988)
Continental shelf waters, south-eastern USA	1975–1976	particulate	1.7 (0.2–4.3)	Waslenchuk (1978)
Northern Chesapeake Bay, USA	1990–1991	< 10 µm	0.66 (0.11–1.96)	Wu et al. (1994)
Rural US sites (National Parks)	1979–1981	0.45 µm	< 1.6–2.3 (range of means)	Davidson et al. (1985)

Table 3 (contd.)

Midwestern USA	1990		1.6 (0.7–2.5)	Burkhard et al. (1994)
Natural geysers, northern California, USA	1989	As(III) As(V)	0.22 & 0.54 (0.06–3.08) 0.46 (0.08–1.3) & 2.29 (0.7–6.54)	Solomon et al. (1993) Solomon et al. (1993)
Bagauda, Nigeria	1976		0.6	Beavington & Cawse (1978)
Pelindaba, South Africa	1976		1.7	Beavington & Cawse (1978)
Chilton, United Kingdom	1976		4.2	Beavington & Cawse (1978)
Rural sites, United Kingdom	1972–1973		1.5–2.5 (range of means)	Peirson et al. (1974)
Rural area near Thessaloniki, Greece	1989–1990		2.7	Misaelides et al. (1993)
Birkenes, Norway	1978–1979 1985–1986	particulate particulate	1.2 (0.02–12) 0.63 (< 0.04–4.6)	Amundsen et al. (1992) Amundsen et al. (1992)

[a] As = inorganic As; As = organic As; NS = not stated
[b] Mean and ranges of total As unless stated otherwise

Table 4. Concentrations of As in outdoor air near urban and industrial sources

Location	Distance from source (km)	Sampling period	Particle size and/or species	Concentration (ng/m^3)[a]	Reference
Industrial sites, UK	NS	1972–1973	NS	1.2–24 (ng/kg, range of means)	Peirson et al. (1974)
Urban area, Thessaloniki, Greece	NS	1989–1990	0.45 µm	4.1	Misaelides et al. (1993)
Urban area, Yokohama, Japan	NS	1988	0.45 µm; inorganic As	2.5 (1–5.1)	Nakamura et al. (1990)
			0.45 µm; organic As	0.01 (0.001–0.64)	Nakamura et al. (1990)
Los Angeles, USA	NS	1987	< 2.5 µm; As(III)	7.4 (< 1.2–44)	Rabano et al. (1989)
	NS	1987	> 2.5 µm; As(III)	1.8 (< 0.9–4.8)	Rabano et al. (1989)
	NS	1987	< 2.5 µm; As(V)	5.2 (< 0.9–18.7)	Rabano et al. (1989)
	NS	1987	> 2.5 µm; As(V)	2.2 (< 0.8–6.6)	Rabano et al. (1989)
Wuhan City, China	NS	1988	< 2.5 µm	25	Waldman et al. (1991)
	NS	1988	≥ 2.5 µm < 10 µm	13	Waldman et al. (1991)
Calcutta, India	NS	NS	0.45 µm	180 (91–512)	Chakraborti et al. (1992)

Table 4 (contd.)

Kola peninsula, Russia near (CuBNi smelter)	NS	1993	particulate	28	Kelley et al. (1995)
Caletones, Chile (near Cu smelter)	< 10	1987–1990	0.4 µm	1483	Romo-Kröger & Llona (1993)
	< 20	1987–1990	0.4 µm	131	Romo-Kröger & Llona
	< 30	1987–1990	0.4 µm	14	(1993)
	< 10	1987–1990	0.8 µm	29	Romo-Kröger & Llona
	< 20	1987–1990	0.8 µm	5	(1993)
	< 30	1987–1990	0.8 µm	3.5	Romo-Kröger & Llona (1993)
	13	1991	< 2.5 µm	241[b]	Romo-Kröger et al.
	13	1991	2.5–10 µm	26	(1994)

[a] Mean and ranges of total As unless stated otherwise
[b] Fine particle concentration was 23 ng/m^3 during a strike period at the smelter
NS = not stated

5.1.2 Precipitation

Arsenic has been detected in rainwater at mean concentrations of 0.2–0.5 µg/litre (Welch et al., 1988). Peirson et al. (1974) report mean arsenic concentrations in rainfall ranging from < 6 µg/litre for a rural site to 45 µg/litre at a North Sea gas platform. Arsenic concentrations in precipitation at the mid-Atlantic coast of the USA ranged from < 0.005 to 1.1 µg/litre with an average of 0.1 µg/litre (Scudlark & Church, 1988). Andreae (1980) collected rainwater samples from non-urban sites in California (USA) and state parks in Hawaii and found mean arsenic concentrations ranging from 0.013 to 0.032 µg/litre. Samples from a rural site in Washington state (USA) contained a mean concentration of 1.1 µg As/litre; the author states that the site is 154 km north of a large copper smelter. Vermette et al. (1995) monitored arsenic levels in wet deposition at three sites (Colorado, Illinois and Tennessee, USA) and found mean concentrations ranging from 0.09 to 0.16 µg/litre. Reimann et al. (1997) monitored rainwater samples during the summer of, 1994 in eight Arctic catchments. Median arsenic concentrations (0.45 µm) ranged from 0.07 µg/litre at the most remote site to 12.3 µg/litre near a smelter.

Barbaris & Betterton (1996) analysed fresh snowpack samples from high-elevation forests of north-central Arizona (USA) during late winter and early spring 1992–1994. Arsenic concentrations ranged from 0.02 to 0.4 µg/litre with a mean value of 0.14 µg/litre.

5.1.3 Surface water

Levels of arsenic in seawater are summarized in Table 5. Concentrations of arsenic in open ocean seawater are typically 1B2 µg/litre. The dissolved forms of arsenic in seawater include arsenate, arsenite, MMA and DMA, with adsorption on to particulate matter being the physical process most likely to limit dissolved arsenic concentrations (Maher & Butler, 1988). Levels of arsenic in estuarine water are summarized in Table 6. Tremblay & Gobeil (1990) noted that arsenic concentrations increased with increasing salinity (0–31 g/litre) from 0.5 to 1.4 µg/litre (6.6 to 18.9 nmol/litre) in the St Lawrence estuary (Canada) and from 0.1 to 1.4 µg/litre (1.1 to 18.7 nmol/litre) in its tributary Saguenay fjord. Penrose et al. (1975) monitored seawater in Moreton's Harbour, Newfoundland

Table 5. Background concentrations of As in seawater

Location	Sampling period	Sampling details and/or species	Concentration (µg/litre)[a]	Reference
Gulf of Mexico	NS	0.2 µm filtered	0.04	Chakraborti et al. (1986)
Pacific Ocean	NS	no arsenite detected	1.8 (1.6–2.1) 1.2–1.5	Bodewig et al. (1982) Andreae (1978, 1979)
Coastal waters, South Australia	NS	dissolved; particulate As below limit of detection (0.6 ng/litre)	1.3 (1.1–1.6)	Maher (1985a)
Continental shelf waters, south-eastern USA	1975–1976	depth 30 m and 500 m	1.1 and 1.5	Waslenchuk (1978)
Coastal waters, south-east Spain	NS	below surface	1.5 (0.45–3.7)	Navarro et al. (1993)
Baltic Sea	1982–1983	0.45 µm filtered	0.76 (0.45–1.1)	Stoeppler et al. (1986)
Coastal waters, Malaysia	NS	0.45 µm filtered; 66% arsenate; 33% arsenite	0.95 (0.65–1.8)	Yusof et al. (1994)
Bohai Bay, China	1979	39º10′–38º40′N; 117º37′–180º00′E	1.4 (0.56–2.1)	Tan et al. (1983)

[a] Mean and ranges of total As unless stated otherwise
NS = not stated

Table 6. Concentrations of As in estuarine waters

Location	Sampling Period	Sampling details and/or species	Concentration (µg/litre)[a]	Reference
Tamar estuary, UK	1984	Glass fibre filtered	2.7–8.8 (range)	Howard et al. (1988)
Rhone estuary, France	1984–1988	4–24% arsenite; surface	1.3–3.8 (range)	Seyler & Martin (1990)
Gironde estuary, France	1984	4–14% arsenite; surface	0.7–2.5 (range)	Seyler & Martin (1990)
Loire estuary, France	1984	4–25% arsenite; surface	1.5–3.0 (range)	Seyler & Martin (1990)
Schelde estuary, Belgium	1984	2–16% arsenite	1.8–4.9 (range)	Andreae & Andreae (1989)
Huang He river estuary, China	NS	dissolved As, surface water	Total = 3.6 (2.8–4.3) Organic = 2.3 (1.3–2.9) Inorganic. = 1.4 (0.7–2.3) Arsenite = 0.5 (0.3–0.8) Arsenate = 0.8 (0.2–1.4)	Li et al. (1989)

[a] Mean and ranges of total As unless stated otherwise
NS = not stated

near a long-term stibnite mine. Total inorganic arsenic concentrations were 5.3 µg/litre near the mine but declined to normal levels (1–2 µg/litre) within 200 m.

Howard et al. (1988) report that concentrations of methylated arsenic increased with salinity in the Tamar estuary (United Kingdom). Concentrations of monomethylarsenic ranged from 0.02 to 0.46 µg As/litre and dimethylarsenic from 0.02 to 1.27 µg As/litre; these two methylated forms of arsenic were typically 4% and 10% of the total soluble arsenic levels respectively.

Levels of arsenic in surface freshwaters are summarized in Table 7. Surveys of arsenic concentrations in rivers and lakes indicate that most values are below 10 µg/litre, although individual samples may range up to 1 mg/litre (Page, 1981; Smith et al., 1987; Welch et al., 1988). Mean total arsenic concentrations of 2000 µg/litre have been recorded near a pesticide plant, with MMA being the predominant arsenic species (Faust et al., 1983; 1987a). Crearley (1973) measured arsenic in two lakes near a manufacturing plant which had been producing arsenic-based cotton desiccants/defoliants for 30 years. Mean arsenic concentrations of 7900 and 3200 µg/litre were found. During the dry season total dissolved arsenic concentrations (< 0.45 µm) of up to 250 µg/litre were recorded near industrial discharges to the Xiangjiang river (China); however, maximum levels during the rainy season were generally less than 30 µg/litre (Chunguo & Zihui, 1988).

High levels of arsenic have been recorded in thermal waters. Tanaka (1990) found a mean concentration of 570 µg/litre in geothermal waters throughout Japan, with a maximum level of 25.7 mg/litre.

5.1.4 Groundwater

Levels of arsenic in groundwater are summarized in Table 8. Arsenic levels in groundwater average about 1–2 µg/litre, except in areas with volcanic rock and sulfide mineral deposits where arsenic levels can range up to 3400 µg/litre (Page, 1981; Welch et al., 1988; Robertson, 1989). In some mining areas arsenic concentrations of up to 48 mg/litre have been reported (Welch et al., 1988). Korte & Fernando (1991) reported that arsenic levels in arsenic-contaminated

Table 7. Concentrations of As in surface freshwaters

Location	Sampling period	Sampling details and/or As source	Concentration (µg/litre)[a]	Referenc
Brazos river, Texas, USA	NS	0.2 µm filtered, arsenite	0.05	Chakraborti et al. (1986)
Madison river, Montana, USA	NS	geothermal	51	Sonderegger & Ohguchi (1988)
Finfeather lake, Texas, USA	1973	near manufacturing plant for As-based cotton defoliants	7900 (6000–8600)	Crearley (1973)
Municipal lake, Texas, USA	1973	as above	3200 (1700–4400)	Crearley (1973)
Maurice river, NJ, USA	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, USA	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)
Asososca lake, Nicaragua	1991–1992	volcanic crater; includes surface, intermediate and bottom samples	5.9 (0.85–15.8)	Cruz et al. (1994)

Table 7 (contd.)

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/As mine dumps	13–96 (range of means)	Jonnalagadda &
Odzi river, Zimbabwe	1993	2.2 km downstream from gold/As mine dumps (after confluence with Mutare river)	1–3 (range of means)	Nenzou (1996b)
Xolotlan lake, 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)

[a] Mean and ranges of total As unless stated otherwise
NS, not stated

Table 8. Concentrations of As in groundwater

Location	Sampling period	As source	Concentration (µg/litre)[a]	Reference
Hungary	NS	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, USA	1977–79	well-waters	1 (median) 1160 (maximum)	Page (1981) Page (1981)
Western USA	NS	geochemical environments	48 000 (maximum)	Welch et al. (1988)
South-west USA	1970	alluvial aquifers	16–62 (range of means)	Robertson (1989)
Southern Iowa and western Missouri, USA	NS	natural origin	34–490 (range)	Korte & Fernando (1991)
North-eastern Ohio, USA	NS	natural origin	< 1–100 (range)	Matisoff et al. (1982)
Lagunera region, northern Mexico	NS	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)

Table 8 (contd.)

Pampa, Cordoba, Argentina	NS	2–15 m, 61º45′–63ºW; 32º20′–35º00′S	100–3810 (range)	Nicolli et al. (1989)
Kuitun-Usum, Xinjiang, PR China	1980	well-waters	850 (maximum)	Wang et al. (1993)
Hsinchu, Taiwan	NS	well-waters	< 0.7	Chen et al. (1994)
West Bengal, India	NS	As-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	< 50–23 080 (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)

[a] Mean and ranges of total As unless stated otherwise
NS = not stated

water supply wells in southern Iowa and western Missouri (USA) ranged from 34 to 490 µg/litre. The authors state that the arsenic appears to be of natural origin. Similarly, Matisoff et al. (1982) found no evidence for an anthropogenic source contributing to elevated groundwater levels of arsenic (< 1 to 100 µg/litre) in north-eastern Ohio (USA). Arsenic levels in groundwater were found to exceed 10 µg/litre in 5.6–9.5% of samples collected in Germany during the period 1992–1994 (Umweltbundesamt, 1997). Varsanyi (1989) found arsenic concentrations in deep groundwater in Hungary to range from 1 to 174 µg/litre with an average value of 68 µg/litre. High arsenic levels originating from arsenic-rich bedrock were found in drilled wells in south-west Finland, with concentrations ranging from 17 to 980 µg/litre (Kurttio et al., 1998). Del Razo et al. (1990) monitored groundwater in the Lagunera region of northern Mexico. Total arsenic concentrations ranged from 8 to 624 µg/litre with over 50% of samples > 50 µg/litre. The predominant arsenic species in 93% of samples was arsenate, although in 36% of samples 20–50% arsenite was found. Chen et al. (1994) report that arsenic levels in the groundwater of south-west Taiwan contained mean dissolved arsenic levels of 671 µg/litre. Arsenic levels in the well-waters of Hsinchu (Taiwan) were less than 0.7 µg/litre.

Arsenic contamination of groundwater from arsenic-rich sediment has been reported 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 µg/litre with a maximum value of 3700 µg/litre. Mean arsenite levels in the groundwater were around 50% of the total arsenic. Mandal et al. (1996) reported that 44% of groundwater samples collected in West Bengal (India) up to January 1996 contained total arsenic levels > 50 µg/litre. Dhar et al. (1997) found that 38% of groundwater samples collected from 27 districts of Bangladesh contained total arsenic levels > 50 µg/litre.

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/litre; the highest total arsenic level included 75% arsenite.

5.1.5 Sediment

Arsenic concentrations in sediments are summarized in Table 9. Sediments in aquatic systems often have higher arsenic concentrations than those of the water (Welch et al., 1988). Most sediment arsenic concentrations reported for rivers, lakes and streams in the USA range from 0.1 to 4000 mg/kg, with higher levels occurring in areas of contamination (Welch et al., 1988). Arsenic concentrations of < 10 000 mg/kg (dry weight) were found in surface sediments near a copper smelter (Crecelius et al., 1975). Sediment arsenic concentrations of < 3500 mg/kg were reported for lakes in the Northwest Territory (Canada) which had received past inputs from gold-mining activity (Wagemann et al., 1978). Mean total arsenic concentrations of 500 mg/kg (dry weight) were measured in sediment near a pesticide plant and at a lake 14–17 km downstream mean concentrations of almost 3000 mg/kg had accumulated (Faust et al., 1987a). Arsenate was the predominant arsenic species, with inorganic arsenic amounting to 70–90% of the total arsenic measured (Faust et al., 1983). Bright et al. (1996) found total arsenic concentrations ranging from 1043 to 3090 mg/kg in the top 10 cm of sediment from subarctic lakes contaminated by gold-mining activity. Total dissolved arsenic levels in porewater ranged from 800 to 5170 µg/litre (0.7% organic arsenic). Ebdon et al. (1987) reported that methylated arsenic species represented 1–4% of the total arsenic in sediment porewater from the Tamar estuary, south-west England (United Kingdom). Similar findings were reported by de Bettencourt (1988) for the Tagus Estuary (Portugal).

Chunguo & Zihui (1988) studied arsenic accumulation in sediment of the Xiangjiang river (China), which receives inputs from a variety of industrial plants. Total arsenic concentrations upstream of industrial inputs were 13.2 mg/kg during the rainy season and 81.4 mg/kg during the dry season. Near to industrial discharges maximum total arsenic concentrations exceeded 1000 mg/kg during the dry season (approximately 70% as iron or aluminium arsenate) but rarely reached 100 mg/kg during the rainy season.

Farmer & Lovell (1986) monitored arsenic concentrations in surface sediments of Loch Lomond (Scotland, UK); no recent significant sources of environmental arsenic contamination were identified. They found natural enrichment of sediment to levels of up

Table 9. Concentrations of As in sediment

Location	Sampling period	Sampling details and/or As source	Concentration (mg/kg dry weight)[a]	Reference
Estuarine/marine				
UK estuaries	1977–1979	100 µm sieved	2–94 (range)	Langston (1980)
Estuaries, south-west England, UK	1978–1979	past mining activity	7–2500 (range)	Langston (1980)
Tamar estuary, UK	1984	inorganic As	29.2	Howard et al. (1988)
Northern Tyrrhenian/eastern Ligurian Seas, Italy	1985–1989	surface sediment	4–88 (range)	Leoni & Sartori (1996)
Bohai bay, China	1979	39º00′–38º40′N; 117º37′–180º00E	12.8 (9.9–16.4)	Tan et al. (1983)
Eastern Mississippi bight, USA	1987–1989	surface sediment	7.5 (< 1–16)	Presley et al. (1992)
Commencement bay, Washington, USA	1981	surface sediment; industrial inputs	12–288 (range of means)	Schults et al. (1987)

Table 9 (contd.)

Bothnian sea, Sweden/Finland	1991–1993	surface sediment; open sea basin (water depth > 60 m)	61	Leivuori & Niemistö (1995)
Bothnian bay, Sweden/Finland	1991–1993	surface sediment; open sea basin (water depth >60 m); industrial inputs	278	Leivuori & Niemistö (1995)
Moreton's Harbour, Newfoundland	1972–1974	< 40 m from stibnite mine	847–2600 (range)	Penrose et al. (1975)
	1972–1974	> 40 m from stibnite mine	9.1–34.4 (range)	Penrose et al. (1975)
Continental shelf, south-east Australia	1972		18 (2–180)	Davies (1974)
Upper Spencer gulf, South Australia	NS	surface sediment; smelting activity	5.8 (0.34–160)	Tiller et al. (1989)
Freshwater				
Clark Fork river, Montana, USA	1991	past mining, milling and smelting activity	4–404 (range)	Brumbaugh et al. (1994)

Table 9 (contd.)

Location	Sampling period	Sampling details and/or As source	Concentration (mg/kg dry weight)[a]	Reference
Maurice river, NJ, USA	1982–1983	upstream of pesticide plant	25.3 (4.1–48.5)	Faust et al. (1987a)
	1982–1983	0.6 km downstream	515 (291–809)	Faust et al. (1987a)
	1982–1983	4.2 km downstream	23.5 (16–30.2)	Faust et al. (1987a)
Union lake, NJ, USA	1982–1983	14–17 km downstream	2922 (83.6–23 200)	Faust et al. (1987a)
Bowron lake, British Columbia, Canada	1992	reference lake; no mining activity	19 (16–23)	Azcue et al. (1994a)
Lake water, British Columbia, Canada	1992	past mining (gold)	342 (80–1104)	Azcue et al. (1994a)
Subarctic lakes, Northwest territories, Canada	1991	gold mining activity; 0–10 cm sampling depth	1716 (1043–3090)	Bright et al. (1996)
Lakes, northern Sweden	1988	within 80 km smelter; 0–1 cm sampling depth	584 (9–4169)	Johnson et al. (1992)

[a] Mean and ranges of total As unless stated otherwise
NS = not stated

to 675 mg As/kg compared with typical background concentrations of 15–50 mg/kg.

5.1.6 Sewage sludge

Zhu & Tabatabai (1995) monitored total arsenic levels in sewage sludges from waste treatment plants in Iowa (USA). Concentrations ranged from 2.4 to 39.6 mg/kg with a mean of 9.8 mg/kg.

