WHO FOOD ADDITIVES SERIES: 63

FAO JECFA MONOGRAPHS 8

Safety evaluation of certain contaminants in food

Prepared by the
Seventy-second meeting of the Joint FAO/ WHO Expert Committee on Food Additives (JECFA)

ARSENIC
(addendum)
(pages 153 – 316)

World Health Organization, Geneva, 2011

Food and Agriculture Organization of the United Nations, Rome, 2011

ARSENIC (addendum)

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1. EXPLANATION

Arsenic is a metalloid that occurs in different inorganic and organic forms, which are found in the environment both from natural occurrence and from anthropogenic activity. Arsenic was previously evaluated by the Committee at its tenth, twenty-seventh and thirty-third meetings (Annex 1, references *13*, *63* and *84*). At its twenty-seventh meeting (in 1983), it was concluded that "on the basis of the data available the Committee could arrive at only an estimate of 0.002 mg/kg b.w. as a provisional maximum tolerable daily intake for ingested inorganic arsenic; no figure could be arrived at for organic arsenicals in food" (Annex 1, reference *63*). This was based on the observation that arsenicism can be associated with water supplies containing an upper arsenic concentration of 1 mg/l or greater and that a concentration of 0.1 mg/l may give rise to presumptive signs of toxicity. Assuming a daily water consumption of 1.5 litres, the Committee concluded that inorganic arsenic intakes of 1.5 mg/day were likely to result in chronic arsenic toxicity and that daily intakes of 0.15 mg may also be toxic in the long term to some individuals. The Committee noted that the International Programme on Chemical Safety (IPCS) had estimated that an arsenic concentration of 0.2 mg/l in drinking-water would lead to a 5% lifetime risk of skin cancer, but that skin cancer did not occur in the absence of other toxic effects due to arsenic. The Committee also noted a need for information on:

- arsenic accumulation in humans exposed to various forms of arsenic in the diet and drinking-water;
- the identification, absorption, elimination and toxicity of arsenic compounds in food, with particular reference to arsenic in fish;
- the contribution of arsenic in fish to human body burden of arsenic;
- epidemiological studies on populations exposed to elevated intakes of arsenic of known speciation.

At its thirty-third meeting (in 1988), the Committee considered information relevant to assessing the significance of organoarsenicals in fish. The previous evaluation was confirmed by assigning a provisional tolerable weekly intake (PTWI) of 0.015 mg/kg body weight (bw) for inorganic arsenic, "with the clear understanding that the margin between the PTWI and intakes reported to have toxic effects in

epidemiological studies was narrow" (Annex 1, reference *84*). The Committee noted that the organic forms of arsenic present in seafood needed different consideration from the inorganic arsenic in water. It concluded that there had been no reports of ill-effects among populations consuming large quantities of fish that result in organoarsenic intakes of about 0.05 mg/kg bw per day, but further investigation would be desirable to assess the implications for human health of exposure to naturally occurring organoarsenic compounds in marine products.

Inorganic arsenic has also been evaluated on a number of occasions by the International Agency for Research on Cancer (IARC). In 1973, IARC concluded that there was a causal relationship between skin cancer and exposure to inorganic arsenic in drugs, in drinking-water with a high arsenic content or in the occupational environment and that the risk of lung cancer was clearly increased in certain smelter workers who inhaled high levels of arsenic trioxide. However, the causative role of arsenic was uncertain, as the influence of other constituents of the working atmosphere could not be determined. In 1980, IARC concluded that there was sufficient evidence that inorganic arsenic compounds are skin and lung carcinogens in humans (Group 1). In 2004, IARC concluded that there was sufficient evidence in humans that arsenic in drinking-water causes cancers of the urinary bladder, lung and skin, whereas the evidence for carcinogenicity in experimental animals was limited. In 2009, IARC again concluded that arsenic in drinking-water causes cancers of the urinary bladder, lung and skin and that the evidence was "limited" for cancers of the kidney, liver and prostate (Straif et al., 2009).

At its present meeting, the Committee was asked to consider all information related to the toxicology and epidemiology, exposure assessment, including biomarker studies, analytical methodology, speciation and occurrence in food and drinking-water, in order to re-evaluate and review the PTWI for inorganic arsenic. The literature relating to arsenic is extensive, and the present Committee used three recent reviews—ATSDR (2007), EFSA (2009) and IARC (in press)—as the starting point for its evaluation and also took into account newer studies that were considered to be informative for the evaluation. The arsenic-containing compounds found in water, foods and biological samples are shown in Table 1.