5.1.7 Soil

Levels of arsenic in soil are summarized in Table 10. Arsenic is found in the earth's crust at an average level of 2 mg/kg. Most natural soils contain low levels of arsenic, but industrial wastes and pesticide applications may increase concentrations. Background concentrations in soil range from 1 to 40 mg/kg, with a mean value of 5 mg/kg (Bowen, 1979; Beyer & Cromartie, 1987). Naturally elevated levels of arsenic in soils may be associated with geological substrata such as sulfide ores. Anthropogenically contaminated soils can have concentrations of arsenic up to several percent (NAS, 1977; Porter & Peterson, 1977). Arsenic concentrations of up to 27 000 mg/kg were reported in soils contaminated with mine or smelter wastes (US EPA, 1982). Chatterjee & Mukherjee (1999) reported arsenic levels of 20 100–35 500 mg/kg in soil around the effluent dumping point of an arsenical pesticide manufacturing plant. Peat may contain considerable quantities of arsenic. Minkkinen & Yliruokanen (1978) found maximum arsenic concentrations in various Finnish peat bogs of between 16 and 340 mg/kg dry peat. However, Shotyk (1996) analysed peat cores from the Jura mountains (Switzerland) and found mean total arsenic concentrations of 3.6 mg/kg at a depth of < 30 cm and 0.16 mg/kg at between 69 and 84 cm. Higher levels of arsenic were found in the mineral sediments underlying the peat bogs, with mean concentrations of 6.4 mg/kg at 170 cm and 15.9 mg/kg at 650 cm. Soil on agricultural land treated with arsenical pesticides may retain substantial amounts of arsenic. Mean total arsenic concentrations of 50–60 mg/kg have been recorded for agricultural soils treated with arsenical pesticides (Takamatsu et al., 1982; Sanok et al., 1995). Walsh & Keeney (1975) reported that arsenic-treated soils contained up to 550 mg As/kg. Stilwell & Gorny (1997) found mean arsenic concentrations ranging

Table 10. Concentrations of As in soil

Location	Sampling period	Soil depth (cm)	Notes	Concentration (mg/kg) (dry weight)[a]	Reference
USA	1961–1975	20	1318 sampling sites	7.2 (< 0.1–97)	Shacklette & Boerngen (1984)
Annapolis valley, USA	NS	NS	non-orchard	TR–7.9 (range)	Bishop & Chisholm (1962)
			orchard soil treated with arsenicals	9.8–124.4 (range)	Bishop & Chisholm (1962)
NY, USA	1992–1993	0–25	orchard soil	1.8–3.0 (range)	Merwin et al. (1994)
	1992–1993	0–25	orchard soil previously treated with lead arsenate	1.6–141 (range)	Merwin et al. (1994)
Manitoba, Canada	1982–1984	surface	peat soil	4 (1–19.6)	Zoltai (1988)
Alberta, Canada	NS	NS	acid sulfate soil; soil horizons E-C	1.5–45 (range)	Dudas (1984)
Upper Austria	NS	surface		6.2 (1–39)	Aichberger & Hofer (1989)
The Netherlands	1976–1977	0–20	agricultural soil	12 (0.1–110)	Wiersma et al. (1986)
Norway	NS	0–60	agricultural soils	2.4 (0.8–17)	Esser (1996)
Southern Norway	1981–1983	3–5	< 50 km from coast	5 (1.4–14.8)	Steinnes et al. (1989)
	1981–1983	3–5	> 100 km from coast	2.2 (1.3–5)	Steinnes et al. (1989)
Poland	1982–1986	0–20	arable soils	2.6 (0.5–15)	Dudka & Markert (1992)
South-east Spain	NS	10–15		16.8 (8.75–34.5)	Navarro et al. (1993)

Table 10 (contd.)

Mekong delta, Vietnam	NS	0–140	acid sulfate soil	6–41 (range)	Gustafsson & Tin (1994)
Taiwan	1983	0–15	agricultural soil	5.65 (0.01–16.16)	Chang et al. (1999)
Japan	NS	NS	agricultural soil	9.9	Harako (1986)
			agricultural soil; volcanic region; < 1% of total As was organic	609 (maximum 1400)	Harako (1986)
Nagpur city, India	1992	NS	urban	6.3	Chutke et al. (1995)
South Australia	1974–1979	0–10	uncontaminated	3.9	Merry et al. (1983)
Tasmania	1974–1979	0–10	uncontaminated	0.6	Merry et al. (1983)
South Australia and Tasmania	1974–1979	0–10	orchard soil	29 (< 0.5–115)	Merry et al. (1983)
Long Island, NY, USA	NS	0–18	sandy loam soil	2.3	Sanok et al. (1995)
	NS	0–18	sandy loam soil; potato soils treated with lead arsenate	27.8–51 (range of means)	Sanok et al. (1995)
Japan	1980	0–15	orchard soil treated with arsenicals; < 1% of total As was organic	10.6–61.5 (range of means)[b]	Takamatsu et al. (1982)
	1980	0–15	orchard soil treated with arsenicals; < 1% of total As was organic	0.27–1.9 (range of means)[c]	Takamatsu et al. (1982)
	1980	0–15	paddy soil polluted by mining activity; < 3% of total As was organic	2.5–81.9 (range of means)[b]	Takamatsu et al. (1982)

Table 10 (contd.)

Location	Sampling period	Soil depth (cm)	Notes	Concentration (mg/kg) (dry weight)[a]	Reference
	1980	0–15	paddy soil polluted by mining activity; < 3% of total As was organic	0.43–5.7 (range of means)[c]	Takamatsu et al. (1982)
South-west England, UK	1984	0–15	past mining activity	322 (144–892)	Xu & Thornton (1985)
	NS	NS	contaminated with mine and smelter waste; water soluble As 0.5–2.9 mg/kg	8510–26 530 (range)	Porter & Peterson (1977)
North-west England, UK	NS	surface	control site	5.0	Ismael & Roberts (1992)
	NS	surface	250 m from As refinery	155.9	Ismael & Roberts (1992)
Zimbabwe	NS	0–10	gold/As mine dumps	9530	Jonnalagadda & Nenzou (1996a)
Northern Peru		0–10	near copper mine	143–3052 (range of means)	Bech et al. (1997)
Obuasi, Ghana	1992–1993		0.3 km from gold ore processing plant	48.9	Amonoo-Neizer et al. (1996)
Southern Ontario, Canada	1974	0–5	urban area	9.8 (2.7–41)	Temple et al. (1977
	1974	0–5	<700 m from secondary lead smelter	107 (4.7–2000)	Temple et al. (1977)

Table 10 (contd.)

Toronto, Canada	NS	0–1	near secondary lead smelter	17.9–3007 (range of means)	Dolan et al. (1990)
Utah, USA	NS	surface	1–2 km from copper smelter	75–540 (range of means)	Ball et al. (1983)
	NS	surface	10–25 km from copper smelter	6–150 (range of means)	Ball et al. (1983)
Nakato, Niigata Prefecture, Japan	1994	15	site of factory producing As sulfide (35 years before)	2.4–72.7 (range of means)	Nakadaira et al. (1995)
Australian Capital Territory, Australia	NS	surface and subsurface	urban area, former site of arsenical pesticide plunge sheep dip for tick control (1946-1960)	32–1597	Ng et al. (1998b)
New South Wales, Australia	NS	NS	urban area, former arsenical pesticide plunge cattle dip sites	730–2100	Ng & Moore (1996)
	NS	NS	copper chrome arsenate contaminated site	52–138	Ng & Moore (1996)
Queensland, Australia	NS	0–12.5	site of tannery (1891–1972)	80 (< 1–435)	Sadler et al. (1994)
	NS	25–72.5	site of tannery (1891–1972)	121 (< 1–1010)	Sadler et al. (1994)

[a] Mean and ranges of total As unless stated otherwise
[b] Arsenate
[c] Arsenite
NS = not stated; TR = trace

from 9 to 139 mg/kg (dry weight) in soil (upper 5 cm) below decking treated with copper chrome arsenate (CCA).

Uptake and effects of arsenic on organisms are related to bioavailable arsenic rather than total arsenic. Xu & Thornton (1985) measured mean total arsenic levels of 300 mg/kg in garden soils (south-west England, UK) at sites of past mining activity; however, water-soluble and acid-fluoride extractable arsenic represented < 1% and < 2% of total arsenic respectively. Kavanagh et al. (1997) report total arsenic concentrations ranging from 174 to 477 mg/kg for agricultural soil and from 1200 to 22 290 mg/kg for mine waste in the Tamar valley, south-west England. The proportion of water-extractable arsenic in agricultural topsoils ranged from 0.05 to 0.3% and in mine wastes from 0.02 to 1.2%. Similarly, McLaren et al. (1998) found total arsenic concentrations of 37–3540 mg/kg (dry weight) in surface soil (0–10 cm) contaminated by cattle dip (sodium arsenite) compared with water-extractable arsenic concentrations in the same samples ranging from 0.2 to 22.4 mg/kg . The highest total arsenic level recorded was 14 800 mg/kg (water-extractable arsenic = 1.2 mg/kg) at a depth of 40–45 cm. Ng et al. (1998b) measured total arsenic concentrations of 32–1597 mg/kg in soil which had been contaminated 30 years previously with arsenical pesticides. Chemical speciation showed that arsenite ranged from 0.32–56% of total arsenic. In a rat model, the absolute bioavailability of these contaminated soils relative to arsenite and arsenate ranged from 1.02 to 9.87% and 0.26 to 2.98% respectively.

Doyle & Otte (1997) found that the presence of vegetation and burrowing organisms significantly increased the concentration and accumulation of arsenic in salt-marsh soils.

Chutke et al. (1995) analysed dust samples collected in Nagpur city (India) during 1992. Mean arsenic levels for residential/commercial areas, industrial areas and highways were respectively 10.2, 18 and 17 mg/kg (dry weight). Stone & Marsalek (1996) collected samples of sediment from road surfaces in an urban area of Ontario (Canada) during 1991 and found total arsenic concentrations ranging from 1 to 33 mg/kg with a mean of 3.4 mg/kg.

5.1.8 Biota

Background arsenic concentrations in living organisms are usually less than 1 mg/kg (fresh weight) in freshwater and terrestrial biota. The levels are higher in biota collected from mine waste sites, arsenic-treated areas, near smelters and mining areas, near areas with geothermal activity and near manufacturing sites of arsenical defoliants and pesticides (Eisler, 1988). Marine organisms, however, can normally contain arsenic residues ranging from 1–2 mg/kg to more than 100 mg/kg (Lunde, 1977; Maher & Butler, 1988; Phillips, 1990). Neff (1997) reviewed levels of total arsenic in marine organisms and calculated geometric means ranging from < 1 mg/kg for marine mammals to 50 mg/kg for snails. An overall geometric mean for a wide variety of marine biota was calculated to be 11 mg/kg (dry weight). There is a substantial number of publications on the levels of arsenic in biota, and the following examples have been chosen to provide an overview.

5.1.8.1 Freshwater

Freshwater plants in uncontaminated environments tend to contain arsenic concentrations < 10 mg/kg (Reay, 1972; Outridge & Noller, 1991). Reay (1972) reported a considerable accumulation of arsenic in freshwater plants in the Waikato river (New Zealand). The elevated arsenic concentrations in the water (30–70 µg/litre) arising from geothermal activity gave rise to concentrations of < 971 mg As/kg in aquatic plants. Arsenic concentrations of < 1200 mg/kg (dry weight) were reported by Mudroch & Capobianco (1979) for aquatic macrophytes growing in an area of the Lake Ontario drainage basin (Canada) contaminated with mine effluent. Wagemann et al. (1978) reported arsenic concentrations ranging from 150 to 3700 mg/kg for macrophytes in lakes (Northwest Territory, Canada) which had received past inputs from gold-mining activity. During 1983, Tanner & Clayton (1990) analysed macrophytes from Lake Rotoroa (New Zealand), which had been sprayed with sodium arsenite herbicide in 1959. Arsenic concentrations ranged from 540 to 780 mg/kg (dry weight) in surficial sediments and from 193 to 1200 mg/kg in macrophytes. Similar levels of arsenic accumulation to that seen in aquatic plants has been observed for zooplankton (700–2400 mg/kg) in lakes receiving mine drainage water (Wagemann et al., 1978).

Freshwater bivalves have been used to measure arsenic in several biomonitoring programmes. Leland & Scudder (1990) monitored freshwater bivalves (*Corbicula fluminea*) in the San Joaquin valley (California, USA), an area influenced by high levels of elements in irrigation wastewater. Mean concentrations of arsenic in bivalves ranged from 5.3 to 13.9 mg/kg (dry weight). A highly significant relationship was observed between arsenic residues and the HNO_3-extractable arsenic : iron ratio of suspended matter. Similarly, Johns & Luoma (1990) found mean arsenic levels ranging from 5.4 to 11.5 mg/kg (dry weight) for the same species for the Sacramento/San Joaquin river delta (California, USA). Arsenic levels in mussels from the St Lawrence river (Canada) ranged from 2.8 to 8.6 mg/kg (dry weight) (Metcalfe-Smith, 1994).

Freshwater fish have not been shown to accumulate arsenic to the same degree as lower aquatic organisms. Arsenic residues in freshwater fish have been monitored in the USA over a period of approximately 10 years. The geometric means (mg/kg wet weight), with the range in parentheses, of total arsenic concentrations were 0.27 (0.05–2.92) during 1976–1977, 0.14 (0.05–1.69) during 1980B1981 and 0.14 (0.27–1.5) during 1984 (May & McKinney, 1981; Lowe et al., 1985; Schmitt & Brumbaugh, 1990). Mean total arsenic residues in freshwater fish near a copper smelter (Sweden) ranged from 0.05 to 0.24 mg/kg (wet weight) compared with 0.06 to 0.09 mg/kg for a control lake (Norin et al., 1985). Takatsu & Uchiumi (1998) analysed fish from a naturally acidified volcanic lake (Lake Usoriko, Japan) with low phosphate levels (< 0.02 mg/litre). Mean arsenic levels were 0.28 and 0.27 mg/kg (wet weight) for gills and bone respectively and 6.1 mg/kg for eye tissue. Arsenic residues have also been measured in fish from the San Joaquin valley area of California (USA) exposed to agricultural subsurface drainage water. Mean arsenic concentrations ranged from 0.18 to 0.44 mg/kg (dry weight) (maximum value 0.97 mg/kg) for bluegill sunfish (*Lepomis macrochirus*) and from 0.23 to 0.39 mg/kg (maximum value 1.5 mg/kg) for common carp (*Cyprinus carpio*) (Saiki & May, 1988). Mean arsenic concentrations for striped bass (*Morone saxatilis*) from the same area ranged from 0.23 to 0.65 mg/kg (dry weight) compared with mean values of 1.23B1.44 mg/kg for bass from San Francisco bay (California, USA) (Saiki & Palawski, 1990).

Clark et al. (1998) found a mean arsenic concentration of 6.87 mg/kg (wet weight) in tadpoles of the cricket frog (*Acris crepitans*) collected in 1994 downstream from Finfeather Lake (Texas, USA); the lake was contaminated during 53 years (1940B1993) of industrial production of arsenic-based cotton desiccants/defoliants.

5.1.8.2 Marine

Marine biota tend to accumulate much higher levels of arsenic than freshwater species (see section 4.2.3.2). Very little information is available on arsenic levels in natural phytoplankton populations. Benson & Summons (1981) reported 9 mg/kg total arsenic in a mixed marine phytoplankton population near Cape Ferguson (Queensland, Australia). Sanders (1979a) found that mean total arsenic concentrations in marine macroalgae ranged from 1.4 mg/kg (*Rhodophyceae*) to 10.3 mg/kg (*Phaeophyceae*). The absolute concentration of inorganic arsenic was not significantly different between groups, suggesting that the variation is due to metabolic differences between algal classes rather than to differences in the environmental concentration of arsenic. Mean total arsenic concentrations in macroalgae collected in the South Atlantic ranged from 5.3 to 70.2 mg/kg, with inorganic arsenic residues ranging from 0.2 to 2.0 mg/kg (Muse et al., 1989). Lai et al. (1998) report seasonal changes in arsenic speciation in the brown alga *Fucus gardneri* in Vancouver (Canada). During the summer algae contain 9 mg As/kg with most (79–98%) being extractable, whereas during the winter months residues range from 16 to 22 mg/kg with extraction efficiencies of 5.8–49%. Klumpp & Peterson (1979) found mean arsenic concentrations ranging from 83.7 to 141.4 mg/kg (dry weight) (maximum 189.3 mg/kg) for macroalgae in Restronguet creek, south-west England (UK) (an estuary influenced by past mining activity). Penrose et al. (1975) monitored marine biota near the site of a disused stibnite mine (pre–1916). Mean arsenic residues were 17.2 mg/kg for macroalgae and 3.8–11.5 mg/kg for invertebrates near the mine site compared with 9.8–12.1 mg/kg for macroalgae and 1.6–4.0 mg/kg for invertebrates at a control site.

Stronkhorst (1992) reported mean arsenic concentrations in mussels of 1 mg/kg (wet weight) for two Dutch estuaries. Similar levels (mean values ranging from 1.1 to 2.7 mg/kg) were reported in

clams and oysters collected from U.S. coastal waters in use for shellfish production during 1985 and 1986 (Capar & Yess, 1996). Shellfish from the Arabian Gulf contained mean arsenic concentrations ranging from 3 to 15.8 mg/kg (wet weight) (Attar et al., 1992; Madany et al., 1996). Molluscs sampled in Restronguet creek contained arsenic concentrations ranging from 35 to 64 mg/kg (dry weight) (Klumpp & Peterson, 1979). Benson & Summons (1981) found that arsenic was accumulated to substantial levels in the kidney of molluscs from the Great Barrier Reef (Australia) with residues ranging from 481 to 1025 mg/kg (dry weight).

Langston (1980) found that the highest arsenic concentrations in estuarine benthic organisms (< 190 mg/kg [dry weight]) were found at sites where high arsenic : iron ratios exist in the sediment. Concentrations of arsenic in estuarine organisms correlated more significantly with the arsenic : iron ratio in sediments than arsenic levels alone.

Arsenic residues in marine fish appear to show substantial variation. Hellou et al. (1992) found mean arsenic residues of 3.2 mg/kg (dry weight) (1.6–4.2 mg/kg) in Atlantic tuna (*Thunnus thynnus*). Engman & Jorhem (1998) reported arsenic residues in marine fish muscle ranging from 0.59 to 17 mg/kg (fresh weight) with a mean value of 4.5 mg/kg. The mean value was 60 times greater than that found for freshwater fish in the same study. Several studies of marine fish from the Arabian Gulf have shown that in general mean arsenic concentrations range from < 1 to < 10 mg/kg in muscle (Tariq et al., 1991; Attar et al., 1992; Madany et al., 1996). However, higher concentrations have been reported, for example, Attar et al. (1992) found mean muscle concentrations of up to 32.3 mg As/kg (wet weight) in black-banded bream (*Acanthopagrus bifasciatus*). Bohn (1975) reported mean arsenic concentrations for marine fish from West Greenland ranging from 21.9 to 240 mg/kg (dry weight).

Maher (1983, 1988) analysed a variety of marine biota and found mean total arsenic concentrations (dry weight) ranging from 2.7 mg/kg (fish muscle) to 114 mg/kg (macroalgae: *Cystophora moniliformis*). Mean inorganic arsenic concentrations were low (0.02–3.6 mg/kg) in all marine organisms with organic arsenic representing 70–98% of the total arsenic. Arsenobetaine was the

most abundant arsenic species found in marine invertebrates and fish muscle tissue (Edmonds & Francesconi, 1981c; Shiomi et al., 1984; Maher, 1985b; Matsuto et al., 1986).

Mean arsenic concentrations in the liver and muscle tissue of marine mammals were found to be generally less than 1 mg/kg (Julshamn et al., 1987; Muir et al., 1988; Skaare et al., 1990; Miles et al., 1992; Varanasi et al., 1994).

5.1.8.3 Terrestrial

The arsenic content of plants grown on soils that had never been treated with arsenic-containing pesticides varied from 0.02 to about 5 mg/kg (dry weight). Plants grown on arsenic-contaminated soils may, however, contain considerably higher levels, especially in the roots. Plants growing on arsenical mine wastes (south-west England, UK) contained mean arsenic levels ranging from 350 to 2040 mg/kg (dry weight); a maximum concentration of 6640 mg/kg was reported for *Jasione montana* (Porter & Peterson, 1975). Benson et al. (1981) reported mean arsenic concentrations of 1480 and 1070 mg/kg (dry weight) for the grasses *Agrostis stolonifera* and *A. tenuis* growing on arsenical mine waste. De Koe (1994) found arsenic concentrations of up to 1800 and 1900 mg/kg in senescent shoots and roots respectively of grass species growing on gold-mine spoils (north-east Portugal). Jonnalagadda & Nenzou (1997) report arsenic concentrations in couch grass (*Cynodon dactylon*) growing on or near gold/arsenic mine dumps (Zimbabwe) ranging from 200 to 1660 mg/kg (dry weight) in stems and from 1020 to 10 880 mg/kg in roots. Mean concentrations of arsenic in the leaves of plants growing near a copper mine (northern Peru) ranged from 111 to 1651 mg/kg (dry weight) (Bech et al., 1997). Temple et al. (1977) found mean arsenic levels of 5.8 mg/kg in grass samples and 7.4 mg/kg in tree and shrub foliage from within 700 m of a secondary lead smelter; samples collected at a control site contained < 1 mg/kg.

Grass growing on plots which had been previously treated (7B11 years before) with lead arsenate contained mean arsenic residues of 1.5 mg/kg, compared with 0.9 mg/kg in grass from untreated sites. After a further 2 years mean arsenic concentrations were 0.88 and 0.56 mg/kg for treated and untreated sites respectively (Chisholm & MacPhee, 1972). Merry et al. (1986) reports that

pasture plants growing at sites formerly used as orchards (soil concentration 80 mg As/kg) contained less than 2.5 mg As/kg (dry weight).

Biomonitoring studies at six background sites in Norway found mean arsenic concentrations in moss (*Hylocomium splendens*) ranging from 0.1 to 2.2 mg/kg (Berg et al., 1995a); an overall mean of 0.36 (< 0.03–3.2) mg/kg was reported by Berg et al. (1995b). Similarly, Glooschenko & Arafat (1988) sampled sphagnum moss (*Sphagnum fuscum*) throughout northern Canada. A mean background concentration of 0.66 mg As/kg (dry weight) was found, with elevated levels (> 3 mg/kg; maximum 31 mg/kg) in the vicinity of mining and smelting areas. Lichen biomonitoring of arsenic in a geothermal area of central Italy revealed a mean concentration of 1.19 mg/kg (0.19–3.55 mg/kg) (dry weight) (Loppi & Bargagli, 1996).