Table 1. Arsenic compounds found in water, foods and biological samples

Name	Synonyms and abbreviations	Chemical Abstracts Service Registry No.
Arsenate	As^{V}	—
Arsenite	As^{III}	—
Methylarsonic acid	Monomethylarsonic acid, methylarsonate, MMA^{V}	124-58-3
Dimethylarsinic acid	Dimethylarsinite, cacodylic acid, DMA^{V}	75-60-5
Methylarsonous acid	Monomethylarsonous acid, MMA^{III}	—

Table 1 (contd)

Name	Synonyms and abbreviations	Chemical Abstracts Service Registry No.
Dimethylarsinous acid	DMA^{III}	—
Arsenobetaine	AB	64436-13-1
Arsenocholine	AC	39895-81-3
Trimethylarsine oxide	TMAO	4964-14-1
Tetramethylarsonium ion	TMA^{+}	27742-38-7
Dimethylarsionylethanol	DMAE	—
Trimethylarsoniopropionate	TMAP	—
Dimethylarsionylribosides	Oxo-arsenosugars	—
Dimethylmonothioarsinic acid	$DMMTA^{V}$	—
Dimethyldithioarsinic acid	$DMDTA^{V}$	—

Note: Except for biochemical and toxicological studies of specific arsenic compounds, the valency of MMA and DMA is usually not specified. The analysis of MMA^{III} and DMA^{III} has become possible only recently. In this monograph, the terms MMA and DMA are used as cited in the original papers. Where MMA and DMA are measured in foods, they have been measured as the pentavalent form. Where biological samples have been analysed, it is assumed that MMA and DMA refer to total [MMA^{III} + MMM^{V}] and total [DMA^{III} + DMM^{V}], respectively.

2. BIOLOGICAL DATA

2.1 Biochemical aspects

2.1.1 Absorption, distribution and excretion

Pentavalent and trivalent arsenicals are readily absorbed via the gastrointestinal tract. The absorption of arsenic is in the range 0.70–0.98 (Owen, 1990), indicating that soluble arsenicals (in water) are highly bioavailable for absorption. The degree of bioavailability of arsenic is variable, depending on the matrix. For example, about 33% of arsenic in rice with a relatively high content of dimethylarsinic acid (DMA^{V}) is available for absorption, compared with 89% from rice containing mainly sodium arsenate with a low DMA^{V} content and cooked in arsenic-contaminated water (Juhasz et al., 2006). It is difficult to determine if this higher bioavailability of arsenic is from arsenic accumulated in the rice grain or the arsenic absorbed by rice from the water during the cooking process. The variation in absorption of arsenic from soil covers a wider range, from a few per cent to about 70% (Freeman et al., 1993, 1995; Ng & Moore, 1996; Ng et al., 1998; Bruce et al., 2003; Bruce, 2004; Diacomanolis, Ng & Noller, 2007; Juhasz et al., 2007, 2008). Generally, soil contains insoluble arsenic sulfide forms such as galena and arsenopyrite, which would have a lower absorption.

The absorption depends on the arsenic species and its solubility. For example, Ng & Moore (1996) demonstrated differences in the absorption of sodium arsenite, sodium arsenate and calcium arsenite in a rodent model. Arsenite has been shown to be more extensively absorbed from the gastrointestinal tract of mice compared with arsenate when given lower doses (0.4 mg/kg bw as arsenic), whereas the reverse is true at higher doses (4.0 mg/kg bw as arsenic). Fasting and food restriction can increase arsenic absorption. Other dietary factors can also influence the absorption. Much less pentavalent arsenic was absorbed from the gastrointestinal tract of mice following oral administration in a study by Odanaka, Matano & Goto (1980) (48.5% of the 5 mg/kg bw dose excreted in urine) than in a study by Vahter & Norin (1980) (89% of the 4 mg/kg bw dose excreted in urine). This difference can be explained by the fact that mice in the Vahter & Norin (1980) study were not fed for at least 2 h before and 48 h after dosing, whereas mice in the Odanaka, Matano & Goto (1980) study were not food restricted. Kenyon, Hughes & Levander (1997) reported that feeding a diet lower in fibre or "bulk" to female B6C3F1 mice increased the absorption of pentavalent arsenic by about 10% compared with standard rodent chow diet.

Inorganic arsenic is rapidly cleared from blood in humans and most experimental animal species that have been tested. The exception is rats, in which arsenic binds to erythrocytes, delaying clearance (IPCS, 1981, 2001). Accumulation of arsenic in tissues increases with age. In a study conducted in Glasgow, Scotland, arsenic levels in liver, lung and spleen from adults were higher than those from infants (Raie, 1996), and this is consistent with observations in laboratory animals (Marafante et al., 1982).

Most ingested arsenic is rapidly excreted via the kidney within a few days (Tam et al., 1979; Vahter, 1994). For example, healthy male volunteers excreted 62.3% ± 4.0% of a 0.06 ng dose of 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 (Pomroy et al., 1980). Several other studies reported that between 45% and 75% of the dose of various trivalent forms of arsenic are excreted in the urine within a few days, which suggests that gastrointestinal absorption is both relatively rapid and extensive. No quantitative data were available that directly addressed biliary excretion of trivalent or pentavalent arsenic in humans.

Ingested inorganic arsenic is excreted in human urine as inorganic arsenate and arsenite (10–15%) and its methylated metabolites, including monomethylarsonic acid (MMA^{V}) (10–15%) and DMA^{V} (60–80%) (Tam et al., 1979; Foa et al., 1984; Vahter et al., 1995a; Hopenhayn-Rich et al., 1996). Monomethylarsonous acid (MMA^{III}) and dimethylarsinous acid (DMA^{III}) have been detected in human urine at relatively lower levels (Aposhian et al., 2000a,b; Le et al., 2000a,b; Del Razo et al., 2001; Mandal, Ogra & Suzuki, 2001).

Arsenic is also excreted in human milk, although the levels are low. In a study of Andean women in Argentina, the average concentration of arsenic in breast milk was quite low (3.1 µg/l), even when urinary arsenic excretion was high (230–300 µg/l) (Concha, Nermell & Vahter, 1998).

High levels of arsenic are retained for a longer period in bone, skin, hair and nails compared with other tissues of exposed humans (Karagas et al., 2000; Mandal, Ogra & Suzuki, 2003). Hence, arsenic levels in hair and nails have been used as biomarkers reflecting longer-term exposure than those in blood or urine (see section 2.3.1).

2.1.2 Biotransformation

Unlike inorganic arsenic, ingested organic arsenicals, such as "fish arsenic" and arsenosugars, undergo very little biotransformation and are excreted almost entirely unchanged. However, it has been reported that urinary DMA^{V} is increased after consumption of DMA^{V}-containing seafood or from metabolism of arsenosugars (IPCS, 2001). Arsenolipids present in cod liver can also be metabolized into DMA^{V} (Schmeisser, Goessler & Francesconi, 2006). Organoarsenicals can be metabolized into DMA^{V}, although the mechanism underpinning this biotransformation is not clear.

Inorganic arsenic undergoes stepwise reduction of pentavalent arsenic to trivalent arsenic followed by oxidative addition of a methyl group to the trivalent arsenic. The sequential reduction and oxidation pathway shown in Figure 1 is generally believed to be the biotransformation pathway for inorganic arsenic in humans and experimental animals (Aposhian et al., 2000b).

The methylation of arsenite is catalysed by a specific methyltransferase with *S*-adenosylmethionine (SAM) as a methyl group donor (Zakharyan et al., 1995). Both in vivo and in vitro studies have shown that SAM and glutathione (GSH) are essential cofactors in enzymatic arsenic methylation (Hirata et al., 1989; Styblo, Delnomdedieu & Thomas, 1996).