Monitoring of conifer needles has been carried out at sites remote from pollution sources, with mean arsenic concentrations ranging from 5 to 58 µg/kg for Norway spruce (*Picea abies*) and from 2 to 8 µg/kg for balsam fir (*Abies balsamea*) (Lin et al., 1995; Wyttenbach et al., 1997). However, much higher concentrations (0.46–3.1 mg/kg) have been reported for leaves from loblolly pine trees (*Pinus taeda*) growing on land affected by coal-pile leachate (Carlson & Carlson, 1994). Dmuchowski & Bytnerowicz (1995) monitored Scots pine (*Pinus sylvestris*) needles at three sites in Poland during 1983–1985. Mean arsenic concentrations were 0.54 mg/kg (dry weight) in a primeval forest (eastern Poland), 0.88 mg/kg near the city of Warsaw and 1.5 mg/kg at a polluted site in Silesia. Mankovska (1986) analysed pine needles (*Pinus silvestris*) from the vicinity of a smelter and found arsenic concentrations ranging from ~15 to ~22 mg/kg within 1000 m of the smelter (soil concentrations ranged from 30 to > 120 mg/kg).

Byrne & Tusek-Znidaric (1983) found arsenic concentrations ranging from 34 to 182 mg/kg (dry weight) in caps and stalks of the common mushroom (*Laccaria amethystina*) from rural sites in Slovenia; soil arsenic concentrations ranged from 3.2 to 27 mg/kg.

Beyer & Cromartie (1987) analysed earthworms from a diverse variety of sites in Maryland, Pennsylvania and Virginia (USA). Arsenic concentrations ranged from trace levels to 0.8 mg/kg (dry weight) at uncontaminated sites, mining sites and industrial sites.

However, a single earthworm sample at a mining site contained 10 mg/kg (soil concentration 20 mg/kg) although all other samples from mining sites contained only trace amounts of arsenic. Total arsenic concentrations ranging from 3.2 to 17.9 mg/kg (dry weight) were found in earthworms sampled from six sites in Austria. There was no correlation between the total arsenic concentrations in the earthworms and the soil. The major arsenic compounds detected in the earthworms were arsenous acid and arsenic acid; arsenobetaine, dimethylarsinic acid and two dimethylarsinoylribosides were also detected (Geiszinger et al., 1998).

Arsenic residues in birds tend to be low (< 1 mg/kg) with little accumulation even at sites with higher environmental concentrations (Martin & Nickerson, 1973; Blus et al., 1977; White et al., 1980; Ohlendorf et al., 1991; Pain et al., 1992; Vermeer & Thompson, 1992; Custer & Hohman, 1994; Guitart et al., 1994; Hothem & Welsh, 1994). Of 18 osprey (*Pandion haliaetus*) livers analysed by Wiemayer et al. (1980), 14 contained less than 1.5 mg/kg (wet weight); arsenic concentrations in the other four birds ranged from 2 to 16.7 mg/kg. The bird with the highest concentration was in a weak condition with very low fat reserves. Erry et al. (1999) analysed tissue samples from raptors in south-west England, an area with naturally and anthropogenically (through mining) elevated arsenic levels and compared the results with birds from another geographical area. Mean arsenic residues of 0.278, 0.346 and 0.187 mg/kg (dry weight) in the kidney, liver and muscle of kestrels (*Falcio tinnunculus*) were approximately three times higher in south-west England than in south-west Scotland. However, in another two raptors (sparrowhawk *Accipiter nisus* and barn owl *Tyto alba*) arsenic levels were not elevated in south-west England. The authors suggested that the difference could be attributed to differences in both diet and arsenic metabolism. Vermeer & Thompson (1992) analysed livers from birds collected in the vicinity of a copper mine; mean arsenic concentrations ranged from 0.08 to 3.23 mg/kg (wet weight). Goede (1985) found mean arsenic concentrations ranging from 0.5 to 3.2 mg/kg in the feather shafts of wading birds (Waddenzee, Netherlands); liver concentrations ranged from 4 to 14 mg As/kg (dry weight).

Elfving et al. (1979) analysed small mammals (voles and mice) from apple orchards which had received lead and calcium arsenate applications for many years. Arsenic concentrations in the soil

ranged from 31 to 94 mg/kg (dry weight) and in the small mammals from 0.05 to 0.96 mg/kg (whole-body). Arsenic concentrations at a control site were 2.4 mg/kg in soil and < 0.03 mg/kg in small mammals. Ismael & Roberts (1992) monitored arsenic residues in vegetation and small mammals near an arsenic refinery. Mean arsenic levels in vegetation were 0.2 and 37.3 mg/kg for a control site and 250 m from the arsenic refinery respectively. Mean whole-body arsenic residues in four species of small mammal ranged from 0.4 to 3.2 mg/kg (fresh weight) at the control site and from 0.4 to 2.4 mg/kg near to the refinery. Significantly higher levels were found at the control site for three of the four species; the common shrew *Sorex araneus*, a carnivorous species, accumulated the highest levels of arsenic at both sites.

Arsenic was not detected (detection limit 5 µg/kg) in kidney tissue of mink (*Mustela vison*) collected in Georgia, North Carolina and South Carolina (USA) (Osowski et al., 1995). Langlois & Langis (1995) did not detect arsenic in muscle tissue (detection limit 50 µg/kg) of hares or martens in northern Quebec (Canada). Norstrom et al. (1986) found a mean arsenic concentration of 0.07 mg/kg (dry weight) in livers of polar bears (*Ursus maritimus*) in the Canadian Arctic. Norheim et al. (1992) reported mean arsenic concentrations of 0.06 and 0.04 mg/kg (wet weight) in the livers of adult and juvenile polar bears respectively at Svalbard (Norway).

5.2 General population exposure

Arsenic is widely distributed and human exposure is inevitable. Exposure of the general population to the various species of arsenic (inorganic and organic) will vary according to local geochemistry and the level of anthropogenic activity and can occur through the intranasal, oral and dermal routes.

5.2.1 Air

Arsenic in ambient air is associated with particulate matter and is predominantly a mixture of arsenite and arsenate. Organic species are of negligible significance except in areas where there has been substantial use of methylated arsenic pesticides or in areas with high biotic activity (ATSDR, 1993). As discussed in section 5.1.1 (see Tables 3 and 4), arsenic concentrations associated with particulate

matter vary world wide as follows: 0.007–1.9 ng/m^3 in remote areas; 1–28 ng/m^3 in rural locations, and 2–2320 ng/m^3 in urban environments (Schroeder et al., 1987). The highest concentrations are found near non-ferrous-metal smelters.

5.2.2 Food and beverages

Arsenic has been found in all foodstuffs analysed. Although most monitoring data is given as the concentration of total arsenic, arsenic in foods is a mixture of inorganic species and organo-arsenicals including arsenobetaine. The actual total arsenic concentrations in foodstuffs from various countries will vary widely depending on the food type, growing conditions (type of soil, water, geochemical activity, use of arsenical pesticides) and processing techniques.

From monitoring studies in the USA (Gunderson, 1995, Yost et al., 1998; US NRC, 1999), in the United Kingdom (UK MAFF, 1997), Canada (Dabeka et al., 1993) and Australia (ANZFA, 1994), by far the highest concentrations of total arsenic is found in seafood. Meats and cereals have higher concentrations than vegetables, fruit and dairy products. On the basis of limited data, it has been estimated that the percentage of inorganic arsenic is about 75% in meats, 65% in poultry, 75% in dairy products, and 65% in cereals (US EPA, 1988; Yost et al., 1998). Tao & Bolger (1998) estimated an inorganic arsenic intake for US men and women aged 60B65 years of 13 and 10 µg respectively. Other age groups had lower estimated daily intakes of inorganic arsenic, varying from 1.3 µg for infants to 9.9 µg for men aged 25–30 years. Additional samples, and a wider range of foodstuffs, need to be analysed in various countries before a definite conclusion can be reached on the normal range of inorganic arsenic in foods. In fruits, and vegetables and seafood the organic species predominate, with inorganic arsenic contributing 10%, 5% and 0–10% respectively. On the basis of these preliminary data it has been estimated that approximately 25% of the daily intake of dietary arsenic is inorganic (US EPA, 1988, Yost et al., 1998). A report from the Netherlands (Vaessen & van Ooik, 1989) estimated that inorganic arsenic in seafood was 0.1 to 41% of the total. Edmonds & Francesconi (1993) reviewed all data on inorganic arsenic in seafoods (excluding algae) available at that time and concluded that inorganic arsenic represented less than 1% of

total arsenic at low arsenic burdens and fell to about 0.5% of total arsenic at concentrations of about 20 mg/kg. Mohri et al. (1990) estimated that the customary Japanese diet contained 5.7% inorganic arsenic with an intake ranging from 27 to 376 µg total arsenic/day.

Concentrations of arsenic in various food groups found in Canada are given in Table 11. Analysis of various beverages from Denmark found 3–11 µg/litre (Pedersen et al., 1994). Very few data were found on the concentration of arsenic in human breast milk. One study of 10 lactating women by Concha et al. (1998c) found a range of 0.83–7.6 µg/kg fresh weight (median 2.3 µg/kg) in breast milk from women consuming > 200 µg arsenic per day from drinking-water. Thus breast-feeding provided 1–2 µg As/day, compared to 100–200 µg As/day from formula mixed with the arsenic-rich water.

Table 11. Total As concentrations in various food groups from Canada[a]

Food category	Sample size	Mean	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
Fish and shellfish	40	1662	77.0–4830
Soups	28	4.2	< 0.2–11
Bakery goods and cereals	177	24.5	< 0.1–365
Vegetables	262	7.0	< 0.1–84
Fruit and fruit juices	176	4.5	< 0.1–37
Fats and oils	21	19.0	< 1.0–57
Sugar and candies	49	10.9	1.4–105
Beverages[b]	45	3.0	0.4–9
Miscellaneous[c]	33	12.5	< 0.8–41

[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, gelatine desserts, raisins, baked beans, weiners, and raw and canned beets.

Examples of mean total daily intakes of arsenic from food and beverages in different countries are given in Table 12. The variation in dietary intake of total arsenic in adults reflects in large part the variability in the consumption patterns of arsenic-rich food groups (fish/shellfish and meats) confirming the need to consider such regional variations in arsenic intake when assessing human health effects for arsenic.

Table 12. Estimated average dietary intake of As in various countries

Country	Sampling method [a]	Total As intake (µg/day)	Reference
Australia	MB		ANZFA (1994)
	adult male	73	
	adult female	53	
	2-year old	17	
Brazil	DD (students)	19	Fávaro et al. (1994)
	S. Catarina 1 region	53	
	Manaus region	140–159	
		16–17	
Canada	TD		Dabeka et al. (1993)
	5 cities, adult males	59	
	5 cities, 1–4 years	15	
Croatia	MB	12	Sapunar-Postruznik et al. (1996)
Japan	DD (adult-male and female)	182	Mohri et al. (1990)
Spain	TD (Basque region, adults)	291	Urieta et al. (1996)
UK	TD (adults)	63	UK MAFF (1997)
USA	MB		Yost et al. (1998)
	adults	53	
	0.5–2 years	28	

[a] DD = duplicate diet study; MB = market basket survey; TD = total diet study; mean concentrations not reported.

The risk of arsenic exposure to populations living in or near arsenic-contaminated environments (i.e. mine-tailing sites, CCA and arsenical pesticide contamination soils), must be considered. In particular, contamination of home-grown vegetables and reared livestock, or wild collected foods must be considered. Helgesen & Larsen (1998) demonstrated that 0.47–0.6% of total soil arsenic (from a CCA plant) was bioavailable to carrot. Woolson (1973) dosed soils with 0–500 mg/kg arsenate and showed that at the arsenate dose that limited growth by 50%, arsenic in edible parts was up to 87 mg/kg (see section 4.2.4.5).

5.2.3 Drinking-water

Concentrations of arsenic in fresh surface water and groundwater, potential sources of drinking-water, are given in sections 5.1.3 and 5.1.4. Arsenate is the predominant species, but some groundwaters have been found to contain a high proportion of arsenite (section 5.1.4). Concentrations of methylated species in natural waters are usually less than 0.3 µg/litre (ATSDR, 1993). Unless stated otherwise in this section, monitoring data for drinking-water is reported as total arsenic.

A summary of the monitoring of drinking-water carried out in the USA by the US EPA during 1976–1993 has been published by Borum & Abernathy (1994). Concentrations of arsenic were in the range of < 2.5–28 µg/litre for surface waters and < 5–48 µg/litre for groundwater sources. Detection limits of 2 or 5 µg/litre preclude more accurate estimates of the lower limit of these ranges. On the basis of these data, it was estimated that approximately 2% of the population of the USA is exposed to > 10 µg/litre arsenic in drinking-water. Additional data sources (US EPA, 1993) provide support for this estimate, and have identified areas with higher concentrations of arsenic in drinking-water. In 1978 arsenic was detected in 67% of the 3834 drinking-water samples analysed (detection limit 0.1 µg/litre) with a mean concentration of 2.4 µg/litre (Borum & Abernathy, 1994). In areas with elevated geological concentrations of arsenic (e.g. California and Nevada) mean arsenic concentrations up to 80 µg/litre have been reported, with maximum reported levels of > 1400 µg/litre.

A limited summary of the monitoring data collected in 1985B1988 for total arsenic in drinking-water in six Canadian provinces has been published (NHW/DOE, 1993). Of the 717 samples of surface water, 3.6% were > 5 µg/litre and 5% of the 600 groundwater samples contained arsenic at concentrations > 5 µg/litre.

Although arsenic levels in natural waters are usually low (a few µg/litre), there are several areas in the world where humans consume drinking-water containing > 100 µg As/litre resulting from natural geochemical activity. In the West Bengal region of India it was estimated that over 1 000 000 people consume drinking-water containing > 50 µg/litre (up to 3.7 mg/litre) arising from normal geochemical processes (Das et al., 1995; Chowdhury et al., 1997). In the areas of West Bengal and Bangladesh, 38% of groundwaters sampled in 27 districts were > 50 µg/litre (Dhar et al., 1997). Natural geochemistry resulted in the pre–1970 exposure of about 100 000 people in the south-western coastal region of Taiwan to variable but high (10–1800 µg/litre, mean 500 µg/litre) concentrations of arsenic in drinking-water (Guo et al., 1994). A similar problem was reported in Chile where 100 000 people consumed drinking-water containing 800 µg As/litre between 1959 and 1970, when the concentration was lowered to about 50 µg/litre(Borgono et al., 1977). About 200 000 people in north central Mexico were reported to be exposed to >50 µg/litre arsenic in drinking-water (410 µg/litre in at least one village) (Cebrian et al., 1983).

In major Australian drinking-water systems levels of arsenic range up to 15 µg/litre, but typical concentrations are usually < 5 µg/litre (NHMRC, 1996).

5.2.4 Soil

Although ingestion of arsenic in soil and dust may not be a significant source of arsenic intake in adults, it may be significant for children, particularly in locations near industrial and hazardous waste sites. As described in section 5.1.7 (Table 10), background concentrations of total arsenic in soil are 1–40 mg/kg dry weight with a mean of 5 mg/kg (Beyers & Cromartie, 1987). The comparative bioavailability of arsenic in soil from a CCA-contaminated site and soil contaminated by arsenic solutions used in cattle tick control

were reported by Ng & Moore (1996). In a rat model, soil from the cattle dip site had a bioavailability of 8.1 ± 4%; 14.4 ± 7% and 60 ± 3.4% when compared with orally administered sodium arsenite, calcium arsenite and sodium arsenate respectively. For CCA-contaminated soil the corresponding comparative bio-availabilities were 13.0 ± 4.5%; 32.2 ± 11.2% and 38.0 ± 13.2%. Also using a rat model, Ng et al. (1998b) have reported the absolute bioavailability of arsenic in soils containing 32–1597 µg As/kg (0.32–56% arsenite) from a combination of arsenical pesticides and natural geological formations in a residential area. The absolute bioavailability ranged from 1.02 to 9.87% relative to arsenite and from 0.26 to 2.98% relative to arsenate.

Freeman et al. (1993) determined both the absolute and comparative bioavailability of arsenic in soil from a smelter site using male rabbits and monkeys. When compared to the intravenous administration of sodium arsenate, the absolute bioavailability was reported as 25.9% in rabbits and 24.2% in monkeys. When compared to an oral dose (gavage) of sodium arsenate, the comparative bioavailabilities were 67.8% in rabbits and 43.6% in monkeys, in general agreement to findings of Ng et al. (1998b) in rats. Such data on availability of arsenic in soil needs to be considered in assessing human uptake of arsenic from soil (for more details on bioavailability see Table 15).

5.2.5 Miscellaneous exposures

Smokers are exposed to arsenic by the inhalation of mainstream cigarette smoke. It has been estimated that someone in the USA smoking 40 cigarettes per day would inhale about 10 µg of arsenic (ATSDR, 1993).

Proprietary herbal asthma medicines have been shown to contain up to 107 mg/g of inorganic arsenic (Chan, 1994).

5.3 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 inhalation of arsenic-containing particulates, but ingestion and dermal exposure may be significant in particular situations. (e.g. preparation of CCA-treated timber). It is extremely rare for workers to be exposed to arsenic alone: the exposure is usually to arsenic in combination with other elements. Data on typical exposure levels of arsenic in the workplace are difficult to obtain and may vary considerably between different locations of the same industry because of the level of occupational hygiene in place and the chemical properties of the materials processed. Also, they are often out of date with regard to the current level of industrial hygiene. Currently, countries which have occupational regulations for arsenic have set the limit for inorganic arsenic between 0.01 and 0.1 mg/m^3 (ILO, 1991; DFG, 1999; Ministerie van Soziale Zaken en Werkgelegenheid, 2000; OSHA, 2000). The following examples are given to illustrate levels found in specific industries in various locations worldwide and provide some information on present and past exposures of workers to arsenic. They should not be considered as representative of all similar industrial sites.

Some workplace exposures dating from before 1980 are summarized in IPCS (1981). For example, in a Swedish copper smelter during the mid-1950s levels of arsenic ranged between 0.06 and 2 mg/m^3, but at the same facility in the 1970s levels of arsenic between 0.002 and 0.23 mg/m^3 in the air breathed by the workers were reported. Several other studies described in IPCS (1981) reported levels of arsenic in non-ferrous metal production to be between 0.001 and 0.3 mg/m^3 depending on the job location and the level of ventilation.

Welch et al. (1982), on the basis of industrial hygiene measurements made from 1943 to 1965, estimated average arsenic concentrations of workers in various departments of a copper smelter in the USA who were employed before 1956. Very high exposures (> 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 (7 mg/m^3). High exposures (0.5B4.99 mg/m^3) were estimated in these departments: masons' shop (3 mg/m^3), ore roaster (1 mg/m^3), materials crushing (1 mg/m^3) and reverberatory furnaces (0.6 mg/m^3). Medium (0.1–0.49 mg/m^3) or low exposures (< 0.1 mg/m^3) were estimated in the 10 other

departments of the smelter in which arsenic measurements were carried out. In another copper smelter in the USA, Pinto et al. (1976) reported an overall mean arsenic concentration of 0.05 mg/m^3 (range 0.003–0.3 mg/m^3) on the basis of data from 24 workers wearing personal air samplers on 5 consecutive days. For 1973, a more detailed exposure estimation within the 32 departments of the smelter was made on the basis of the individual 24-h urinary excretion of arsenic in 1000 workers (Pinto et al., 1978). The highest average urinary arsenic excretions (µg As/litre of urine) were calculated for the following departments: electrostatic precipitator (526 mg As/litre), arsenic plant (516 µg As/litre), roaster (414 µg As/litre) and boiler room (409 µg As/litre). Eleven other departments had urinary excretion levels between 289 and 201 µg As/litre of urine, and the remaining 17 areas had levels between 180 and 58 µg As/litre, the lowest level calculated for the refined casting department. On the basis of a study by Enterline & Marsh (1982) airborne arsenic levels (as µg/m^3) will be about one-third of the urinary excretion concentrations (as µg As/litre of urine). These authors also summarized the airborne arsenic levels in the smelter between 1938 and 1957. Levels varied by department, but were all high. For example, between 1947 and 1953, in a total of 25 samples from the arsenic plant they found airborne arsenic concentrations ranging from 0.8 to 41.4 mg/m^3.

Vahter et al. (1986) reported airborne arsenic levels (8 h TWA) of 1–194 µg/m^3 in a copper smelter. Daily urinary excretion of total arsenic metabolites ranged from 16 to 328 µg As/g creatinine. Correlation between urinary excretion of arsenic species and 8-h TWAs of arsenic between 0.8–45 µg/m^3 in 24 workers in a copper smelter and an As_2O_3 refinery were reported by Hakala & Pyy (1995). The best correlation was obtained between urinary excretion of the sum of arsenite and arsenate species in urine samples taken 8 h after exposure. An exposure to an 8-h TWA of 10 µg/m^3 was calculated to lead to an inorganic arsenic concentration of 5 µg/litre in urine. Jakubowski et al. (1998) reported levels of arsenic in a copper smelter between 1 and 746 µg/m^3 in the worker's breathing zone (8-hTWA) resulting in daily urinary excretion of 2–850 µg As/g creatinine. On the basis of results from this study and three others, the authors calculated that daily exposure to arsenic concentrations of 10 or 50 µg/m^3 corresponded to concentrations of total urinary metabolites of 30 µg/litre and 70 µg/litre (specific

gravity 1.024) respectively. This compares to urinary excretions (total As metabolites) of 5–30 µg As/litre in people not excessively exposed via the workplace or from the consumption of seafood (Foa et al., 1984; Vahter et al., 1986). Simonato et al. (1994) reported urinary excretion of 183–205 µg As/g creatinine of arsenic metabolites in a cohort of gold-miners and refinery workers. Using airborne arsenic data for 1952–1991, Ferreccio et al. (1996) categorized workers' exposure to arsenic in various units of a copper mine and smelter complex (in µg As/m[3)] as follows: workshop and administration, 9.8; administrative area, 1.6; mine, 2.3; oxide production, 3.1; sulfur plant, 8.4; smelter, 201.7. In comparison, Offergelt et al. (1992) reported levels of arsenic (TWA) between 6 and 502 µg/m^3 in a sulfuric acid plant. As part of an epidemiological investigation on lung cancer mortality of workers in non-ferrous mines, Liu & Chen (1996) measured airborne arsenic levels in 1978, 1981 and 1988. In chronological order, concentrations of arsenic reported (in mg/m^3) were 0.23 (range 0.004–0.577 in 6 samples); 0.06 (range 0.003–0.166 in 14 samples) and 0.32 (range 0.028–1.442 in 8 samples).