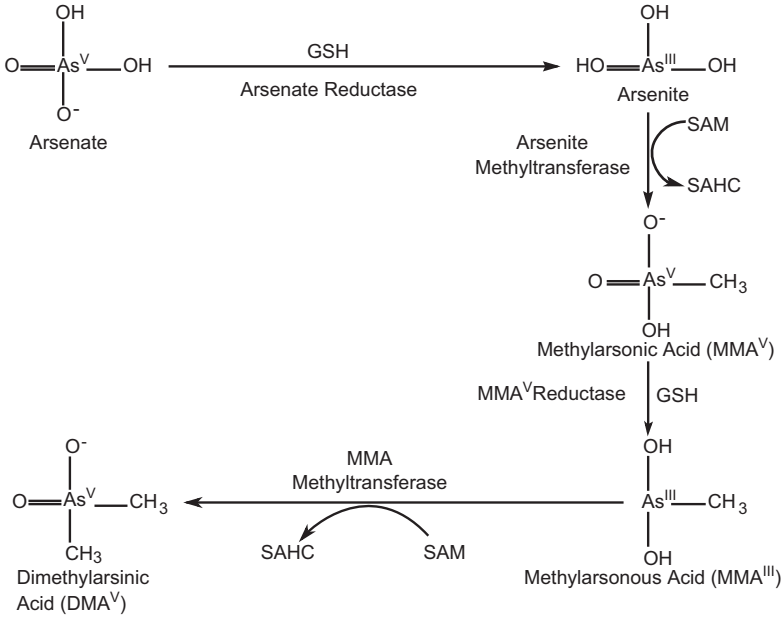
Besides the repeated reduction and oxidative methylation reactions in the arsenic metabolic pathway, the function of conjugation reaction involving GSH, resulting in excretion from the liver, has been discussed by Suzuki (2005).

An alternative, but controversial, metabolic pathway of arsenic via arsenic–GSH complexes was proposed by Hayakawa et al. (2005). The authors claimed that metabolism of inorganic As^{III} to methylated arsenicals by human recombinant Cyt19 was via arsenic triglutathione and monomethylarsonic diglutathione rather than by oxidative methylation of inorganic As^{III} and MMA^{III}.

In a study by Naranmandura, Suzuki & Suzuki (2006), it was proposed that inorganic arsenic was successively methylated reductively in the presence of GSH, rather than by a stepwise oxidative methylation, and pentavalent arsenicals (MMA^{V} and DMA^{V}) were present as end products of metabolism, rather than intermediates.

The recent study by Naranmandura et al. (2007) demonstrated the presence of monomethylthioarsonic acid ($MMMTA^{V}$), dimethylmonothioarsinic acid ($DMMTA^{V}$) and dimethyldithioarsinic acid ($DMDTA^{V}$) in the urine of hamsters and $MMMTA^{V}$ and $DMMTA^{V}$ in the urine of rats administered a single oral dose of arsenite (inorganic As^{III}) at 5.0 mg/kg bw.

Figure 1. Pathway for biotransformation of arsenic (GSH, glutathione; SAHC, S-adenosylhomocysteine; SAM, S-adenosylmethionione) (adapted from Aposhian et al., 2000b)



In another study, it was shown that the protein Cyt19 can completely methylate inorganic arsenic to trimethyl species (Thomas et al., 2007). This is unlike what Aposhian et al. (2000b) proposed, which involves two separate enzymes. However, all these studies support the view that arsenic biotransformation is via oxidative methylation, whereas an alternative reductive methylation pathway has also been proposed by other researchers (Hayakawa et al., 2005; Naranmandura, Suzuki & Suzuki, 2006). It would appear that there are two or more competing proposed pathways, and additional studies are needed.

As MMA^{III} and DMA^{III} are more toxic than inorganic arsenic and have high affinity for thiols and cellular proteins (Styblo, Hughes & Thomas, 1996; Styblo & Thomas, 1997), the hypothesis of methylation as a detoxification pathway needs to be re-evaluated.

2.1.3 Effects on enzymes and other biochemical parameters

Arsenic has higher affinity for binding to dithiol (vicinal sulfhydryl group) compared with monothiol groups of a variety of essential enzymes and proteins. When arsenic binds to critical dithiols, it can interfere with the activity of many enzymes and inhibit important biochemical events, resulting in cell damage and toxicity (Hughes, 2002). For example, arsenic is known to affect enzymes involved in haem synthesis and alter porphyrin profiles in experimental animals and humans

(Fowler & Mahaffey, 1978; Garcia-Vargas et al., 1994; Ng et al., 2005; Krishnamohan et al., 2007a,b).

Impacting on functions of some enzymes, such as glutathione peroxidase, catalase and superoxide dismutase and particularly glutathione *S*-transferase (GST), arsenic affects malondialdehyde production (Delnomdedieu et al., 1993, 1994). Malondialdehyde is a by-product of lipid oxidation. Yamanaka et al. (1990) showed a metabolic pathway of arsenic during oxidative stress in which a reactive oxidative species ($(CH_3)_2As\bullet$ radical) can be produced within the body. Other reports (Kitchin & Ahmad, 2003; Shi et al., 2004) have also provided evidence of oxidative damage induced by arsenic exposure in both experimental animals and humans. Similarly, 8-hydroxydeoxyguanine, an oxidative stress biomarker of deoxyribonucleic acid (DNA) damage, is induced by arsenic (Yamauchi et al., 2004).