Workers in certain glass-manufacturing industries may be exposed to airborne arsenic through the use of As_2O_3 (IARC, 1993). Workers in the heavy crystal industry in Germany were found to have urinary arsenic concentrations ranging from 3 to 114 µg/g creatinine, with 36% of the cases in 1976 and 18% of cases in 1981 being above the upper normal limit of 25 µg As/g creatinine (Schaller et al., 1982). A study in the USA of 35 crystal glassworkers within the mix-and-melt and batch-house areas indicated the potential for arsenic exposure (Chrostek et al., 1980). Personal air monitoring of 8 workers found airborne arsenic concentrations of 2B11 mg/m^3. The mean urinary arsenic excretion in 18 workers involved in weighing and mixing chemicals in a specialist glass-manufacturing facility was 79.4 µg/g creatinine compared to 4.4 µg/g creatinine in controls (Farmer & Johnson, 1990). In a Belgian glass factory, Roels et al. (1982) measured urinary excretion of arsenic in 10 workers ranging between 10 and 941 µg/g creatinine compared to a range of 7.6 to 59 µg/litre in control workers. The authors concluded that the high urinary arsenic concentrations in the workers were more related to oral intake due to poor hygienic practices than to pulmonary uptake.

Airborne arsenic levels in a wood joinery shop handling treated wood were reported to be 0.043–0.36 mg/m^3 (IPCS, 1981). In a more recent study of joinery shops (Nygren et al., 1992), airborne arsenic concentrations between 0.54 and 3.1 µg/m^3 were reported. In two workshops machining wood impregnated with CCA, levels of arsenic in personal air samples were reported to be 30–67 µg/m^3 in plant A (8 workers) and 10–62 µg/m^3 in plant B (8 workers) (Subra et al., 1999).

Workers in coal-powered power plants may also be exposed to arsenic found in the coal, or more likely that found in the fly ash during cleaning. Yager et al. (1997) reported arsenic concentrations (8-h TWA) between 0.17 and 375.2 µg/m^3 (mean 48.3) in the breathing zone of maintenance workers in a coal-fired power plant in Slovakia. The urinary excretion of total urinary arsenic metabolites ranged between 2.6 and 50.8 µg As/g creatinine (mean 16.9). The authors estimated a mean urinary excretion of 13.2 µg As/g creatinine, in workers exposed to fly ash, from an 8-h TWA exposure to 10 µg As/m^3, suggesting that the bioavailability of arsenic in coal fly ash is approximately one-third that seen in smelters. Concentrations of arsenic in the breathing zone of underground gold-miners in Ontario (Canada) were reported to range between 2.4 and 5.6 µg/m^3 (geometric mean) with urinary arsenic concentrations reported to range between 23.5 and 25.9 µmol As/mol creatinine (Kabir & Bilgi, 1993). The median total urinary arsenic concentration of the miners was significantly higher than that of a control group, but no correction was made for differences in dietary habits of the two groups. In a study relating arsenic exposures to lung cancer among tin-miners in Yunnan province (China), Taylor et al. (1989) reported mean concentrations of airborne arsenic to range from 0.42 mg/m^3 in 1951 to 0.01 mg/m^3 in 1980.

5.4 Total human intake of arsenic from all environmental pathways

For healthy humans who are not occupationally exposed the most significant pathway of exposure to arsenic is through the oral intake of food and beverages. In areas with elevated concentrations of arsenic in drinking-water, this source make a significant contribution to the total intake of inorganic arsenic. For example, a consumption of 1.4 litres of drinking-water containing > 50 µg

As/litre could provide over 70 µg inorganic arsenic compared to an estimated daily intake, based on very preliminary data, of 12–14 µg inorganic arsenic from typical North American diets (Yost et al., 1998).

As shown in Table 12, the total estimated daily dietary intake of arsenic may vary widely, mainly because of wide variations in the consumption of fish and shellfish. Data in Table 12 are for total arsenic intake and do not reflect the possible variation in intake of the more toxic inorganic arsenic species (see sections 5.2.2 and 5.2.3). In areas where drinking-water contains > 50 µg As/litre, water may be the major source of inorganic arsenic. All other routes of intakes of arsenic (intranasal and dermal) are of minor importance in comparison to the oral route (ATSDR, 1993). For example, inhalation would add about 1 µg As/day from airborne particulates and approximately 6 µg As /day may be inhaled from 20 cigarettes.

The most appropriate approach to determining the internal dose of inorganic arsenic in individuals in specific populations is to measure the arsenic species in urine. Concentrations of total urinary arsenic and metabolites of inorganic arsenic (inorganic arsenic, MMA and DMA) provides estimates of the exposure (uptake) to total arsenic and inorganic arsenic, respectively (see section 6.3). Reported concentrations of metabolites of inorganic arsenic in urine with no known exposure to arsenic are generally < 10 µg/litre in European countries (Apel & Stoeppler, 1983; Valkonen et al., 1983; Foa et al., 1984; Vahter & Lind, 1986; Andren et al., 1988; Jensen et al., 1991; Buchet et al., 1996; Trepka et al., 1996; Kristiansen et al., 1997; Kavanagh et al., 1998). Similar or slightly higher concentrations are reported from studies in some parts of the USA (Smith et al., 1977, Morse et al., 1979; Binder et al., 1987; Kalman et al., 1990; Pollisar et al., 1990; Gottlieb et al., 1993; Bates et al., 1995; Lewis et al., 1999) and around 50 µg/litre in Japan (Yamamura et al., 1979; Yamauchi et al., 1992). In West Bengal and Bangladesh arsenic concentrations > 1 mg/litre have frequently been observed (Chatterjee et al., 1995; Das et al., 1995).

The concentration of arsenic metabolites in urine correlates well with the concentration of arsenic in the drinking-water. However, the relationship may vary considerably depending on the amount of water consumed and the amount of water used for preparation of

drinks and food. For example, studies from California and Nevada (USA) showed that a water concentration of 400 µg/litre corresponded to about 230 µg/litre in urine (total arsenic) and 100 µg/litre in water corresponded to 75 µg/litre in urine (Valentine et al., 1979). Similarly, people in Alaska drinking water containing about 400 µg/litre had on average 180 µg/litre in urine, and those drinking water containing 50–100 µg/litre had on average 45 µg/litre in urine (Harrington et al., 1978). Thus, urinary arsenic concentration was about half of that in the water. However, people living in areas of northern Argentina with drinking-water containing 200 µg/litre had much higher arsenic concentrations in the urine (metabolites of inorganic arsenic) – on average 250–450 µg/litre (Vahter et al., 1995a; Concha et al., 1998a). The fluid intake of these people consisted mainly of drinking-water or drinks prepared at home from the drinking-water. Also, most of the food consumed was prepared at home using the local drinking-water. In areas in the north-east of Taiwan where drinking-water concentrations were 50–300 µg/litre, people had similar concentrations in the urine; about 140 µg/litre (Chiou et al., 1997a).

Soil (section 5.2.4) may be a significant source of arsenic intake, particularly for children. However, the bioavailability may vary considerably.

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 either to children from areas of low arsenic exposure or 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 mg/kg) compared to a community with low arsenic levels in soil (44 mg/kg). In first-morning urine samples taken in July in the high-arsenic community, mean total arsenic in urine averaged 54 µg/litre (53.8 µg/g creatinine) compared to 16.6 µg/litre (17.1 µg/g creatinine) in the low-arsenic community.

Trepka et al. (1996) studied differences in arsenic exposure among children of different age groups in various areas of Germany, as assessed by urinary arsenic excretion. They reported no marked age- or gender-related differences, although urinary arsenic excretion

was significantly increased in children from the most polluted area (5.1 µg/litre vs. 4 µg/litre in the control area). However, the authors did not consider this increase to be toxicologically significant. In contrast, Diaz-Barriga et al. (1993) reported increases in urinary arsenic in children living closest to a copper smelter (median soil levels ~500 mg/kg arsenic; range 69–594 µg/g creatinine in urine) compared to children living 7–25 km away (median soil levels ~11-14 mg/kg arsenic). Urinary arsenic excretion (normalized to creatinine) was more than doubled, and arsenic levels in hair were more than 10-fold higher.

6. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Humans are exposed to many different forms of inorganic and organic arsenic species (arsenicals) in food, water and other media. Study of the kinetics and metabolism of arsenicals in animals and humans can thus be quite complex, as a result of differences in physicochemical properties and bioavailability of the various forms of arsenic. Arsenic metabolism is also characterized by relatively large qualitative and quantitative interspecies differences. Given the relatively large interspecies differences in arsenic metabolism, and that there is considerable information on human metabolism of arsenicals, discussion of animal studies focuses on areas where human data is inadequate or where animal data can serve to aid in the interpretation of toxic effects caused by arsenicals. This chapter covers both inorganic and organic arsenicals.

6.1 Inorganic arsenic

The metabolism and disposition of inorganic arsenic may depend on its valence state, particularly at high doses. The two most common valence states to which humans might be environmentally exposed are the trivalent and pentavalent forms. Since these two forms are readily interconverted, studies cited in this review were evaluated with particular attention to whether methods used were appropriate to ensure that inorganic arsenic was maintained in the intended valence state until the time of administration. Arsenite, but not arsenate, exists mainly in the non-ionized form at physiological pH and relatively low Eh.

6.1.1 Absorption

6.1.1.1 Respiratory deposition and absorption

Human inhalation exposure to inorganic arsenic can occur as a consequence of industrial activity (e.g. smelting of ores) and energy production (e.g. coal-fired power plants), and during cigarette smoking. Arsenic in air exists on particulate matter and thus respiratory absorption of arsenic is a two-stage process, involving

deposition of the particles on to airway and lung surfaces, followed by absorption of arsenic from deposited particulates. The extent of deposition of inhaled arsenic will depend largely on the size of the inhaled particulates, and absorption of deposited arsenic is highly dependent on the solubility of the chemical form of arsenic.

a) Animal studies

Quantification of the relative amount of airborne arsenic that is deposited in various parts of the respiratory tract is not possible because there is a lack of such animal inhalation studies. However, intratracheal instillation studies provide information on the extent of absorption of various chemical forms of inorganic arsenic. In general, solubility appears to be the most important physicochemical property determining the extent of lung clearance, although wetting capacity and pulmonary toxicity may also have an important influence. It is important to note that clearance of particulates by the mucociliary escalator may also result in oral exposure.

Pershagen et al. (1982) found that lung concentrations of arsenic in hamsters given weekly intratracheal instillations of As_2O_3, arsenic trisulfide or calcium arsenate differed by a factor of approximately 10-fold after 4 weeks. The much more rapid clearance of As_2O_3 was attributed to its being much more soluble *in vivo* than the other two arsenicals. The authors speculated that the clearance of calcium arsenate was much slower than that of arsenic trisulfide because of its higher wetting capacity, which would result in more calcium arsenate being transported to the alveolar regions of the lung where clearance is slower. The authors also indicated that the pulmonary toxicity of calcium arsenate may have impaired normal clearance mechanisms which would have prolonged lung retention.

Marafante & Vahter (1987) reported that the extent of absorption of inorganic arsenicals from the lungs of hamsters after intratracheal instillation was directly correlated with their *in vivo* solubility as determined by the amount of radiolabelled arsenical retained at an intramuscular injection site. The lung retention of arsenic (2 mg As/kg) 3 days after an intratracheal instillation of sodium arsenite, sodium arsenate, arsenic trisulfide and lead arsenate was respectively 0.06%, 0.02%, 1.3% and 45.5% of the dose. Similar observations have been reported by Buchet et al. (1995), who found that 24 h after

a single intratracheal instillation of soluble arsenic salts in hamsters ($NaAsO_2$ and Na_2HAsO_4) at 50 and 100 µg/kg, the amount of arsenic detected in the lung was not different from that found in the control animals. Buchet et al. (1995) also observed that both lung retention and urinary excretion indicate a prolonged contact of the lung tissue with particulate arsenic rather than soluble arsenic salts. Some 48 h after intratracheal administration of arsenic in the form of fly ash or copper smelter dust, lung retention amounted to 25–35% of the administered dose (50–100 µg As/kg). Rosner & Carter (1987) also reported, based on results of intratracheal instillation studies in hamsters, that the more soluble forms of arsenic, sodium arsenate and sodium arsenite (5 mg/kg dose), had a relative bioavailability 10-fold greater than gallium arsenide (GaAs). Webb et al. (1987) also reported that decreasing the particle size by a factor of 2 increased the *in vivo* dissolution rate and toxicity of GaAs in rats after intratracheal instillation.

b) Human studies

The available human data are insufficient to allow quantitative estimation of regional arsenic deposition in the respiratory tract. Occupational studies in which both the concentration of inorganic arsenic in the breathing zone and the urinary excretion of inorganic arsenic and its metabolites were determined provide information on arsenic absorption. These studies (e.g. Vahter et al., 1986; Yamauchi et al., 1989a; Offergelt et al., 1992; Hakala & Pyy, 1995; Yager et al., 1997) demonstrate that excretion of inorganic arsenic and sometimes total arsenicals and methylated metabolites are significantly increased in workers exposed to arsenic in their breathing zone. This indicates that arsenic is absorbed from the respiratory tract, but does not provide sufficient information for quantitative estimation of arsenic absorption after inhalation because the contribution of oral exposure after mucociliary clearance – and in some instances probably also from diet and drinking-water – cannot be assessed.

Comparison of studies relating occupational arsenic exposure in different industrial settings to urinary arsenic excretion suggests that there are differences in respiratory absorption depending on the form of arsenic. Using equations relating urinary arsenic excretion to air concentrations, Yager et al. (1997) noted that in several studies the

predicted urinary arsenic output for workers exposed to 10 µg/m^3 arsenic was more than one-third lower for boiler maintenance workers in a coal-fired power plant than it was for copper-smelter workers. This finding was attributed to the fact that the arsenic in coal fly ash in their study was predominantly in the form of calcium arsenate, whereas in the copper smelter work environment the arsenic was in the form of As_2O_3. Such an interpretation is consistent with the much greater retention of calcium arsenate than As_2O_3 in hamster lung that was reported by Pershagen et al. (1982).

6.1.1.2 Gastrointestinal absorption

Arsenic can be absorbed from the gastrointestinal tract after 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 (e.g. food, water, beverages, soil), the solubility of the arsenical compound itself and the presence of other food constituents and nutrients in the gastrointestinal tract.

a) Animal studies

Soluble arsenates and arsenites are rapidly and extensively absorbed from the gastrointestinal tract of common laboratory animals after a single oral dose (Table 13). The mouse data of Vahter & Norin (1980) indicate that arsenite may be more extensively absorbed from the gastrointestinal tract than arsenate at lower doses (e.g. 0.4 mg As/kg), whereas the reverse appears to occur at higher doses (e.g. 4.0 mg As/kg). In these same studies (Vahter & Norin, 1980) about the same percentage faecal elimination was observed following the same dose given orally and subcutaneously, indicating nearly complete gastrointestinal absorption (Table 13).

Studies conducted by Odanaka et al. (1980) suggest that much less pentavalent arsenic is absorbed from the gastrointestinal tract after oral administration – 48.5% of dose (5 mg/kg) in urine, compared to the 89% of dose (4 mg/kg) in urine found by Vahter & Norin (1980) (Table 13). This difference may be attributable to the fact that the mice in the study of Vahter & Norin were not fed for at least 2 h before and 48 h after dosing, whereas the mice in the Odanaka et al. studies were not food restricted. Studies by Kenyon et

Table 13. Cumulative 48-h elimination (% of dose) of As in urine and faeces of laboratory animals after oral and parenteral administration of inorganic As

Species	As form	Dose	Route	Urine	Faeces	Total	Reference
Rat	Arsenic acid	5 mg/kg	oral	17.2	33.0	50.2	Odanaka et al. (1980)
		1 mg/kg	i.v.	51.0	0.8	51.8	
Hamster	Arsenic acid	5 mg/kg	oral	43.8	44.1	87.9	Odanaka et al. (1980)
		1 mg/kg	i.v.	83.9	4.0	87.9	
Hamster	As trioxide	4.5 mg/kg	oral	43.5	9.4	52.9	Yamauchi & Yamamura (1985)
Mouse	Arsenic acid	5 mg/kg	oral	48.5	48.8	97.3	Odanaka et al. (1980)
		1 mg/kg	i.v.	86.9	2.6	89.5	
Mouse[a]	Sodium arsenate	0.4 mg As/kg	s.c.	86 ± 3.6	6.4 ± 2.1	92.4	Vahter & Norin (1980)
		0.4 mg As/kg	oral	77 ± 3.6	8.0 ± 1.6	85	
		4.0 mg As/kg	oral	89 ± 3.6	6.1 ± 1.2	95.1	

Table 13 (contd.)

Mouse[a]	Sodium arsenite	0.4 mg As/kg	s.c.	73 ± 5.3	3.8 ± 1.6	76.8	Vahter & Norin (1980)
		0.4 mg As/kg	oral	90 ± 2.4	7.1 ± 2.0	97.1	
		4.0 mg As/kg	oral	65 ± 2.1	9.1 ± 1.9	74.1	
Mouse	Sodium arsenate	0.00012 mgAs/kg	oral	65.0	16.5	81.5	Hughes et al. (1994)
		0.0012 mgAs/kg	oral	68.3	13.5	81.8	
		0.012 mgAs/kg	oral	72.1	10.5	82.6	
		0.12 mgAs/kg	oral	71.0	14.6	85.6	
		1.2 mgAs/kg	oral	68.7	18.2	86.9	
Rabbit	Sodium arsenite	0.050 mg As/kg	i.p.	75.7	9.9	85.6	Marafante et al. (1982)

[a] Data given as mean ± SEM

al. (1997) suggest that feeding a diet lower in fibre or "bulk" to female $B6C3F_1$ mice increased absorption of sodium arsenate by ~10% compared to a standard rodent chow diet, after a single oral dose of 5 mg As/kg.

Yamauchi et al. (1986b) studied the absorption and metabolism of GaAs (a relatively insoluble arsenical compared to sodium arsenite and sodium arsenate) in hamsters after a single oral or intraperitoneal dose. Faecal elimination of total arsenic after 5 days averaged 87.5 ± 13.8%, 79.4 ± 10.6% and 77.9% after oral doses of 10, 100 and 1000 mg/kg GaAs, respectively. However, after a single intraperitoneal dose of 100 mg/kg GaAs only 0.38% of the total arsenic dose was eliminated in faeces after 5 days. During this same time period less than 1% of the dose was eliminated in urine irrespective of the route of administration, indicating that GaAs is minimally absorbed from the gastrointestinal tract. It is noteworthy that a consistently greater amount of DMA was excreted in urine over time after intraperitoneal administration than after oral administration. This indicates that arsenic liberated from GaAs undergoes methylation, and is consistent with results reported in hamsters after intratracheal instillation of GaAs (Rosner & Carter, 1987).

The bioavailability of arsenic from soils has been assessed using various animal models because this can be a significant issue in risk assessment for contaminated industrial sites where there is potential for arsenic exposure via soil ingestion. As summarized in Table 14, these studies indicate that oral bioavailability of arsenic in a soil or dust vehicle is often lower than that of the pure soluble salts typically used in toxicity studies. However, bioavailability is substantially dependent on the soil type. A study by Vahter (1988) showed that although some soil samples from former wood-treatment plants containing 1.1 mg As/g were highly toxic, other soil samples containing 9 mg As/g were without any effect when tested in mice. Similarly, the mean relative bioavailability of arsenic in mining wastes compared to that of sodium arsenate administered to young swine and analysed as arsenic in urine was found to range from 7B52% (US EPA, 1996). Davis et al. (1992) have pointed out that this is due mainly to mineralogical factors which control solubility in the gastrointestinal tract, such as solubility of the arsenic-bearing mineral itself and encapsulation within insoluble matrices (e.g.

Table 14. Oral bioavailability of As from soil, based on studies in laboratory animals

Species	Duration (h)	Intravenous dose	Soil or sample	Soil dose	Bioavailability[a] (%, mean ± SD)	Method	Reference
Beagle dog	120	2 mg As(V)	Netherlands bog ore[b]	6.6–7.0 mg As	8.3 ± 2.0	AUC[c] for urinary excretion	Groen et al. (1994)
New Zealand white rabbit	120	1.95 mg As(V)/kg	smelter impacted soil (Anaconda, Montana, USA)	0.78 mg As/kg 1.95 mg As/kg 3.9 mg As/kg	24 ± 3.2	AUC for urinary excretion, no dose-dependency observed	Freeman et al. (1993)
			sodium arsenate	1.95 mg/kg	50 ± 5.7		
Cynommolus monkey	168	0.62 mg As(V)/kg	soil (Anaconda, Montana, USA)	0.62 mg As/kg	14 (11)	AUC for urinary excretion (AUC for blood in parentheses)	Freeman et al. (1995)
			house dust (same location)	0.26 mg As/kg	19 (10)		
			sodium arsenate	0.62 mg As/kg	68 (91)		

Table 14 (contd.)

Species	Duration (h)	Intravenous dose	Soil or sample	Soil dose	Bioavailability[a] (%, mean ± SD)	Method	Reference
Immature swine	144	0.01–0.31 mg As/kg	soil[d]	0.04–0.24 mg As/kg	52	AUC for blood	US EPA (1996)
			slag	0.61–1.52 mg As/kg	28		
			sodium arsenate	0.01–0.11 mg As/kg	68		
Rat	96	0.5 mg As(III)/kg	soil (Watson, Australia)[e]	0.5–5.0 mg As/kg	0.55–2.98 (As(V))[f]	AUC for blood	Ng et al. (1998b)
		0.5 mg As(V)/kg			1.02–9.87(As(III))		

[a] Comparison to intravenous administration
[b] Bog ore is naturally high in As
[c] AUC, area under the curve
[d] Soil or slag from Ruston/North Tacoma Superfund site in Tacoma, Washington (USA)
[e] Soil from site contaminated with Arsenical pesticides (former cattle dip); soils contained 32–1597 mg As/kg soil
[f] Figures are relative to sodium arsenate and sodium arsenite

silica). The comparative bioavailabilities of arsenic in soil from a site contaminated with copper chrome acetate (CCA) and soil contaminated by arsenic solutions used in cattle tick control were reported by Ng & Moore (1996), using a rat model. Soil from the cattle dip site had a bioavailability of 8.1 ± 4%, 14.4 ± 7% and 60 ± 3.4% when compared with orally administered sodium arsenite, calcium arsenite and sodium arsenate respectively. For CCA-contaminated soil the corresponding comparative bioavailabilities were 13.0 ± 4.5%, 32.2 ± 11.2% and 38.0 ± 13.2%. Ng et al. (1998b), also using a rat model, have reported the absolute bioavailability of arsenic in soils containing 32–1597 µg As/kg (0.32–56% arsenite) from a combination of arsenical pesticides and natural geological formations in a residential area. The absolute bioavailability ranged from 1.02 to 9.87% relative to arsenite and from 0.26 to 2.98% relative to arsenate.

Several older studies reviewed in the previous IPCS arsenic document (IPCS, 1981, sections 6.1.1 and 6.2) demonstrated that composition of the diet can alter gastrointestinal absorption of arsenic. Some more recent studies have examined the mechanism of arsenical uptake and interaction with nutrients at the intestinal level. Gonzalez et al. (1995), using isolated perfused rat small intestine, demonstrated that uptake of pentavalent arsenic is carried out by a saturable transport process and that addition of phosphate markedly decreased arsenic absorption, most likely because arsenate and phosphate can share the same transport mechanism. Hunder et al. (1993), using isolated rat jejunal segments, found that increasing concentrations of arsenite (2.5–250 µmol/litre) and arsenate (2.5-2500 µmol/litre) caused a dose-dependent decrease in the intestinal transfer of water, sodium, glucose and leucine, with arsenite being about 5-fold more potent than arsenate.

b) Human studies

In common with studies in experimental animals, controlled ingestion studies in humans indicate that trivalent and pentavalent arsenic are both well absorbed from the gastrointestinal tract (Table 15). 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 (As(V)) in urine over a period of 7 days, whereas only 6.1 ± 2.8% of the dose was excreted in the faeces. Few other

Table 15. Metabolism and urinary excretion of inorganic and organic arsenicals in humans after experimental administration

Form	No. of subjects	Dose and frequency	Time interval	% dose in urine	% of total urinary metabolites				Reference
					As(V)	As(III)	MMA	DMA	
As acid	6	0.01 µg	5 days	57.9	27.2 (IAs)[a]		20.6	51.0	Tam et al. (1979)
As acid	6	0.06 ng	7 days	62.3	ND	ND	ND	ND	Pomroy et al. (1980)
As trioxide	1	700 µg	3 days	68.2	7.9	31.7	28.2	32.2	Yamauchi & Yamamura (1979)
Sodium arsenite	3	500 µg	4 days	45.1	25 (IAs)		21.3	53.7	Buchet et al. (1981a)
Sodium metaarsenite	1	125 µg × 5 days	14 days	54	16 (IAs)		34	50	Buchet et al. (1981b)
	1	250 µg × 5 days	14 days	73	7 (IAs)		20	73	
	1	500 µg × 5 days	14 days	74	19 (IAs)		21	60	
	1	1000 µg × 5 days	14 days	64	26 (IAs)		32	42	
Sodium MMA	4	500 µg	4 days	78.3	ND	ND	87.4	12.6	Buchet et al. (1981a)
Sodium DMA	4	500 µg	4 days	75.1	ND	ND	ND	100	Buchet et al. (1981a)

Subjects in all studies cited were adult males

[a] IAs, sum of As(III) and As(V)

controlled human ingestion studies have actually reported data on both urine and faecal elimination of arsenic. However, between 45% and 75% of the dose of various trivalent forms of arsenic is excreted in the urine within a few days (Table 15), which suggests that gastrointestinal absorption is both relatively rapid and extensive.

6.1.1.3 Dermal absorption

Wester et al. (1993) studied the percutaneous absorption of arsenic acid (H_3AsO_4) from water and soil both *in vivo* using rhesus monkeys and *in vitro* with human skin. *In vivo*, absorption of arsenic acid from water (loading 5 µl/cm^2 skin area) was 6.4 ± 3.9% at the low dose (0.024 ng/cm^2) and 2.0 ± 1.2% at the high dose (2.1 µg/cm^2). Absorption from soil (loading 0.04 g soil/cm^2 skin area) *in vivo* was 4.5 ± 3.2% at the low dose (0. 04 ng/cm^2) and 3.2 ± 1.9% at the high dose (0.6 µg/cm^2). Thus, *in vivo* in the rhesus monkey, percutaneous absorption of arsenic acid is low from either soil or water vehicles and does not differ appreciably at doses more than 10 000-fold apart. Wester et al. (19993) also reported that for human skin, at the low dose, 1.9% was absorbed from water and 0.8% from soil over a 24-h period.

Limited data suggest that the *in vitro* percutaneous absorption of inorganic arsenicals may differ substantially depending on chemical form or species used. Rahman et al. (1994) evaluated the percutaneous absorption of sodium arsenate *in vitro* using clipped full-thickness dorsal skin of B6C3F$_1$ mice. They found that a constant fraction of the applied dose was absorbed over a 24-h period irrespective of dose level (5–500 ng or 0.36–360 mg/kg for soil), but that the vehicle or vehicle volume had significant effects. Using 100 µl water as a vehicle resulted in ~60% of applied dose being absorbed, whereas using a volume of 250 µl water resulted in ~37% absorption, which was about the same percentage absorbed if the chemical was applied in the solid form. Absorption of sodium arsenate from soil was minimal (< 0.3%), which is similar to what was reported for arsenic acid in the studies of Wester et al. (1993).

6.1.1.4 Placental transfer

a) Animal studies

Both older and more recent studies have documented the ability of trivalent and pentavalent inorganic arsenic to cross the placenta in laboratory animals. Lindgren et al. (1984) reported that in pregnant mice given a single intravenous injection (4 mg As/kg) of sodium arsenate or sodium arsenite, both forms passed through the placenta easily and to approximately the same extent. These investigators also reported that the rate of placental transfer was lower in a marmoset monkey (non-methylating species) injected intravenously with arsenite than in mice, and suggested that this was a consequence of stronger binding in maternal tissues.

Hood et al. (1987) compared the fetal uptake of sodium arsenate after oral (40 mg/kg) or intraperitoneal (20 mg/kg) administration to pregnant CD-1 mice on day 18 of gestation. Arsenic levels peaked later and over 5-fold lower in fetuses of mice dosed orally, most likely reflecting both slower uptake from the gastrointestinal tract and greater opportunity for methylation in the liver before the arsenic reached the systemic circulation. The quantity of dimethylated metabolite present in the fetuses rose over time (to ~80% of total metabolites present for both routes of administration) and remained relatively constant from ~10 h after dosing until the study ended, 24 h after dosing.

Hood et al. (1988) also compared the fetal uptake of sodium arsenite after oral (25 mg/kg) or intraperitoneal (8 mg/kg) administration to mice that were 18 days pregnant. As was the case with arsenate, injected mice achieved both higher fetal and placental levels of arsenic more quickly than did mice dosed orally. Both valence forms followed similar time-course trends after oral administration. However, levels of arsenic in fetuses of dams injected with arsenite reached a plateau 12–24 h after dosing, whereas levels of arsenic in fetuses of dams injected with arsenate peaked at 2–4 h after dosing and then declined quickly. The proportion of arsenic present in fetuses as methylated metabolite increased over time to 88% and 79% after oral and intraperitoneal administration, respectively. A higher fraction of monomethylated arsenic was present in fetuses of dams dosed with arsenite than with

arsenate. The authors concluded that much of the arsenic reaching the fetus has already been transformed to the less acutely toxic methylated metabolites.

b) Human studies

Case reports of arsenic poisoning in pregnant women resulting in death of the fetus accompanied by toxic levels of arsenic in fetal organs and tissues demonstrate that arsenite (As_2O_3) readily passes through the placenta (Lugo et al., 1969; Bollinger et al., 1992). In a more recent study, Concha et al. (1998b) reported that arsenic concentrations were similar in cord blood and maternal blood (~9 µg/litre) of maternal–infant pairs exposed to drinking-water containing high levels of arsenic (~200 µg/litre). Another study of an "unexposed" population in the southern USA found that concentrations of arsenic in cord blood and maternal blood (about 2 µg/litre) were also similar, and suggests that arsenic readily crosses the placenta (Kagey et al., 1977).

6.1.2 Distribution

6.1.2.1 Fate of inorganic arsenic in blood

a) Animal studies

Inorganic arsenic is rapidly cleared from the blood in most common laboratory animals, including mice, rabbits, and hamsters (Vahter & Norin, 1980; Marafante et al., 1982, 1985; Yamauchi & Yamamura, 1985). The notable exception to this is the rat in which the presence of arsenic is prolonged owing to accumulation in erythrocytes (Vahter, 1981; Marafante et al., 1982; Lerman & Clarkson, 1983). For example, Marafante et al. (1982) reported that levels of arsenic in erythrocytes were 2-fold, 102-fold and 268-fold higher at 1, 16 and 48 h after dosing in rats compared to rabbits that received the same intraperitoneal dose of arsenite; in the plasma of these same animals the rat : rabbit ratio of arsenic never exceeded 1. Lerman & Clarkson (1983) further noted that higher levels of arsenic were achieved much more rapidly in the blood of rats dosed intravenously with arsenite than with arsenate, and that 95% or more of the arsenic in erythrocytes was in the form of DMA by 4 h after dosing. It appears that rat haemoglobin specifically binds DMA, and

this greatly increases the biological half-life of inorganic arsenic and DMA in rats (Vahter, 1981; Vahter et al., 1984).

Although clearance of both arsenate and arsenite from blood in other mammalian species is rapid, differences dependent on both valence state and dose have been observed. Vahter & Norin (1980) reported that at a high oral dose of arsenic (4 mg As/kg), arsenite-dosed mice had a higher erythrocyte to plasma ratio (~2–3), whereas in arsenate-dosed mice the ratio was much closer to 1. No such difference was observed at a lower oral dose (0.4 mg As/kg) of arsenate or arsenite. Delnomdedieu et al. (1994b) investigated the *in vitro* uptake of arsenite and arsenate in intact rabbit erythrocytes. They reported that ~76% of arsenite, compared to ~25% of arsenate, was taken up within 0.5 h, and that arsenite subsequently bound with intracellular glutathione (GSH), whereas arsenate entered the phosphate pathway, depleting ATP and increasing inorganic phosphate levels.

Yamauchi & Yamamura (1985) characterized the forms of arsenic present and their distribution over time in whole blood, plasma and erythrocytes in male Syrian golden hamsters given a single oral dose of 4.5 mg/kg As_2O_3 (As(III)). Arsenic levels in whole blood had dropped to control levels by 72 h after dosing, indicating rapid clearance from the blood. In whole blood, inorganic arsenic, MMA and DMA concentrations peaked 1, 12 and 24 h after dosing, respectively; the levels of MMA and DMA achieved relative were 1/3 and 1/10 as high as those of inorganic arsenic. Inorganic arsenic and MMA were found mainly in erythrocytes and DMA occurred chiefly in plasma.

Marafante et al. (1985) also characterized the forms of arsenic present and their distribution over time in blood of rabbits dosed with arsenate. Male New Zealand white rabbits were injected intravenously with 0.4 mg As/kg and blood samples were taken at intervals from 15 min to 6 h after dosing. Within 15 min after dosing, 10% of the arsenic in the plasma was in the form of arsenite, 30% was present as arsenate and 60% was bound to plasma proteins. Arsenate was rapidly cleared from plasma (first-order $t_{1/2}$ ~1 h). Both arsenite and plasma protein-bound arsenic exhibited biphasic kinetics, with half-times of 10 min and 2 h for arsenite and 15 min and 2.5 h for protein-bound arsenic. In studies of giant Flemish

rabbits using carrier-free ^{74}As (arsenate), DeKimpe et al. (1996) reported biphasic blood clearance rates of about 2 h and 58 h in plasma and 8.6 h and 170 h in erythrocytes. Taken together, the findings of Marafante et al. (1985) and DeKimpe et al. (1996) suggest a triphasic, rather than biphasic, clearance in plasma. These findings indicate that binding of arsenic to plasma protein is not strong. The kinetics and concentration of arsenite in erythrocytes were quite similar to that seen in plasma, but arsenate concentrations in erythrocytes were only about 1/10 as high. DMA levels peaked at about 4 h after dosing in both plasma and erythrocytes, but the concentration in erythrocytes was only about 20% of that found in plasma.

b) Human studies

Inorganic arsenic is reported to be rapidly cleared from blood. Results from some older studies reviewed in the previous arsenic IPCS document (IPCS, 1981, section 6.1.2), suggest that the kinetics of arsenic clearance in plasma and erythrocytes are similar, although levels in erythrocytes tended to be approximately 3-fold higher a few hours after exposure (similar to findings in laboratory animals). Mealey et al. (1959) measured the plasma and erythrocyte levels of radioactive arsenic after intravenous injection of labelled arsenite. The rate of decline of arsenic in the erythrocytes was comparable with that in plasma, but the erythrocytes contained about 3 times more arsenic than the plasma 10 h after the injection. The plasma curve showed a three-compartment model (IPCS, 1981, section 6.1.3). The first half-life seemed to be very short, and the bulk of the arsenic was removed from the plasma at a high rate. Some 24 h after dosing, less than 0.1% of the dose remained. The second phase of the curve showed a half-time of about 30 h. The third phase of the curve, beginning about 1 week after the injection, showed a very low rate of disappearance with a half-time of over 200 h.

Zhang et al. (1996a,b, 1997, 1998a,b) have reported on the distribution of arsenical species in serum and arsenic–protein binding in serum of patients with renal disease. The predominant species of arsenic present in serum were DMA (~15–30%) and arsenobetaine (~54–76%), with the remainder being protein-bound and inorganic arsenic; MMA was undetectable (Zhang et al., 1996a, 1997). Zhang et al. (1998a,b) 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.

6.1.2.2 Tissue distribution

a) Animal studies

Studies in rabbits, rats, mice, hamsters and monkeys demonstrate that arsenic, administered orally or parenterally, in either the trivalent or pentavalent form, is rapidly distributed throughout the body (Lindgren et al., 1982; Marafante et al., 1982; Vahter et al., 1982; Vahter & Marafante, 1985; Yamauchi & Yamamura, 1985). Many of these studies have used radiolabelled arsenic, and it is noteworthy that arsenic-derived radioactivity is generally present in all tissues examined (Lindgren et al., 1982; Marafante et al., 1982; Vahter et al., 1982; Vahter & Marafante, 1985).

Comparative studies of arsenate and arsenite distribution at comparable dose levels provide insights on the influence of valence state on arsenic distribution. Lindgren et al. (1982) studied the distribution of arsenic in male C57BL mice intravenously administered 0.4 mg As/kg as either sodium arsenate or sodium arsenite at 0.5, 6, 24 and 72 h after dosing. Highest concentrations of arsenic-derived radioactivity were present in liver, kidney and gallbladder at 0.5 h after administration of either arsenate or arsenite, reflecting their rapid elimination (see section 6.1.4). Arsenate administration resulted in much lower arsenic concentrations in liver and gallbladder, but higher concentrations in kidney compared to administration of arsenite within 0.5 h after dosing, indicating valence-dependent differences in route of elimination. In general, concentrations of arsenic in organs tended to be higher after administration arsenite than of arsenate, with the notable exception of the skeleton at all time points (Table 16). This latter finding was ascribed to arsenate being a structural analogue of phosphate and substituting for it in the apatite crystal of bone. The greater retention of arsenite in tissues is a consequence of its reactivity and binding with tissue constituents, most notably sulfhydryl groups (Vahter & Marafante, 1983).

Table 16. Comparison of tissue distribution over time in mice given a single intravenous injection of ^{74}As-As (0.4 mg As/kg) as either sodium arsenate or sodium arsenite[a]

Tissue	Valence	Concentration of ^{74}As (ng/g) at specified time			
		0.5 h	6 h	24 h	72 h
Brain	5+	20 ± 3.6	26 ± 2.5	1.8 ± 0.1	0.6 ± 0.1
	3+	21 ± 1.5	41 ± 3.6	3.3 ± 0.3	0.9 ± 0.1
Stomach	5+	165 ± 15	81 ± 10	24 ± 1.6	11 ± 0.7
	3+	418 ± 58	118 ± 13	79 ± 5.2	27 ± 3.6
Duodenum	5+	553 ± 91	77 ± 14	5.6 ± 0.6	2.0 ± 0.5
	3+	1016 ± 96	150 ± 12	14 ± 1.9	4.6 ± 0.6
Small intestine	5+	214 ± 12	53 ± 8.4	3.9 ± 0.9	1.6 ± 0.3
	3+	582 ± 87	124 ± 6.4	9.0 ± 1.1	3.6 ± 0.3
Liver	5+	571 ± 68	77 ± 12	8.1 ± 0.4	3.3 ± 0.2
	3+	1589 ± 222	188 ± 11	29 ± 1.4	12.1 ± 1.0
Gall bladder	5+	1255 ± 298	200 ± 98	< 10	< 10
	3+	5172 ± 3022	422 ± 224	< 10	< 10
Kidney	5+	2355 ± 185	209 ± 33	20 ± 1.5	7.7 ± 0.7
	3+	1603 ± 211	200 ± 15	20 ± 0.9	7.6 ± 0.5
Lung	5+	291 ± 26	131 ± 19	8.0 ± 0.7	2.3 ± 0.1
	3+	540 ± 59	243 ± 37	23 ± 2.9	5.6 ± 0.4
Skin	5+	184 ± 18	46 ± 3.9	16 ± 1.3	9.1 ± 0.9
	3+	205 ± 22	125 ± 5.5	66 ± 7.8	42 ± 4.3
Skeleton	5+	388 ± 52	98 ± 24	41 ± 3.8	17 ± 1.5
	3+	247 ± 34	82 ± 4.5	8.8 ± 1.3	3.6 ± 0.9
Epididymis	5+	127 ± 10	66 ± 11	16 ± 2.3	9.7 ± 1.6
	3+	187 ± 15	151 ± 5.6	61 ± 8.1	36 ± 4.5
Testis	5+	48 ± 4.8	34 ± 4.0	5.7 ± 0.4	0.9 ± 0.3
	3+	47 ± 1.7	60 ± 5.0	11 ± 1.0	1.2 ± 0.4

[a] Table assembled from Lindgren et al. (1982)

Both species-specific and valence-state-dependent differences have been demonstrated in the biliary excretion of arsenic. Studies reviewed in the previous arsenic document (IPCS, 1981, 6.1.2) indicate that excretion of trivalent arsenic into the bile is much more extensive in rats than in rabbits or dogs (Klaassen, 1974). The

studies of Lindgren et al. (1982) suggest that arsenite is excreted to a greater extent than arsenate in the bile of mice (Table 16); these authors also attribute the higher concentrations of arsenite-derived radioactivity in the duodenum of mice to greater biliary excretion of arsenite. Excretion of arsenite into the bile of rats is also more rapid and efficient than that of arsenate – 19% vs. 6% of the dose in 2 h (Gyurasics et al., 1991). Mechanistic studies indicate that transport of either arsenate or arsenite into the bile of rats is dependent on GSH, since agents that decrease hepatobiliary transport of GSH (e.g. diethyl maleate) also decrease hepatobiliary transport of arsenic (Alexander & Aaseth, 1985; Gyurasics et al., 1991). It has been demonstrated in recent studies that arsenite as well as other trivalent arsenicals directly form complexes with GSH (Scott et al., 1993; Delnomdedieu et al., 1994a).

Numerous studies reveal that skin, hair, and tissues high in squamous epithelium (e.g. mucosa of the oral cavity, oesophagus, stomach and small intestine) have a strong tendency to accumulate and maintain higher levels of arsenic (e.g. Lindgren et al., 1982; Yamauchi & Yamamura, 1985). This is apparently a function of the binding of arsenic to keratin in these tissues (Lindgren et al., 1982). Autoradiographic studies have also revealed a tendency for arsenic to accumulate in the epididymis, thyroid and lens of the eye of mice (Lindgren et al., 1982).

Arsenic can cross the blood–brain barrier; it is found in brain tissue after oral or parenteral administration of trivalent or pentavalent inorganic arsenic in all species studied (e.g. see Table 16). However, the levels are uniformly low both across time and relative to other tissues, which indicates that arsenic (when administered in the form of sodium salts) does not readily cross the blood–brain barrier or accumulate in brain tissue after acute dosing (Lindgren et al., 1982; Marafante et al., 1982; Vahter et al., 1982; Vahter & Marafante, 1985; Yamauchi & Yamamura, 1985; Itoh et al., 1990).