Chronic arsenic exposure has been associated with type II diabetes. Wang et al. (2009b) studied biochemical parameters, including urinary *N*-acetyl-β-glucosaminidase (NAG), and blood biochemistry in humans with and without type II diabetes in an arsenic-endemic area of Xinjiang, China. They reported elevated NAG in all patients with diabetes compared with those without diabetes. Further, NAG levels in patients with diabetes from the endemic area were higher than those from the control area. NAG is a lysosomal enzyme involved in the metabolism of glycoproteins. Increased NAG levels in the urine are an early indication of renal disease and can serve as a valuable renal function test in disorders such as nephritis syndrome and other diseases associated with nephropathy (Price, 1992).

2.2 Toxicological studies

2.2.1 Acute toxicity

Inorganic arsenic can be lethal to experimental animals and humans. Arsenic toxicity depends on its solubility, chemical form and route of administration and varies among experimental animals (Table 2). Generally, trivalent arsenic is more toxic than the pentavalent forms. For example, the more soluble sodium arsenite is more toxic than arsenic trioxide (Done & Peart, 1971). Also, the inorganic arsenicals are more toxic than MMA^V and DMA^V.

More details on the acute oral toxicity of inorganic arsenic are given in ATSDR (2007). Reported lowest-observed-adverse-effect levels (LOAELs) for inorganic arsenic causing gastrointestinal irritation are 0.05 mg/kg bw per day for humans, 6 mg/kg bw per day for monkeys and 11 mg/kg bw per day for rats (ATSDR, 2007).

Although inorganic arsenic is more toxic than its major metabolites MMA^V and DMA^V and other organic arsenic, MMA^{III} was found to be more cytotoxic than inorganic arsenite in Chang human hepatocytes (Petrick et al., 2000). In several cell lines, MMA^{III} was more cytotoxic than inorganic As^{III}, whereas DMA^{III} was at least as toxic as inorganic As^{III} for most of the cell types examined, but the pentavalent arsenicals were significantly less cytotoxic (Styblo et al., 1999, 2000). These results show the following order of toxicity: $MMA^{III} > DMA^{III} \approx AsI^{II} > AsV > MMAV > DMAV$.

Table 2. LD_{50} values of different arsenic species in various experimental animal species

Chemical	Species (sex)	Route	LD_{50} (mg/kg bw as arsenic)	Reference
Arsenic trioxide	Mouse (m)	Oral	26	Kaise, Watanabe & Itoh (1985)
Arsenic trioxide	Mouse (m)	Oral	26–48	Harrison, Packman & Abbott (1958)
Arsenic trioxide	Rat (m/f)	Oral	15	Harrison, Packman & Abbott (1958)
Arsenite	Mouse (m)	Intramuscular	8	Bencko et al. (1978)
Arsenite	Hamster (m)	Intraperitoneal	8	Petrick et al. (2001)
Arsenite	Mouse (m)	Intramuscular	22	Bencko et al. (1978)
MMA^{III}	Hamster (m)	Intraperitoneal	2	Petrick et al. (2001)
MMA^{V}	Mouse (m)	Oral	916	Kaise, Watanabe & Itoh (1985)
DMA^{V}	Mouse (m)	Oral	648	Kaise, Watanabe & Itoh (1985)
TMAO	Mouse (m)	Oral	10 600	Kaise et al. (1989)
AB	Mouse (m)	Oral	>10 000	Kaise, Watanabe & Itoh (1985)

f, female; LD_{50}, median lethal dose; m, male

2.2.2 Short-term studies of toxicity

There are very few short-term studies of the toxicity of arsenic reported in the literature. Respiratory effects were observed in rats and mice exposed to very high levels of DMA^{V} (2172 mg/m^3 as arsenic) and MMA^{V} (≤2485 mg/m^3 as arsenic) (Stevens, DiPasquale & Farmer, 1979). DMA^{V} and MMA^{V} at high concentrations are considered to be respiratory irritants.