Relatively few studies have examined the distribution of arsenic metabolites in tissues, owing to limitations in availability of appropriate analytical techniques. Given the vigorous treatment necessary to extract arsenicals from tissues, and the ease with which arsenate and arsenite are interconverted, any reports that distinguish

between arsenate and arsenite in tissues should be interpreted with caution. DeKimpe et al. (1996) reported the tissue distribution of arsenic metabolites at 4, 20 and 120 h after intraperitoneal injection of a trace amount of ^{74}As-arsenate in male Flemish giant rabbits. The analytical methodology used was ion-exchange chromatography separation of ultrafiltrates with radiometric detection. The predominant metabolite present in tissues was DMA, followed by the inorganic arsenic species, with MMA being generally detected in all tissues, although making up a smaller percentage of the total metabolites in most cases. The percentage of total metabolite present as DMA increased steadily in bone marrow, heart, liver, muscle, pancreas, small intestine and spleen, but levelled off or declined in kidney and lung. Marafante et al. (1982) also found that inorganic arsenic was the predominant form of arsenic in rat and rabbit liver and kidney ultrafiltrable fraction (cut-off 25 000 Da) 1 h after intraperitoneal injection of 50 µg As/kg sodium arsenite; the analytical methodology used was ion-exchange chromatographic separation with radiometric detection. However, the fraction of DMA was higher at 16 h after injection in kidney of both rats and rabbits, but only in the liver of rats. The fraction present as MMA was uniformly low, generally less that one-tenth that of inorganic arsenic.

Yamauchi & Yamamura (1985) studied the tissue distribution over time of arsenic metabolites in male Syrian golden hamsters given a single oral dose of 4.5 mg/kg As_2O_3. Hydride generation atomic absorption spectrophotometry (HGAAS) with a cold trap was used to speciate arsenicals in whole tissues after alkaline digestion. The predominant form of arsenic present in all tissues at 1, 6, 12, 24, 72 and 120 h after dosing was inorganic arsenic. Interestingly, concentrations of MMA in tissue were uniformly 2–4-fold greater than DMA at all time points, although much more DMA (22% of the dose) was excreted in urine over 5 days than MMA (2.5% of the dose). Highest concentrations of MMA were achieved in lungs and spleen at 12 h and kidney at 24 h, and highest concentrations of DMA occurred in liver, lung and kidney at 24 h.

The subcellular distribution of total arsenic administered as either sodium arsenate or sodium arsenite has been studied in mice, rats, rabbits and marmoset monkeys (Marafante et al., 1982; Vahter et al., 1982; Vahter & Marafante, 1983; Vahter & Marafante, 1985). In general the subcellular localization and retention of arsenic

accounts for its much slower elimination in rats than in other species. In rats arsenic is strongly associated with high-molecular-weight cellular components in liver and kidney, whereas in rabbits it is associated with low-molecular-weight, more readily diffusible cellular components (Marafante et al., 1982). This research group also reported that in the marmoset monkey arsenic, administered as arsenite or arsenate, shows a unique strong tendency to bind with the rough endoplasmic reticulum in the liver that they had not observed in other laboratory animals (Vahter et al., 1982; Vahter & Marafante, 1985).

b) Human studies

As in experimental animals, postmortem analysis of human tissues reveals that arsenic is widely distributed in the body after either long-term relatively low-level exposure or poisoning (Dang et al., 1983; Gerhardsson et al., 1988; Raie, 1996). Dang et al. (1983) used neutron activation analysis (NAA) to measure total arsenic in various tissues of individuals (age and sex not specified) dying in accidents in the Bombay area (India) (Table 17). Notable results from this study are that arsenic concentrations are quite low in both blood and brain relative to other tissues and that arsenic concentration in any given tissue was quite variable.

Table 17. As levels in human tissues from accident victims in Bombay area of India[a]

Tissue	No. of samples	As concentration (ng/g wet weight)	
		Range	mean ± SD
Blood	8	3.1–13.8	5.9 ± 3.9
Brain	12	2.5–6.0	3.9 ± 1.0
Liver	19	4.5–27.7	14.5 ± 6.9
Kidney	13	1.6–62.8	12.4 ± 20.7
Lung	13	2.5–81.8	19.9 ± 22.7
Spleen	18	3.6–46.2	15.2 ± 16.6

[a] Table assembled from Dang et al. (1983)

Yamauchi & Yamamura (1983) analysed by HGAAS the levels of total arsenic and major arsenic metabolites in a variety of human tissues obtained from adult patients (age 36–79) dying of cerebral haemorrhage, pneumonia or cancer in Kawasaki (Japan) (Table 18). No sex-dependent differences in arsenical tissue levels were observed; inorganic arsenic was 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 levels in brain tended to be more comparable to levels in other tissues. Inter-individual variation in total tissue arsenic was also quite high, as observed in the Dang study using NAA.

Table 18. Tissue concentrations of metabolites and total As in normal tissues and organs of adult Japanese people[a]

Tissue/organ	No. of samples	Arsenical concentration (mean) in tissue (ng/g wet weight)[b]			
		Inorganic As	MMA	DMA	Total As
Aorta	16	535	< LD	16.4	551 ± 350
Adrenal gland	19	301	< LD	25.8	327 ± 364
Cerebellum	30	132	< LD	< LD	132 ± 60.2
Cerebrum	30	76.8	< LD	< LD	76.3 ± 43.9
Kidney	24	97.7	3.6	27.6	129 ± 72.3
Liver	23	116	5.9	14.0	129 ± 39.7
Lung	22	96.9	< LD	7.6	104 ± 29.5
Muscle	22	88.1	< LD	18.9	106 ± 32.7
Pancreas	18	139.7	< LD	14.7	154 ± 71.4
Skin	22	149.6	< LD	3.7	153 ± 97.7
Spleen	20	91.4	< LD	12.6	101 ± 49.4

[a] Table assembled from Yamauchi & Yamamura (1983)
[b] < LD indicates less than limit of detection, which was 1 ng As/g wet tissue weight

Raie (1996) used NAA to compare tissue arsenic levels in infants (1 day–5 months) and adults from the Glasgow (Scotland, UK) area. Mean levels of arsenic (µg/g dry weight) in liver, lung and spleen in infants vs. 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, which is consistent with observations in laboratory animals (Marafante et al., 1982).

Studies have been conducted in humans with the goal of determining whether there are differences in tissue accumulation of arsenic (and other metals as well) in differing disease states. Warren et al. (1983) compared trace element levels in brain and other tissues of multiple sclerosis and non-multiple-sclerosis patients and found no significant difference in any tissue arsenic levels. 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 those in patients who died of non-hepatic-related causes. Collecchi et al. (1985) compared the distribution of arsenic and cobalt in cancerous and non-cancerous laryngeal tissue and plasma of patients with and without laryngeal cancer. Malignant tissue had significantly higher levels of arsenic than normal tissue, and plasma arsenic levels were also significantly higher in cancer patients than in controls. Zhang et al. (1996b, 1997) have reported that arsenic levels in serum are significantly elevated in patients with chronic renal disease (~5B6-fold), whether on dialysis or not, and that accumulation and removal of the dominant species of arsenic in serum (DMA and arsenobetaine) was non-selective for dialysed patients.

6.1.3 Metabolic transformation

Arsenic metabolism is characterized in many species by two main types of reactions: (1) reduction of pentavalent to trivalent arsenic, and (2) oxidative 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 Fig. 3)[1]. One

[1] Although this sequence of methylation reactions is generally considered to be a detoxification reaction, recent publications may indicate that an intermediate, MMA(III), is highly toxic (Styblo and Thomas, 1997; Petrick et al., 2000; Styblo et al., 2000), and is released from the site of methylation as it has been detected in bile and urine (Aposhian et al., 2000; Gregus et al., 2000).

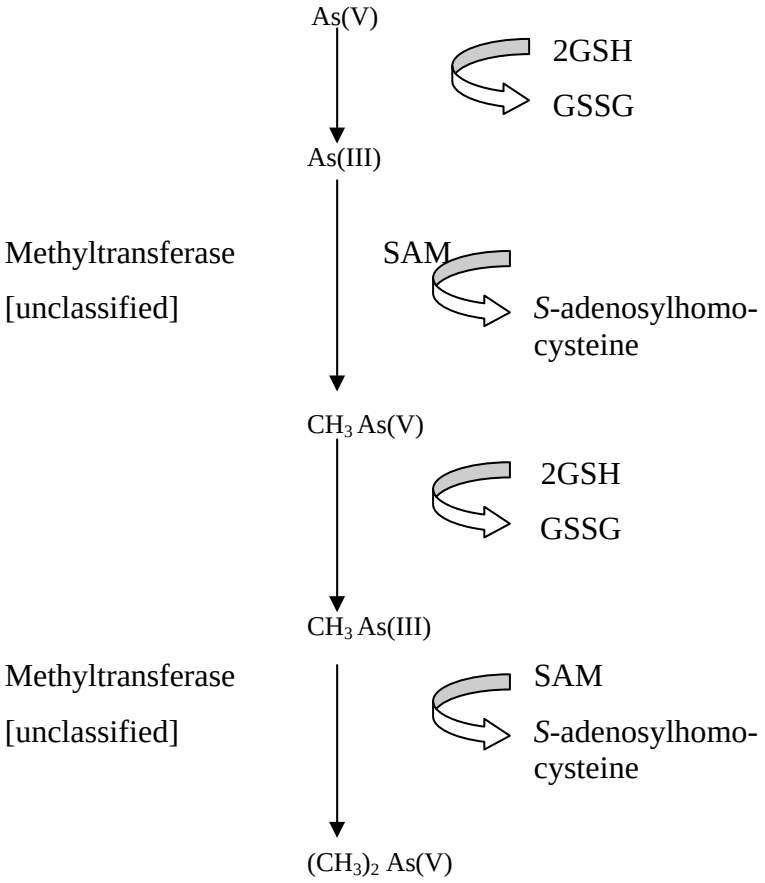

Fig. 3. Arsenic methylation in mammals. Reducing equivalents are supplied by glutathione (GSH) and *S*-adenosyl (methionine (SAM) serves as the methyl donor. Reduction of pentavalent to trivalent forms is required for methylation. Trimethylated forms are produced in small amounts if animals or humans are administered DMA.

unusual 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).

6.1.3.1 Animal studies

Reduction of pentavalent to trivalent arsenic species is required for methylation of arsenic (Lerman et al., 1983; Cullen et al., 1984a,b; Marafante et al., 1985; Thompson, 1993). Arsenate reduction is known to occur non-enzymatically under conditions of low oxygen tension (i.e. an anaerobic environment such as exists in the gut) or over time at pH 2 or lower (Vahter & Envall, 1983). *In vitro* mechanistic studies have demonstrated that the ubiquitous cellular tripeptide GSH is able to reduce arsenate to arsenite in both aqueous systems (Scott et al., 1993; Delnomdedieu et al., 1994a) and in intact erythrocytes (Delnomdedieu et al., 1994b). Interestingly, bacteria have the capability to enzymatically reduce inorganic arsenate to arsenite (Rosen, 1995; see also section 4.2). It has been hypothesized that mammalian cells also have this capability (Healy et al., 1998), but this has not been conclusively demonstrated.

In vivo reduction of arsenate to arsenite before methylation was demonstrated by Vahter & Envall (1983). The appearance of arsenic metabolites in the urine of catheterized New Zealand white rabbits was followed over a period of 4 h after intravenous injection of 0.04 mg As/kg arsenate. Arsenate (unmetabolized) was excreted in greatest amounts during the first hour and thereafter declined, whereas excretion of arsenite progressively increased and cumulatively amounted to 10% of the administered dose. Metabolism of arsenate to DMA, which requires reduction from pentavalent to trivalent form, also progressively increased over the 4-h time period, but peaked later than arsenite. *In vivo* reduction of arsenate to arsenite has also been demonstrated in marmoset monkeys, which exhibit little to no methylation of arsenic. Arsenate levels in the plasma of marmosets injected intravenously with 0.4 mg As/kg peaked at 0.5 h after injection and thereafter declined, whereas the amount of arsenite increased sharply through 6 h (Vahter & Marafante, 1985).

Arsenic methylation activity is localized in the cytosol and appears to occur sequentially and mainly in the liver. Styblo et al. (1996), using a rat liver cytosol system, found that whether the starting material was arsenate or arsenite, MMA was detected sooner and peaked earlier than DMA. Similar findings have been reported using rat liver slices (Buchet & Lauwerys, 1985). Georis et al.

(1990), also using rat tissue slices, reported that liver, kidney and lung all had the capacity to methylate arsenite, but that the capacity of the liver was clearly greater.

Both *in vivo* and *in vitro* studies have demonstrated that SAM and GSH are essential co-factors in enzymatic arsenic methylation (Buchet & Lauwerys, 1985, 1987, 1988; Marafante et al., 1985; Hirata et al., 1988, 1989; Styblo et al., 1996). For example, Marafante et al. (1985) compared the biotransformation and tissue retention in control and periodate-oxidized adenosine (PAD) treated rabbits dosed intravenously with 0.4 mg As/kg ^{74}As[arsenate]. PAD depletes the intracellular SAM pool by inhibiting its synthesis. Approximately 35% of the arsenate dose was excreted in urine as DMA in 24 h in control rabbits, compared to ~5% in the PAD-treated rabbits. Tissue retention of arsenate-derived radioactivity was also significantly higher in PAD-treated rabbits than in controls at 24 h in all major organs examined. These data indicate that methylation is an equally important mechanism for expediting the excretion of both arsenate and arsenite from the body. In addition, since DMA was found only in liver, but not other organs, 1 h after ^{74}As[arsenate] administration, the authors considered this to indicate that the liver is the main site of arsenic methylation.

Healy et al. (1998), using cytosol prepared from liver, lung, kidney and testes of male B6C3F$_1$ mice, reported that all the tissues had the capacity to methylate arsenite. However, the specific activity (defined as pmol [^{3}H] MMA formed per hour/mg protein at 37 ^{o}C and reported as mean ± SEM) was greatest in testes (1.45 ± 0.08) followed by kidney (0.70 ± 0.06), liver (0.40 ± 0.06) and lung (0.22 ± 0.01). These findings suggest that although the liver may have the greatest overall arsenite methylation capacity (on the basis of tissue mass), extrahepatic metabolism may also be significant. This would be particularly the case for routes of exposure such as inhalation, where there is opportunity for first-pass metabolism in the lung.

The capacity of the gut microbiota to metabolize arsenic has also been investigated in rats and mice. Rowland & Davies (1981) demonstrated that the low oxygen environment of the intestine itself stimulates the rapid reduction of arsenate to arsenite, and that arsenate reduction was further stimulated by the presence of bile

acids and gut contents from male Wistar rats. These authors also reported that methylation apparently did not occur in incubations of rat small-intestinal contents, but production of both MMA and DMA occurred in incubations of caecal contents. Hall et al. (1997) reported that caecal contents from male CD-1 mice incubated under physiological conditions methylated 33% of 0.1 µmol/litre arsenite, but only 8% of 0.1 µmol/litre arsenate over a period of 6 h. After 21 h incubation, 36% and 29% of the applied dose of arsenite and arsenate, respectively were in the form of MMA, and DMA accounted for only approximately 3% of the methylated metabolites present. These data suggest that gut microbial metabolism could contribute significantly to methylation in laboratory animals. However, Vahter & Gustafsson (1980) showed that the methylation of arsenic was similar in germfree and conventional mice with normal intestinal microflora, indicating that methylation of arsenic by intestinal microorganisms contributes little to the overall methylation *in vivo*.

Major qualitative and quantitative interspecies differences in arsenic methylation are apparent in laboratory animals when they are compared on the basis of metabolites excreted in urine (e.g. see Tables 19 and 20). For example, methylated metabolites are virtually undetectable in the urine of marmoset monkeys administered either arsenate or arsenite (Vahter et al., 1982; Vahter & Marafante, 1985) and chimpanzees administered arsenate (Vahter et al., 1995b). Studies using liver cytosol from marmoset and tamarin monkeys (Zakharyan et al., 1996) and guinea-pigs (Healy et al., 1997) also indicate that these species are deficient in methyltransferase activity compared to species such as the rabbit.

It is not known with certainty if enzymatic methylation of arsenic is saturable under *in vivo* exposure conditions in laboratory animals. Vahter (1981) reported a significant dose-dependent decrease in the urinary excretion of DMA in mice administered inorganic arsenic as either arsenate or arsenite (see Tables 19 and 20). These findings are consistent with either saturation or inhibition of methylation. No similar clear-cut trend was seen in the study by Hughes (1994), in which a lower dose was used.

In vitro studies have demonstrated that arsenite can inhibit the formation of DMA from MMA. Styblo et al. (1996), using a rat liver

Table 19. Urinary excretion of As metabolites after a single dose of pentavalent inorganic As

Species	Route	Dose (mg/kg)	Time (h)	% dose in urine	Mean (± SD or SE) % dose excreted in urine as metabolite				Reference
					As(V)	As(III)	MMA	DMA	
Mice	s.c.	0.4	0–48	~96	40.9 ± 3.6 (IAs)[a]		0.4 ± 0.1	44.5 ± 2.0	Vahter (1981)
	oral	0.04	0–48	~94	16.6 ± 0.8 (IAs)		0.8 ± 0.1	76.6 ± 4.9	
		0.4	0–48	~93	20.8 ± 2.3 (IAs)		0.9 ± 0.2	71.1 ± 0.9	
		2.0	0–48	~92	37.9 ± 4.4 (IAs)		1.7 ± 0.5	52.4 ± 5.9	
		4.0	0–48	~84	39.5 ± 2.3 (IAs)		1.3 ± 0.2	43.7 ± 2.7	
Mice[b]	oral	0.00012	0–48	~65	5.2 ± 2.4	0.6 ± 0.4	0.12 ± 0.01	59.1 ± 6.2	Hughes et al.
		0.0012	0–48	~68	3.2 ± 0.2	0.7 ± 0.3	0.22 ± 0.13	64.2 ± 9.9	(1994)
		0.012	0–48	~72	14.6 ± 6.6	0.7 ± 0.4	0.35 ± 0.09	56.4 ± 11.0	
		0.12	0–48	~70	6.0 ± 1.7	1.2 ± 0.2	0.65 ± 0.18	63.1 ± 3.2	
		1.2	0–48	~68	10.2 ± 1.4	6.1 ± 1.7	1.01 ± 0.04	51.4 ± 2.4	
Mice	oral	5.0	0–48	48.5	16.7 (IAs)		1.8	30	Odanaka et al.
	i.v.	1.0	0–48	86.9	47.4 (IAs)		2.1	37.4	(1980)

Table 19 (contd.)

Species	Route	Dose (mg/kg)	Time (h)	% dose in urine	Mean (± SD or SE) % dose excreted in urine as metabolite				Reference
					As(V)	As(III)	MMA	DMA	
Rat	oral	5.0	0–48	17.2	14.1 (IAs)		0.9	2.2	Odanaka et al. (1980)
	i.v.	1.0	0–48	51.0	47.6 (IAs)		0.7	2.7	
Hamster	oral	5.0	0–48	43.8	17.7 (IAs)		4.6	21.5	Odanaka et al. (1980)
	i.v.	1.0	0–48	83.9	42.4 (IAs)		1.8	39.7	
Rabbit	i.v.	0.04	0–72	65.5 ± 3.8	31.5 ± 7.1 (IAs)		–	34.0 ± 3.3	Vahter & Marafante (1983)
Marmoset	i.v.	0.4	0–72	39.3 ± 3.8	~20	~20	–	< 0.1	Vahter & Marafante (1985)

[a] IAs is inorganic As, figures are mean ± SE
[b] Figures are mean ± SD

Table 20. Urinary excretion of As metabolites after a single dose of trivalent inorganic As

Species	Route	Dose (mg/kg)	Time (h)	% dose in urine	Mean (± SE) % dose excreted in urine as metabolite			Reference
					Inorganic As	MMA	DMA	
Mice	s.c.	0.4	0–48	~75	11.9 ± 0.8	0.9 ± 0.2	62.0 ± 3.4	Vahter (1981)
	oral	0.04	0–48	~88	7.9 ± 1.2	1.0 ± 0.1	79.4 ± 0.5	
	oral	0.4	0–48	~91	7.8 ± 1.1	0.7 ± 0.1	82.7 ± 2.7	
	oral	2.0	0–48	~86	37.9 ± 1.1	1.9 ± 0.1	68.8 ± 3.0	
	oral	4.0	0–48	~75	39.5 ± 0.8	1.3 ± 0.1	55.9 ± 2.3	
Rat	oral	0.4	0–48	~6	2.3 ± 0.3	0.2 ± 0.1	3.7 ± 0.3	Vahter (1981)
Rat	i.p.	0.05	0–48	~5.5	~1.6	~0.1	~4.0	Marafante et al. (1982)
Hamster	oral	4.5	0–120	48.5	23.3	2.5	22.1	Yamauchi & Yamamura (1985)
Rabbit	i.v.	0.04	0–72	52.8 ± 4.8	8.1 ± 1.3	----	43.9 ± 4.4	Vahter & Marafante (1983)
Rabbit	i.v.	0.4	0–72	88.5 ± 2.2	17.0 ± 1.4	5.9 ± 0.2	65.5 ± 3.8	Vahter & Marafante (1987)
Marmoset	i.p	0.4	0–96	29.8	~29.8	ND	ND	Vahter et al. (1982)

ND = not detected

cytosol system, found that as the initial concentration of arsenite was increased from 0.1 to 50 µmol/litre, the amount of DMA produced decreased and there was an increased time lag before DMA was detected. Production of MMA from arsenite increased in proportion to the amount of arsenite in the assay system.

On the basis of case reports in the medical literature, it has been theorized that prolonged exposure to arsenic can result in the development of tolerance. This hypothesized tolerance could in theory be a result of increased excretion due to enhanced methylation, or an increase in some other excretory mechanism. Healy et al. (1998) investigated the possibility that arsenite methyltransferase activity is inducible by exposure to arsenic itself. When male $B6C3F_1$ mice received 25 or 2500 µg As/litre arsenate in their drinking-water for 32 or 91 days, there was no increase in arsenite methyltransferase activity in liver, testes, kidney or lung. This is consistent with the finding of Hughes & Thompson (1996) that subchronic exposure of mice to 25 or 2500 µg As/litre arsenate in their drinking-water for 28 days resulted in no increased urinary excretion of methylated metabolites.

Although studies in mice exposed to arsenate do not provide evidence for induction of arsenite methyltransferases, studies in the older literature (Bencko & Symon, 1969; Bencko et al., 1973) of mice exposed to arsenite suggest that there is enhanced tissue clearance upon continuous exposure. Interestingly, enhanced efflux of arsenite has been demonstrated to be a mechanism of resistance to arsenic toxicity in Chinese hamster V79 cells (Wang et al., 1996b). Albores et al. (1992) have reported that the metal-binding protein metallothionein is inducible *in vivo* in rats injected with arsenite, but not with arsenate. Kreppel et al. (1990) have also reported that arsenite is a much more effective inducer of metallothionein in mice *in vivo* than *in vitro*. Healy et al. (1998) have suggested that this may be a factor in older reports of enhanced arsenic clearance in mice dosed with arsenite. However, it should be noted that arsenite does not bind metallothionein (Albores et al., 1992).

The question of whether alterations in nutritional status can influence arsenic methylation has also been investigated in animal models. Vahter & Marafante (1987) examined the effect of low dietary intake of methionine, choline or protein on excretion of

methylated metabolites in rabbits given a single intravenous dose of 0.4 mg As/kg as arsenite. Total arsenic excretion in urine was significantly decreased compared to controls in all diet groups. DMA excretion (expressed as percentage of the dose) was also significantly decreased relative to controls (65.5 ± 3.1) by diets low in choline (43.9 ± 1.6), methionine (39.3 ± 1.7) and protein (51.9 ± 4.3).

6.1.3.2 Human studies

Controlled ingestion studies indicate that both arsenate and arsenite are extensively methylated in humans, as is also observed in laboratory animals, with DMA being the principle methylated metabolite excreted in human urine (Table 15). A noteworthy difference between humans and laboratory animals is that MMA is excreted in the urine of humans to a greater extent (see Tables 18, 19 and 20). The biological basis for this difference is unknown, but it is consistent with the large interspecies differences observed in arsenic methylation among experimental animals. It is also noteworthy that, on the basis of data summarized from a number of studies of different human populations by Hopenhayn-Rich et al. (1993), the proportion of MMA excreted in human urine is highly variable.

In some studies, ratios of arsenic metabolites in urine (e.g. DMA/inorganic arsenic, MMA/inorganic arsenic or DMA/ MMA have been used to draw conclusions regarding saturation or inhibition of methylation. Such conclusions should be evaluated with caution because of the inherent numerical and statistical properties of ratio data. Two specific problems are that (1) small changes in a metabolite present in small amounts can result in large changes in the ratio, which can exaggerate or distort the magnitude of observed differences and (2) metabolites present at levels near the detection limit may be associated with a higher degree of measurement error, which could also distort the magnitude of differences when used to calculate ratio data. Application of statistical analysis to metabolite ratio data is also complex because of the degree of correlation in metabolite data, particularly when expressed as a percentage of total metabolites excreted. All of these factors require that conclusions based on ratio data be evaluated critically and independently.

Humans acutely intoxicated by high doses of inorganic arsenic show a marked delay in the urinary excretion of DMA (Mahieu et al., 1981; Foa et al., 1984). However, in the case of exposure to arsenic via drinking-water, even at very high arsenic concentrations, the methylation of arsenic seems to be relatively unaffected by the dose. In a case study by Kosnett & Becker (1988), after subacute exposure to drinking-water containing arsenic at a concentration of 25 000 µg/litre, a 36-year-old man yielded a urinary arsenic collection containing about 6000 µg/24 h, 26% as inorganic arsenic and 74% as methylated metabolites. Results from *in vitro* studies using human hepatocytes suggested that the delay in urinary excretion of DMA might occur because the high tissue concentration of arsenite inhibits or saturates the methyltransferase catalysing the second methylation step (Styblo et al., 1999).

The proportion of methylated metabolites in urine can vary considerably. For example, in the literature review performed by Hopenhayn-Rich et al. (1993), the average proportions of MMA and DMA in urine of occupationally and environmentally exposed population groups (range of average total urinary arsenic from 10.2 to 245 µg/litre) ranged from 9 to 20% and 61 to 70%, respectively. Data on the variation in human populations have been comprehensively reviewed (NRC, 1999).

Studies focused on populations highly exposed to arsenic in drinking-water also indicate that methylation patterns are not highly correlated with exposure level, but that there is a high level of inter-individual variability (Warner et al., 1994; Hopenhayn-Rich et al., 1996a). In another study (Hopenhayn-Rich et al., 1996b), methylation patterns in a population of northern Chilean subjects (n = 73) were compared (each subject served as their own control) before and after changing from drinking-water containing higher (600 µg/litre) to lower (45 µg/litre) levels of arsenic. There was a small but significant decrease in urinary inorganic arsenic (from 17.8% to 14.1%). The authors note that there was large inter-individual variation in methylation profiles and that factors such as smoking, gender, age, years of residence and ethnicity accounted for only ~20% of the variation observed. They further speculate that much of the observed inter-individual variation 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 concentration in the drinking-water of this population was ~200 µg/litre. These women excreted mainly inorganic arsenic (median 25%, range 6.5–42%) and DMA (median 74%, range 54–93%) in their urine and very little MMA (median 2.1%, range of 0.6–8.3%). The authors suggest that this finding indicates the existence of genetic polymorphism in the control of arsenic methyltransferases. They also suggest that the higher urinary DMA excretion in women in the village with the highest arsenic in drinking-water (~200 µg/litre) compared to that of women in the villages with lower arsenic in drinking-water (2.5B31 µg/litre) indicates induction of DMA excretion. It is worthy of note that differences in the activities of other methyltransferases have been explained by the existence of genetic polymorphisms (Weinshilboum, 1992).

In further studies of that Andean Argentinian population, Concha et al. (1998a) reported striking differences in urinary excretion patterns of arsenic metabolites in children compared to adult women. In one village with a predominantly indigenous Indian population consuming drinking-water high in arsenic (~200 µg/litre), 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); this difference was observed even though the median concentrations of arsenic metabolites in urine (sum of inorganic arsenic plus both methylated metabolites) did not differ greatly for the children and the women (323 µg/litre vs. 303 µg/litre). A low median percentage of MMA excreted in urine was also observed both in the women (2.1%) and in the 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., 1998b). It should be noted that in the very 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 studies arsenic exposure was relatively low, as indicated by total concentration of arsenic metabolites excreted in urine (i.e. < 20 µg/litre).

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 relatively more DMA was excreted by women than men. In this connection it is also of interest to note that Concha et al. (1998b) reported significant increases in the percentage of DMA excreted in urine in Argentinian women during pregnancy which is one possible reason for gender differences reported in some studies.

Inorganic arsenic metabolism is known to be affected by liver disease in humans. Buchet et al. (1984) compared the urinary excretion of inorganic arsenic and its methylated metabolites in normal human subjects and patients with various forms of liver disease after intravenous injection of 7.14 µg As/kg as sodium arsenite. Liver disease had no effect on the total amount of arsenic excreted within 24 h, 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 patients compared to controls (6.1 ± 0.7 vs. 12.8 ± 0.7) and the percentage of DMA was increased (40.7 ± 1.9 vs. 24.3 ± 1.6). Geubel et al. (1988) reported similar findings in subjects with cirrhotic liver disease. They further noted that in patients with other non-hepatic disease, the arsenic methylation was unaffected.

6.1.4 Elimination and excretion

6.1.4.1 Animal studies

Urine is the primary route of elimination for both pentavalent and trivalent inorganic arsenicals in most common laboratory animals (Table 14). With the exception of the rat, which exhibits slower overall elimination of arsenic, 50% or more of a single oral dose of arsenic is usually eliminated in urine within 48 h. Urine is also the primary route of elimination in species such as the marmoset which do not methylate arsenic. Vahter et al. (1982) reported that when arsenite was administered intraperitoneally to marmosets at a dose of 0.4 mg As/kg, 29.8% of the dose was eliminated in urine

over 4 days, compared to only 4.1% in the faeces. Similarly, when administered an intravenous dose of 0.4 mg As/kg arsenate, marmosets excreted 39.3% of the dose in the urine and only 2.1% in the faeces over 72 h (Vahter & Marafante, 1985).

Comparison of urinary and faecal elimination in mice that have been given the same dose of arsenic by oral and parenteral routes (e.g. Vahter & Norin, 1980) reveals that only ~4–8% of the dose is eliminated in faeces irrespective of route of administration. This suggests that, for both arsenate and arsenite, biliary elimination in mice is quite low (< 3% over 48 h – see Table 13) and that most arsenic appearing in the faeces after oral dosing was unabsorbed from the gastrointestinal tract.

Urinary elimination of arsenate in laboratory animals – at least for mice – does not appear to be capacity-limited or dose-dependent. Hughes et al. (1994) reported that 66–79% of a single oral dose of sodium arsenate was eliminated in the urine in 48 h over a 10 000-fold dose range. Vahter & Norin (1980) reported a significant decrease in both urinary and total excretion of arsenic in mice when administered as arsenite, which is apparently a function of greater arsenite binding in tissues with increasing dose.

6.1.4.2 Human studies

Inorganic arsenic is eliminated primarily via the kidney in humans as well as laboratory animals. Studies in adult human males voluntarily ingesting a known amount of either trivalent or pentavalent arsenic indicate that 45–75% of the dose is excreted in the urine within a few days to a week (Table 13). Relatively few studies in volunteers have included measurement of arsenic in both faeces and urine. However, Pomroy et al. (1980) reported that 6.1% ± 2.8% of a single oral dose of arsenic acid (As(V)) was excreted in the faeces over a period of 7 days, compared to 62.3% ± 4.0% of the dose excreted in urine. It should be noted that Pomroy et al. used radiolabelled arsenate, which enabled distinction between ingested arsenic acid and dietary arsenic. No quantitative data was available that directly addressed the issue of biliary excretion of trivalent or pentavalent arsenic in humans.

Arsenic is excreted by routes other than just urine and faeces, but in general these routes of excretion are quantitatively minor. Studies reported in the previous IPCS arsenic document (IPCS, 1981, section 6.1.3) indicate that arsenic is excreted in sweat to some degree. Owing to its ability to accumulate in keratin-containing tissues, skin, hair and nails could also be considered potential excretory routes for arsenic, although they would in general be quantitatively minor.

Both earlier (IPCS, 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., 1998b). For example, in the Bombay area (India) Dang et al. (1983) reported arsenic levels ranging from 0.2 to 1.1 ng/g in breast milk of nursing mothers 1–3 months postpartum. Concha et al. (1998b) found that the average concentration of arsenic in breast milk of was quite low (3.1 µg/litre) even when urinary arsenic excretion was high (230–300 µg/litre) from 3 weeks to 5 months postpartum in a study of Andean women in Argentina consuming drinking-water high in arsenic (~200 µg/litre). Significantly, low-arsenic excretion in breast milk of nursing mothers led to a decrease in urinary arsenic concentration of their infants during the nursing period.

6.1.5 Retention and turnover

6.1.5.1 Animal studies

Lindgren et al. (1982) compared the whole-body retention of arsenate and arsenite administered intravenously as the sodium salts to male C57BL mice at a dose of 0.4 mg As/kg. Retention was higher in arsenite-treated mice than in arsenate-treated mice at all times measured, i.e. 44.4% vs. 20.4% at 6 h after dosing, 14% vs. 3.3% at 24 h and 5.6% vs. 1.7% at 72 h after dosing. Vahter & Norin (1980) earlier reported that, in male CBA mice dosed orally with 0.4 mg As/kg arsenate or arsenite, whole-body retention was similar over the 35-day time course of the experiment. In contrast, and similar to what was observed with intravenously dosed mice in the study by Lindgren et al. (1982), whole-body retention was clearly consistently higher in arsenite-dosed mice than in arsenate-dosed mice when dosed orally with 4 mg As/kg: 35 days after

administration the high/low dose retention ratios were 11 for arsenite-dosed and 6 for arsenate-dosed mice.

6.1.5.2 Human studies

Pomroy et al. (1980) studied the whole-body retention of ^{74}As (6.4 µCi, 0.06 ng As) administered once orally as arsenic acid (As(V)) in healthy male volunteers (age 28–60 years) using whole-body counting for periods of < 103 days. Although the averaged whole-body clearance data for the six subjects in the study were best described by a triexponential model, it should be noted that the inter-individual 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 was located for trivalent inorganic arsenic.

6.1.6 Reaction with body components

Numerous mechanistic studies have documented basic differences in the interaction of pentavalent and trivalent inorganic arsenic with body components, and this is an important determinant in observed differences in tissue distribution. Pentavalent inorganic arsenic can act as a phosphate analogue. At the molecular level this means that arsenate can compete with phosphate for active transport processes. This is why the addition of phosphate can decrease intestinal uptake (Gonzalez et al., 1995) and renal tubular reabsorption of arsenate (Ginsburg & Lotspeich, 1963). Arsenate can also substitute for phosphate in the hydroxyapatite crystal of bone, which 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 inhibit glycolysis by competing with phosphate to form the dysfunctional compound 1-arseno-3-phosphoglycerate, rather than 1:3-diphosphoglycerate (Mayes, 1983).

Arsenite reacts readily with vicinal sulfhydryl groups of a variety of essential enzymes and proteins. It is the affinity of arsenite for sulfhydryl groups that accounts for its accumulation in keratin-

rich tissues such skin, hair and nails. Arsenite also interacts with the ubiquitous sulfhydryl-containing cellular tripeptide GSH at many different levels in the methylation process. These include, but may not be limited to, reduction of arsenic from pentavalency to trivalency following the addition of a methyl group, and formation of complexes with trivalent arsenicals which may be substrates for methylation (Styblo et al., 1996). See section 7.1.10.1 for further discussion.

6.2 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, organoarsenicals are less extensively metabolized than inorganic arsenic and more rapidly eliminated in both laboratory animals and humans.

6.2.1 Absorption

6.2.1.1 Respiratory deposition and absorption

No quantitative data concerning the respiratory deposition and absorption of organoarsenicals are available for humans or laboratory animals. However, increased urinary excretion of arsenic during the work week with a return to baseline levels on weekends in workers spraying the herbicide monosodium methanearsonate indicates that respiratory absorption of organoarsenicals can occur under occupational exposure conditions (Abdelghani et al., 1986).

6.2.1.2 Gastrointestinal absorption

a) Animal studies

Methylated arsenicals are absorbed from the gastrointestinal tract after oral administration to experimental animals. In male Syrian golden hamsters administered a single oral dose of 50 mg/kg MMA, 36.6 and 60.9% of the dose was eliminated in urine and faeces, respectively, within 5 days. When the same dose was administered by intraperitoneal injection, much more was eliminated in urine (82.6%) and much less in faeces (1%) during the same time

period (Yamauchi et al., 1988). The authors noted that this indicated that a relatively large fraction of the administered oral dose was unabsorbed from the gastrointestinal tract compared to their previous studies with DMA (Yamauchi & Yamamura, 1984a) and arsenobetaine (Yamauchi et al., 1986a).

Yamauchi & Yamamura (1984a) reported that 48.9% of a single oral dose of 40 mg/kg DMA was eliminated in the urine of hamsters within 5 days (~36% in faeces). Similarly, Marafante et al. (1987) reported that 56.3% of a single oral dose of 40 mg As/kg DMA was eliminated in urine of male Syrian golden hamsters within 48 h (41.2% in faeces). Gastrointestinal absorption of DMA may be more extensive in mice. In this same study 67.6% and 29.2% of the dose was eliminated in the urine and faeces, respectively, of male ICR mice administered the same oral dose of DMA.

For the trimethylated organoarsenicals – TMA and TMAO – absorption from the gastrointestinal tract of male Syrian golden hamsters is extensive (Yamauchi et al., 1989b; 1990). Yamauchi et al. (1990) reported that 76.9 ± 2.4% of a single oral dose of 10 mg As/kg TMA was eliminated in urine within 48 h but only 0.11 ± 0.03% in faeces. Similarly, 88.2 ± 9.57% of a single oral dose of 10 mg As/kg TMAO was eliminated in urine within 48 h but only 0.55 ± 0.44% in faeces.

Arsenobetaine, sometimes referred to as “fish arsenic” because it is the predominant organoarsenical present in a number of species of fishes and crustacea, undergoes rapid and almost complete absorption from the gastrointestinal tract of laboratory animals. Vahter et al. (1983) reported in that male NMRI mice given an oral dose of ^{73}As-arsenobetaine (4 mg As/kg), 73% and 95% of the dose was recovered in the urine after 24 and 72 h respectively. Similarly, Yamauchi et al. (1986a) found that male Syrian golden hamsters dosed orally with 36 mg/kg arsenobetaine excreted 70% of the dose in urine within 12 h and 90% within 5 days. Arsenocholine, also found in seafood, is extensively absorbed from the gastrointestinal tract of mice and rats, with ~70% of the administered oral dose (4 mg As/kg) excreted in the urine within 72 h (Marafante et al., 1984).

b) Human studies

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

Studies have been conducted on the metabolism of organoarsenicals ingested in seafood. In one study in which an adult male Japanese volunteer consumed ~10 µg As/kg trimethyl arsenic in prawns (98.8% trimethylarsenic by analysis, presumably in the form of arsenobetaine), ~90% of the ingested arsenic was excreted in urine within 72 h (Yamauchi & Yamamura, 1984b). In another study conducted in human volunteers consuming flounder, in which the predominant form of arsenic is arsenobetaine, an average of 60% or more of the dose was eliminated in urine within 2 days (Freeman et al., 1979). This suggests that arsenobetaine is readily and rapidly absorbed from the gastrointestinal tract.

6.2.1.3 Dermal absorption

No data concerning the dermal absorption of organoarsenicals in humans were located, but both *in vivo* and *in vitro* dermal absorption data have been reported for arsenical herbicides in laboratory animals. Rahman & Hughes (1994), using clipped dorsal skin of $B6C3F_1$ mice, found that a constant fraction of the dose (~ 12.4%) in water vehicle was absorbed during a 24-h period over the entire applied dose range (10–500 µg) for both the monosodium and disodium salts of monomethylarsonate, and that this was 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-h period. However, vehicle volume exerted a significant effect on absorption, which ranged from ~7–40% and decreased with increasing volume of water. In both these studies percutaneous absorption of the arsenical herbicides from soil was very low (< 1%).

Shah et al. (1987) studied the *in vivo* percutaneous absorption of MMA (monosodium salt) and DMA (disodium salt) in young (33-day-old) and adult (82-day-old) Fischer 344 rats. Three levels of

each compound (MMA [monosodium salt]: 16.4, 98.6 and 496 µg/cm^2; DMA [disodium salt]: 16.4, 98.6 and 496 µg/cm^2) were applied in aqueous vehicle, and absorption over 72 h was determined. Although both compounds exhibited similar absorption values within either young or adult animals over the dose range studied, the young animals absorbed significantly less. The total percutaneous absorption (mean of all doses for both compounds) was 15.1 and 3.01% of the recovered dose in old and young rats, respectively.

6.2.1.4 Placental transfer

No human or animal data directly assessing the ability of organoarsenicals to cross the placenta have been located that have appeared since publication of the last arsenic environmental health criteria document (IPCS, 1981). Older studies have demonstrated that dimethylarsenic acid is capable of crossing the placenta of rats (Stevens et al., 1977). Studies in laying hens also indicate that the organoarsenical feed additive Roxarsone (3-nitro-4-hydroxyphenyl-arsonic acid) accumulates in significantly in eggs as the level in the diet is increased (Chiou et al., 1997b).

6.2.2 Distribution

6.2.2.1 Fate of organic arsenic in blood

a) Animal studies

Yamauchi et al. (1988) reported the time-course distribution of MMA and DMA in whole blood and plasma after a single oral dose of 50 mg MMA/kg body weight in hamsters. MMA concentration in blood peaked at 6 h after dosing, and thereafter declined to control values at 120 h. Distribution of MMA was similar between plasma and erythrocytes through 12 h, but then more tended to be associated with blood cells. DMA levels in plasma peaked at 12 h, but there was no significant change in inorganic or trimethylated arsenic in blood of control compared to dosed hamsters.

Yamauchi & Yamamura (1984b) also studied the time-course distribution in the whole blood of DMA and its metabolites after a single oral dose of 50 mg DMA/kg (mean arsenic dose 1440 µg) in

hamsters. Total arsenic in blood peaked at 6 h and consisted of 61% DMA, 26.2% TMAO, 11.8% inorganic arsenic and 1.07% MMA. DMA levels had returned to control values by 24–72 h after dosing. Vahter et al. (1984) reported the distribution of total arsenic between plasma and erythrocytes of mice at 0.5 and 6 h after intravenous injection of 0.4 mg As/kg ^{74}As-DMA. The plasma : erythrocytes ratio of arsenic at was 2.2 at 0.5 h and 1.4 at 6 h, and levels had declined 76-fold in plasma and 50-fold in erythrocytes 6 h after administration.

The trimethyl arsenic compounds, TMA and TMAO, are even more rapidly cleared from the blood of hamsters than are MMA and DMA. Yamauchi et al. (1990) reported that the half-life of TMA in blood was 3.3 h in hamsters administered a single oral dose of 10 mg As/kg. In hamsters administered a single oral dose of 10 mg As/kg TMAO, arsenic levels in whole blood and plasma peaked within 1 h and thereafter declined very rapidly (Yamauchi et al., 1990). In both studies, only trimethylated arsenic levels detected in blood were related to exposure since levels of inorganic arsenic did not differ between exposed and control animals and other methylated arsenicals were not detected (Yamauchi et al., 1989b, 1990).

b) Human studies

Studies concerning the fate of organoarsenicals in human blood are almost totally lacking. After ingestion of 10 µg/kg of trimethylarsenic (98.8% by analysis, presumably arsenobetaine) in prawns, trimethylarsenic levels were approximate 2.5-fold higher in plasma than in erythrocytes at 2 h after ingestion in the single subject studied. Levels declined thereafter and were at background by 24 h (Yamauchi & Yamamura, 1984b).