In a 28-day study (Hughes & Thompson, 1996) in which mice were exposed to sodium arsenate (0.025 and 2.5 mg/l as arsenate), hepatic vacuolar degeneration was observed in a dose–response manner, but no effect was observed in the kidney. Short-term exposure of guinea-pigs to arsenic trioxide resulted in a significant decrease in total hepatic carbohydrates (Reichl et al., 1988). This observation is thought to be due to inhibition of gluconeogenesis and may lead to serious toxic effects (Reichl et al., 1988; Szinicz & Forth, 1988).

2.2.3 Long-term studies of toxicity and carcinogenicity

Oral exposure to inorganic arsenicals has a number of effects, including effects on the cardiovascular, respiratory, gastrointestinal, haematological, immune, reproductive and nervous systems (reviewed in IPCS, 2001; ATSDR, 2007).

In 2-year feeding studies, there was evidence of gastrointestinal injury in dogs exposed to arsenite at 2.4 mg/kg bw per day, but not in rats at doses of arsenate or arsenite up to 30 mg/kg bw per day (ATSDR, 2007).

MMA^{V} has been shown to have effects on the gastrointestinal tract, kidney, thyroid and reproductive system (ATSDR, 2007). The most sensitive effect is diarrhoea, which has been reported in rats, mice, rabbits and dogs, occurring at decreasing doses with increasing duration of treatment. Histological alterations in the gastrointestinal tract generally occurred at higher doses than the lowest dose resulting in diarrhoea. The lowest no-observed-adverse-effect level (NOAEL) following dietary administration was 3.0 mg/kg bw per day in a 2-year dietary study in rats in which the LOAEL for diarrhoea was 25.7 mg/kg bw per day (Arnold et al., 2003).

DMA^{V} has effects on the urinary bladder, kidneys, thyroid and fetal development (ATSDR, 2007).

The evidence for the carcinogenicity of arsenical compounds has been reviewed in detail by IARC (in press). Most studies in experimental animals have not shown increased tumour incidences following chronic oral exposure to inorganic arsenic. Arsenic trioxide, various arsenate salts and sodium arsenite were not carcinogenic when administered via the oral route in mice and rats, and sodium arsenite and arsenate were not carcinogenic in dogs (IARC, 1973, 1980).

There are two exceptions to this general observation. Administration of sodium arsenate in the drinking-water (0, 1, 10 and 100 mg/l) to groups of 30 male A/J mice for 18 months resulted in a dose-related increase in lung tumour multiplicity and lung tumour size. In this study, some mice of all except the highest dose group died from 10 months onwards. The survival at the end of the study was 19/30, 14/30, 16/30 and 30/30 at 0, 1, 10 and 100 mg/l, respectively (Cui et al., 2006).

In a study for which detailed results are so far reported only in a PhD thesis, groups of 70 C57BL/6J mice were given drinking-water containing arsenic at concentrations of <0.0001 (controls, $n = 105$), 0.1, 0.25 or 0.5 mg/l in the form of sodium arsenate (As^{V}) or MMA^{III} ad libitum for 24 months. There were no significant differences in body weight, feed or water consumption in the treatment groups compared with controls. Some animals died suddenly, some for unknown reasons and some from the bursting of a blood-filled ovarian cyst or from tumorous lesions. Treatment with both sodium arsenate and MMA^{III} resulted in a dose-related, statistically significant increased incidence of lymphoma. At the highest dose, MMA^{III} treatment resulted in a higher lymphoma incidence than sodium arsenate, but this difference was not seen at the other doses (Krishnamohan, 2007). DMA^{III} has not been tested for carcinogenicity.

MMA^{V} was not carcinogenic in 2-year cancer bioassays when administered to male rats at concentrations up to 200 mg/l in drinking-water (Shen et al., 2003a) or to mice or rats at dietary concentrations up to 400 mg/kg feed (Arnold et al., 2003). The dietary concentrations were comparable to doses in the region of 100 mg/kg bw per day.

Trimethylarsine oxide (TMAO) (200 mg/l in drinking-water for 2 years) induced hepatocellular adenomas in rats, possibly by a mechanism involving oxidative damage and cell proliferation (Shen et al., 2003b).