6.2.2.2 Tissue distribution

a) Animal studies

Yamauchi et al. (1988) reported data on the time-course tissue distribution of hamsters given a single oral dose of 50 mg/kg MMA. Peak MMA concentrations were achieved within 6–12 h after dosing and were highest in the kidney, followed by spleen, lung, skin, liver, muscle and brain. MMA itself accumulated in the kidney and

declined very slowly. DMA was also detected in several tissues, with highest levels achieved in lung, followed by kidney and liver. Trimethylated arsenic was not detected in any tissues.

Long-term pharmacokinetic studies are generally lacking for organoarsenicals, but Jaghabir et al. (1994) have performed such a study in New Zealand white rabbits administered multiple oral doses of MMA as the monosodium salt (MSMA). The limitation of this study is that only total arsenic was measured. Rabbits were given an oral dose of 5 mg MSMA/kg 4 days a week for 4 weeks with serial sacrifices at 2 weeks and 4 weeks after the start of exposure and then 1 week and 2 weeks after exposure ended. Significant accumulation of arsenic was observed in muscle and fur after 4 weeks of exposure with significant clearance of arsenic from muscle 1 week after exposure ended, but no significant clearance from fur after 2 weeks of no exposure. Levels of arsenic in kidney were significantly higher than liver at both 1 and 2 weeks after the end of exposure, but did not differ greatly during exposure.

Yamauchi & Yamamura (1984a) studied the tissue distribution of DMA and metabolites in hamsters administered a single oral dose of 50 mg/kg DMA. DMA levels were elevated in all tissues examined, including the brain, indicating that DMA passes the blood–brain barrier, though not to a large degree. DMA concentrations peaked at 6 h in all tissues examined except hair, with levels highest in lung, followed by kidney, spleen, liver, skin, muscle and brain. It is notable that the peak DMA concentration in lung was over 4-fold higher than in the next highest organ. DMA concentrations had declined to control levels by 120 h after dosing. TMA concentrations peaked in most tissues at 6 h after DMA dosing; the highest concentration was achieved in lung, which had a 5-fold higher level than the next highest tissue, which was kidney. Interestingly, MMA levels were also elevated in some tissues of DMA-dosed hamsters compared to controls.

The tissue distribution of DMA has also been studied in mice. Vahter et al. (1984) reported that after intravenous administration of ^{74}As-DMA (0.4 mg As/kg) to male NMRI mice, the highest levels of ^{74}As-derived radioactivity were present in kidney at all time points (5–60 min after injection). Tissues with the longest retention of ^{74}As were the lungs, intestinal walls, thyroid and lens. Some of the

^{74}As-DMA present in liver and kidney was in the form of complexes, whereas this was not the case in lung or plasma. The authors reported that there was no evidence of *in vivo* demethylation of DMA. Examination of the subcellular distribution of ^{74}As-DMA-derived radioactivity indicated that it was predominantly (70%–95%) localized in the cytosol.

TMA undergoes more rapid absorption and tissue distribution than does either MMA or DMA in hamsters. Yamauchi et al. (1990) found that tissue levels of TMA peaked 1 h after male Syrian golden hamsters were given a single oral dose of 10 mg As/kg TMA and had returned to control levels by 24 h after dosing. Concentrations were highest in lung, followed by liver, kidney, spleen and brain. Levels of DMA and inorganic arsenic detected in tissues of dosed animals were similar to unexposed controls. Yamauchi et al. (1989b) also reported that clearance of TMAO from both liver and blood was even more rapid than clearance of TMA when a comparable oral dose was given to hamsters.

Vahter et al. (1983) examined ^{73}As-arsenic tissue distribution in mice and rabbits after intravenous administration of 4 mg As/kg arsenobetaine. Distribution to and clearance from all tissues was rapid, and somewhat faster in mice than in rabbits. Somewhat longer retention in rabbits was attributable to accumulation in muscle, which makes up a larger proportion of their total body mass. Highest tissue concentrations were attained in kidney, liver and pancreas, respectively, in both species; concentrations in testes and epididymis also remained highest at 72 h in both species. In hamsters administered a single oral dose of 36 mg/kg arsenobetaine, tissue concentrations peaked at 1–6 h after administration and declined rapidly thereafter. Highest concentrations were detected in the liver, kidney, lung, spleen, muscle, skin and brain (Yamauchi et al., 1986a).

b) Human studies

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.

6.2.3 Metabolic transformation

6.2.3.1 Animal studies

Studies by Yamauchi et al. (1988) demonstrate that MMA undergoes *in vivo* methylation to dimethylated and trimethylated products, but that methylation is not extensive. After a single oral dose of 5, 50 or 250 mg/kg MMA, hamsters excreted respectively 8.4, 1.4 and 0.4% of the dose as DMA and respectively 1.9, trace, and < 0.1% of the dose as TMA in urine. Most of the absorbed MMA was excreted unchanged in urine and this did not differ significantly with dose. There was no evidence that MMA was demethylated in these studies. Similar findings were reported by Hughes & Kenyon (1998) for female $B6C3F_1$ mice administered MMA intravenously. After a single intravenous injection of 0.6 or 60 mg As/kg MMA, respectively 72.5 ± 4.2 and 77.7 ± 14.1% of the dose was excreted as MMA and respectively 8.1 ± 1.5 and 2.2 ± 0.7% was excreted as DMA in urine within 24 h. The decrease in DMA excretion with increasing dose that was observed in both hamsters and mice after MMA administration could be due to either dose-dependent saturation or inhibition of MMA methylation (Hughes & Kenyon, 1998).

DMA is methylated to trimethylarsenic compounds to a limited extent in mice, rats and hamsters (Yamauchi & Yamamura, 1984a; Marafante et al., 1987;Yoshida et al., 1997, 1998). Marafante et al. (1987) reported that in mice and hamsters 3.5 ± 0.4 and 6.4 ± 0.5% respectively of a single oral dose of 40 mg As/kg DMA was eliminated in urine as TMAO within 48 h, TMAO was not detected in the faeces of either species in this study. An unidentified DMA complex was also excreted in both urine (7–11% of the dose) and faeces (4–5% of the dose) in mice and hamsters in this study, with the remainder of the dose excreted as unmetabolized DMA. Hughes & Kenyon (1998) also reported an unidentified and readily oxidizable metabolite in urine of mice administered DMA intravenously. Marafante et al. (1987) speculated that this metabolite might be some type of thiol complex.

Since methylation serves to expedite the excretion of inorganic arsenic, which is more toxic than organoarsenicals, issues such as whether demethylation occurs and if methylation is saturable, inducible, or inhibitable under expected environmental exposure conditions are critical. The fact that radiolabelled inorganic arsenic is not detected in the urine of mice, rats, hamsters and humans after administration of ^{74}As-DMA indicates that demethylation is insignificant in these species (Vahter et al., 1984; Marafante et al., 1987). However, Yoshida et al. (1997) recently compared the time-course of urinary excretion of DMA and its metabolites after a single oral or intraperitoneal injection of 50 mg/kg DMA to rats. They reported that more arsenite was excreted in urine of rats administered DMA orally than by intraperitoneal injection. The authors interpreted their data as being indicative of *in vivo* demethylation, most likely by intestinal microorganisms. It is worthy of note however, that Hall et al. (1997) found no evidence of demethylation in studies using the caecal microbiota from mice in an *in vitro* anaerobic culture system. Subsequent studies by Yoshida et al. (1998) showed that essentially no inorganic arsenic was excreted in urine of rats exposed to DMA in drinking-water at 100 mg/litre for 7 months.

On the basis of limited studies in hamsters, it appears that neither TMA or TMAO is further methylated or demethylated, but they do undergo *in vivo* redox reactions. Yamauchi et al. (1990) found that ~80% of a 10 mg As/kg oral dose of trimethylarsine (TMA) was oxidized to TMAO and excreted in urine within 120 h of administration. Similarly, when TMAO was administered orally to hamsters at a dose of 10 mg As/kg, only TMAO and no arsenobetaine was eliminated in urine. Interestingly a fraction of the dose (unquantified) was reduced to TMA and excreted in expired air when hamsters were given a single oral or intraperitoneal dose of 50 mg As/kg TMAO (Yamauchi et al., 1989b).

Studies in mice, rats, rabbits and hamsters administered arsenobetaine intravenously or orally indicate that it is not biotransformed or demethylated (Vahter et al., 1983; Yamauchi et al., 1986a). Arsenocholine is also not demethylated, but is metabolized extensively to arsenobetaine. Specifically, Marafante et al. (1984) reported that in mice, rabbits and rats administered 4 mg As/kg arsenocholine intravenously, approximately 40, 50 and 60% of

the dose, respectively, was eliminated in urine as arsenobetaine within 48 h. No major difference in urinary excretion or arsenobetaine was noted after oral administration of arsenocholine to rats or mice.

6.2.3.2 Human studies

On the basis of limited data from controlled ingestion studies, it appears that MMA and DMA are metabolized to a similar extent in laboratory animals and humans (see section 6.2.3.1 and Table 15). Buchet et al. (1981a) reported that after a single oral dose of MMA (500 µg As), 87.4% of the total metabolites excreted in urine in 4 days were in the form of MMA and 12.6% were in the form of DMA. In this same study, it was reported that all of the ingested DMA (500 µg 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 2 days. Metabolic studies in which humans specifically consumed TMA or TMAO alone rather than in seafood were not found.

In common with laboratory animals, humans appear to eliminate arsenobetaine ingested in seafood unchanged in their urine, indicating that arsenobetaine is not metabolized (Tam et al., 1982).

6.2.4 Elimination and excretion

6.2.4.1 Animal studies

Total (urine + faecal) elimination of organoarsenicals is quite rapid in laboratory rodents, with 80% or more of the dose eliminated within 48 h of a single oral or parenteral dose (Table 21). Absorbed MMA and DMA are predominantly eliminated in urine (Table 21). Limited data from studies where multiple dose levels were used (Yamauchi et al., 1988; Hughes & Kenyon, 1998) suggest that urinary elimination is also dose-independent, i.e. the percentage of the dose eliminated in urine does not change with increasing or decreasing dose level.

No studies were identified which directly addressed the issue of biliary elimination of any organoarsenicals. However, given the

Table 21. Cumulative elimination (% of dose) of organoarsenicals in urine and faeces of laboratory animals after oral and parenteral administration

Arsenical	Species	Route	Dose (mg/kg)	Time (h)	Urine	Faeces	Total	Reference
MMA	hamster	oral	5	0–24	38.8	51.6	90.4	Yamauchi et al. (1988)
		oral	50	0–24	28.3	56.0	84.3	
		oral	250	0–24	34.2	46.0	80.2	
MMA	hamster	i.p	50	0–120	82.6	1.0	83.6	Yamauchi et al. (1988)
		oral	50	0–120	36.6	60.9	97.5	
MMA	mouse	i.v	0.6 (As)	0–24	80.6 ± 2.7	3.9 ± 1.4	84.5	Hughes & Kenyon (1998)
		i.v	60 (As)	0–24	79.9 ± 13.6	8.8 ± 2.5	88.7	
DMA	hamster	oral	40	0–120	48.9	36.0	84.9	Yamauchi & Yamamura (1984a)

Table 21 (contd.)

DMA	hamster	oral	40 (As)	0–48	56.3	41.2	97.5	Marafante et al. (1987)
	mouse	oral	40 (As)	0–48	67.7	29.2	96.8	
DMA	mouse	oral	0.4 (As)	0–24	80.2 ± 2.5	15.8 ± 0.6	96.0	Vahter et al.(1984)
	rat	oral	0.4 (As)	0–24	18.2 ± 4.2	2.0 ± 1.0	20.2	
DMA	mouse	i.v.	0.6 (As)	0–24	77.7 ± 8.4	4.4 ± 0.6	82.1	Hughes & Kenyon (1998)
	mouse	i.v	60 (As)	0–24	82.8 ± 5.2	2.3 ± 0.9	85.1	
DMA	rabbit	i.v	0.04 (As)	0–72	93.8 ± 2.5	~2–3	~96	Vahter & Marafante (1983)
TMA	hamster	oral	10 (As)	0–120	79.2 ± 2.7	0.14 ± 0.03	79.4	Yamauchi et al. (1990)
TMAO	hamster	oral	10 (As)	0–120	89.0 ± 9.61	0.56 ± 0.44	89.6	Yamauchi et al. (1989b)

relatively low amounts of MMA and DMA excreted in the faeces (2-9% of the dose) after intravenous administration of these compounds to mice or rabbits (Vahter & Marafante, 1983; Hughes & Kenyon, 1998), it seems unlikely that biliary excretion or other gastric secretory processes contribute significantly to total elimination. Interestingly, however, Hughes & Kenyon (1998) found that the percentage of the dose eliminated in faeces was dose-dependent when either MMA or DMA was administered intravenously to mice (Table 21).

Volatile metabolites of some organoarsenicals are eliminated in expired air after oral administration. After a high oral dose of DMA (1500 mg/kg), mice eliminate dimethylarsine, but not TMA, in expired air (Yamanaka & Okada, 1994). Similarly, in mice orally administered 14 400 mg/kg TMAO, TMA was detected in expired air (Kaise et al., 1989). Hamsters also eliminate TMA in expired air after administration of either TMAO or TMA (Yamauchi et al., 1989b, 1990).

Extensive studies by Vahter et al. (1983) demonstrate that arsenobetaine is rapidly and predominantly eliminated in the urine. After intravenous administration of 4 mg As/kg arsenobetaine 101 ± 5.8%, 94.9 ± 0.8%, and 71.6 ± 0.6% respectively of the dose was eliminated in urine of rats, mice and rabbits with 72 h. The corresponding figures for faecal elimination were 4.5 ± 1.3%, 3.8 ± 1.4%, and 2.3 ± 0.8% of the dose. The pattern of elimination was also very similar in mice administered the same dose of arsenobetaine orally, and the rate of excretion in urine was dose independent in the range of 4–400 mg As/kg arsenobetaine.

Arsenocholine, like arsenobetaine, is predominantly eliminated in the urine of mice, rats and rabbits after intravenous administration (Marafante et al., 1984). However, although the percentage of the dose eliminated in the faeces (2–3%) for the two compounds is quite similar among different animal species, 66% was eliminated in the urine of rabbits compared to 78% in rats and mice within 72 h of administration. Whole-body retention of arsenocholine was consistently significantly greater over a 28-day period in mice dosed intravenously with 4 mg As/kg of either compound. The authors attribute this difference to the fact that arsenocholine can be incorporated into phospholipids whereas arsenobetaine is not (Marafante et al., 1984).

6.2.4.2 Human studies

In common with laboratory animals, humans appear to 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 µg As) of MMA and DMA, respectively, was eliminated in urine of human volunteers within a 4-day period. Arsenic ingested in seafood, most probably in the form of arsenobetaine, is predominantly and rapidly eliminated in urine (Table 22). It is worthy of note that the percentage of the dose eliminated in urine after ingestion of arsenic in seafood is quite similar to that seen in laboratory animals dosed orally with arsenobetaine. No studies were identified that specifically addressed the issue of biliary excretion or other routes of elimination for organoarsenicals in humans.

Table 22. Percentage elimination of As ingested in seafood [a]

Species	As Ingested	No. of subjects	Time (days)	Elimination [b]	Reference
Flounder	5	6	8	77 ± 11 (U)	Freeman et al. (1979)
Flounder	10	15	8	76 ± 8 (U)	Tam et al. (1982)
Plaice	8	8	5	69–85 (U)	Luten et al. (1982)
Cod + labelled arsenobetaine	ND	6	8	92 ± 2 (T)	Brown et al. (1990)

[a] U = urinary elimination; T = total elimination; ND = not determined
[b] Elimination figures are percentage mean ± SD or range

6.2.5 Retention and turnover

Vahter et al. (1984) compared the whole-body retention of ^{74}As-DMA in mice and rats after 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 h, 14% with a half-time of 10 h 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 h and the remaining 55% having a half-time of ~50 days. The longer retention of DMA in the rat was attributed to its tendency to accumulate in erythrocytes.

Yamauchi et al. (1990) calculated the biological half-lives after oral administration of organoarsenicals to hamsters from many studies conducted in their laboratory. They reported half-times of 7.4 h for MMA, 5.6 h for DMA, 5.3 h for TMAO, 3.7 h for TMA and 6.1 h for arsenobetaine. No studies that specifically investigated the retention and turnover of organoarsenicals in humans were identified.

6.3 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. This section emphasizes the utility and limitations of these biomarkers and provides more limited information on arsenic levels associated with specific environmental exposure concentrations in air and water. Issues related to analytical methods relevant to the use of these biomarkers (e.g. preservation, extraction, storage) are discussed in section 2.4.

6.3.1 Arsenic in hair and nails

Because arsenic accumulates in keratin-rich tissues such as skin, hair and nails as a consequence of its affinity for sulfhydryl groups, arsenic levels in hair and nails may be used as an indicator of past arsenic exposure. Hair and nails have the advantage of being readily and non-invasively sampled, but a major issue of concern is whether external contamination can be removed. Sampling of hair from less readily contaminated sites (e.g. occipital area or nape of neck), and closer to the scalp, can minimize some of these problems. When exposed to water containing high arsenic levels, hair can bind arsenic externally and may not be removed readily by washing procedures. In the studies cited in this section, the issue of possible contamination was apparently adequately addressed in the methodology employed.

Paschal et al. (1989) determined levels of a number of elements in hair (0.5 g occipital new growth hair) of both adults and children without known toxic metal exposure in the USA. The geometric mean levels of arsenic in hair of adults and children did not differ significantly and were 0.035 and 0.032 µg/g, respectively. Wolfsperger et al. (1994) reported that hair of males from both Vienna (Austria) and Rome (Italy) contained significantly more arsenic (µg/g) than the hair of females – 0.12 vs. 0.037 and 0.13 vs. 0.044, respectively. In this same study it was reported that smokers had higher levels of arsenic in hair than non-smokers, although the difference was not statistically significant. Zhuang et al. (1990) reported levels of 0.40 ± 0.22 µg/g in hair of adult male Chinese subjects dying accidentally and with no known history of toxic metal exposure. 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.

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

The arsenic content of fingernails and toenails has also been used as a bioindicators of past arsenic exposure, and 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 as a result of occupational arsenic exposure and correlated significantly (r = 0.89) with mean arsenic air concentrations.

The use of toenails rather than fingernails has been recommended in some studies because of the larger amount of sample that can generally be obtained (Garland et al., 1993; Karagas et al., 1996). Karagas et al. (1996) reported that toenail arsenic was significantly elevated in individuals using well-water known to be high in arsenic compared to individuals using water from low-arsenic wells with geometric mean ± SE toenail arsenic levels of 0.39 ± 0.12 µg/g and 0.14 ± 0.02 µg/g, respectively. Regression

analysis of these data indicated that a 10-fold increase in arsenic concentration in water was associated with a two-fold increase in toenail arsenic levels.

6.3.2 Blood arsenic

Inorganic arsenic is rapidly cleared from blood. It is for this reason that blood arsenic is typically used only as an indicator of very recent or relatively high-level exposure (e.g. in cases of poisoning), or chronic stable exposure (e.g. to drinking-water). The limitation of blood arsenic levels as indicators of low-level exposure or drinking-water is that it is difficult to distinguish the contributions of inorganic arsenic from water and organic arsenic from food (NRC, 1999).

Arsenic concentrations in blood are elevated in individuals with chronic high level exposure to arsenic in drinking-water, but not to the same degree as urinary arsenic. For example, Concha et al. (1998a) reported that in a group of Andean women whose drinking-water contained ~0.65 mg As/litre, median blood arsenic was 0.95 µg/litre and median urinary arsenic concentration was 7.6 µg/litre. In contrast, a similar population whose drinking-water contained ~200 mg As/litre had median blood arsenic levels of 7.6 µg/litre (8-fold higher) and a median urinary arsenic concentration of 303 µg/litre (~40-fold higher).

6.3.3 Arsenic and metabolites in urine

Since arsenic is rapidly metabolized and excreted into the urine, 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 common with other biomarkers of arsenic exposure, levels of arsenicals in urine may be a consequence of inhalation exposure or ingestion of arsenic from drinking-water, beverages, soil or foodstuffs (NRC, 1999). However, in the case of exposure to arsenic compounds of low solubility, e.g. GaAs, urinary arsenic will reflect the absorbed dose, but not the inhaled amount (Yamauchi et al., 1989a)

In many older studies, total urinary arsenic was used as a biomarker of recent arsenic exposure. However, this is increasingly

uncommon because organoarsenicals present in substantial amounts in certain foodstuffs (see sections 5.1 and 5.2) are also excreted in urine. For example, the practically non-toxic compound arsenobetaine is present in mg/kg levels in seafood and excreted mainly unchanged in the urine (Kaise & Fukui, 1992; Le et al., 1993, 1994c). In controlled experiments (e.g. Arbouine & Wilson, 1992; Buchet et al., 1994, 1996), it has been found that consumption of seafood (e.g. marine fishes, crustaceans, bivalves, seaweeds – see section 5.1) by human volunteers is associated with increased total urinary arsenic excretion. Under these conditions, assessment of inorganic arsenic exposure using total urinary arsenic would result in overestimation of inorganic arsenic exposure.

To avoid the potential for overestimation 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. Relatively recently it has been found that adding all arsenic metabolites together can give misleading results unless a careful diet history is taken and/or seafood consumption is prohibited for 2–3 days before urine collection (Buchet et al., 1996). There are two reasons for this. First, some seafood, especially bivalves, contain the arsenic metabolites MMA and DMA, particularly DMA, in fairly high amounts (Velez et al., 1996). Secondly, arsenosugars present in seaweeds and some bivalves are extensively metabolized (either by the body itself or by the gut microbiota) to DMA, which is then excreted in urine (Le et al., 1994c; Ma & Le, 1998). The issue of the extent to which consumption of seafoods and other foods can compromise the estimation of inorganic arsenic exposure by the measurement of arsenic and its metabolites in urine remains an active area of investigation.

LINKS TO THE OTHER SECTIONS OF THE DOCUMENT