DMA^{V} (≥50 mg/l in drinking-water) was carcinogenic in the urinary bladder of rats but not in the urinary bladder of mice. The NOAEL was 10 mg/l in drinking-water, equivalent to 0.73 mg/kg bw per day. The mode of action is considered to involve cytotoxicity and sustained increased cell proliferation, and the rat is considered to be particularly sensitive to DMA^{V}, owing to slower elimination and greater potential for metabolism to DMA^{III} compared with other species, including humans (Cohen et al., 2006, 2007; ATSDR, 2007). Similarly, DMA^{V} administered in drinking-water for 50 weeks or more increased the incidence and multiplicity of lung adenoma or carcinoma in A/J mice at 400 mg/l (Hayashi et al., 1998) and increased lung tumours in mutant Ogg–/– mice (which cannot repair certain types of oxidative DNA damage) but not Ogg+/+ mice at 200 mg/l (Kinoshita et al., 2007). Furthermore, DMA^{V} has been reported to promote carcinogenesis in the urinary bladder (≥10 mg/l), kidney (≥200 mg/l), liver (≥200 mg/l) and thyroid gland (≥400 mg/l) (Yamamoto et al., 1995; Wanibuchi et al., 1996).

In addition, studies in mice have shown evidence of transplacental carcinogenesis (Waalkes, Liu & Diwan, 2007; Liu & Waalkes, 2008). Sodium arsenite (0, 42.5 and 85 mg/l) was administered in drinking-water to pregnant mice during days 8–18 of gestation, and the offspring were observed for up to 2 years. There were dose-related increases in hepatocellular carcinoma and adrenal cortical carcinoma in male offspring and in ovarian tumours, lung adenocarcinomas and proliferative lesions of the uterus and oviduct of female offspring (Waalkes, Liu & Diwan, 2007). Combined prenatal exposure to the tumour promoter 12-*O*-tetradecanoyl phorbol-13-acetate (TPA) (Waalkes, Ward & Diwan, 2004), diethylstilbestrol (DES) or tamoxifen (Waalkes et al., 2006a,b) enhanced the carcinogenic response of prenatal arsenic exposure in a variety of mouse tissues. Arsenic exposure in utero did not cause skin cancer, but exacerbated the skin cancer response after TPA exposure, possibly by altering tumour stem cell response (Waalkes et al., 2008).

Sodium arsenite (≥1.25 mg/l in drinking-water) was co-carcinogenic with solar ultraviolet (UV) light (Rossman et al., 2001; Burns et al., 2004), and arsenate (25 mg/l in drinking-water ad libitum for a period of 25 weeks) was co-carcinogenic with 9,10-dimethyl-1,2-benzanthracene (Motiwale, Ingle & Rao, 2005).

A recent study that evaluated the impact of early life stage and prolonged arsenic exposure on arsenic-induced proliferative lesions and neoplasia reported that C3H mice treated for 1 year with inorganic arsenic at 85 mg/l in drinking-water (~8 mg/kg bw per day) during gestation, pre-pubescence and post-pubescence exhibited differential proliferative lesions and tumour outcomes (Ahlborn et al.,

2009). The authors observed that urinary bladder hyperplasia incidence was significantly increased in female mice chronically exposed to arsenic from either gestational day (GD) 8 or postnatal day (PND) 21 through 1 year. In contrast, male mice continuously exposed to arsenic from GD 8 through 1 year had significantly decreased incidence of liver and adrenal tumours, in comparison with both mice exposed in utero only and untreated control mice. These results suggest that continuous inorganic arsenic exposure at 85 mg/l from gestation through 1 year increases the incidence and severity of urogenital proliferative lesions in female mice and decreases the incidence of liver and adrenal tumours in male mice. The paradoxical nature of these effects may be related to altered lipid metabolism, the effective dose in each target organ or the shorter 1-year observational period (Ahlborn et al., 2009).

Nelson et al. (2009) investigated the hepatic gene expression patterns that may lead to the apparent protective effect of continuous arsenic treatment of C3H mice seen at 1 year, using liver tissue samples taken from the different treatment regimens of the companion study (Ahlborn et al., 2009). The authors found that continuous arsenic treatment altered expressions of genes involved in cellular growth and proliferation, cell death, oxidative stress, protein ubiquitination and mitochondrial dysfunction, and many of these genes are known to be involved in liver carcinogenesis. Furthermore, the study demonstrated a marked reduction in stearoyl-coenzyme A desaturase-1 messenger ribonucleic acid (mRNA) in mice continuously exposed to arsenic for 1 year compared with controls and the in utero–only treatment group. The authors concluded that the unexpected liver tumour–protective effect of continuous arsenic exposure from GD 8 until 1 year in C3H mice can most likely be attributed to gene pathways involving gene expression, oxidative stress and cell death.

In previous experimental studies, DES was shown to enhance the carcinogenic response of prenatal arsenic exposure in a variety of mouse tissues. A new study by Liu et al. (2009) examined interactions of in utero arsenic exposure and postnatal DES treatment in the neonatal adrenal gland and evaluated the resulting gene expression related to estrogen signalling and steroid metabolism. Pregnant CD1 mice were exposed to drinking-water containing sodium arsenite at an arsenic concentration of 85 mg/l from day 8 to day 18 of gestation and were allowed to deliver normally. The offspring were subsequently injected subcutaneously on postpartum days 1–5 with DES (2 µg/pup per day) and killed on PND 12. The study found that fetal arsenic exposure greatly enhanced DES-induced, estrogen-linked gene expression (such as estrogen receptor-α and trefoil factors), as well as the expression of genes involved with steroid metabolism and/or methionine metabolism, including genes encoding for 17β-hydroxysteroid dehydrogenase type 5 (*HSD17β5*) and androstenedione 15α-hydroxylase (*Cyp2a4*). In addition, the transcripts for homocysteine cycling genes (betaine-homocysteine methyltransferase and thioether *S*-methyltransferase) and developmental marker genes (α-fetoprotein, insulin-like growth factor [IGF] 2 and IGF binding protein-1) were higher with arsenic plus DES than with either treatment alone. The authors concluded that exposure of the mice to arsenic during a critical period of fetal development may potentially alter adrenal genetic programming,

leading to endocrine disruption and potentially enhancing tumour formation together with DES at other sites much later in life.

In its most recent evaluation, IARC concluded that there is sufficient evidence for carcinogenicity of inorganic arsenic compounds in experimental animals and sufficient evidence for carcinogenicity of DMA^V in experimental animals (IARC, in press).

2.2.4 Genotoxicity

Evidence from a wide range of studies has led to the conclusion that arsenic compounds do not react directly with DNA (EFSA, 2009; IARC, in press). Inorganic arsenic does not covalently bind to DNA (Kitchin & Wallace, 2008). It does not induce point mutations in bacterial or mammalian test systems, and it has been shown to be an extremely weak (or insignificant) mutagen at single gene loci, such as thymidine kinase (*TK*) or hypoxanthine guanine phosphoribosyltransferase (*HPRT*) (ATSDR, 2007; EFSA, 2009). However, as a secondary result of genomic instability, chronic exposure to low, non-cytotoxic concentrations of arsenite (≥0.1 µmol/l) has been shown to induce delayed mutagenesis at the *HPRT* locus and cell transformation after 20–30 generations in cultured human osteogenic sarcoma cells (Mure et al., 2003). At higher concentrations, arsenite (≥7 µmol/l) induced large deletion (multilocus) mutations in hamster human hybrid cells (Hei, Liu & Waldren, 1998), micronuclei and chromosomal aberrations, aneuploidy and sister chromatid exchanges in various mammalian cells (ATSDR, 2007). In vivo, oral treatment with arsenite induced chromosomal aberrations in mouse peripheral blood lymphocytes and in mouse bone marrow (IPCS, 2001; USEPA, 2007).

Studies in mammalian cells have shown the induction of DNA damage (strand breaks, oxidative base modifications, apurinic/apyrimidinic sites, DNA–protein crosslinks) by non-cytotoxic (nanomole per litre to micromole per litre) arsenite concentrations (≥0.1 µmol/l, Wang et al., 2002; ≥10 nmol/l, Schwerdtle et al., 2003). Thus, chromosomal alterations may be a secondary result of arsenite-induced DNA damage and interference with DNA damage response pathways. Li & Broome (1999) proposed that arsenite crosslinks tubulin and inhibits guanosine triphosphate binding, resulting in disturbed tubulin polymerization, and mitosis, which may contribute to micronuclei formation. Additionally, inorganic arsenic can cause gene amplification in mouse 3T6 cells (Lee et al., 1988).

Inorganic arsenic increases the genotoxicity, mutagenicity and clastogenicity of other DNA-damaging agents, including UV light, benzo[*a*]pyrene and alkylating agents (Okui & Fujiwara, 1986; Rossman, Molina & Klein, 1986), which may be mediated via interference with DNA damage response processes. Arsenite strongly increased micronuclei induced by benzo[*a*]pyrene in mouse bone marrow (sodium arsenite at 50 mg/l, 7 days; Lewinska et al., 2007) and increased the mutagenicity of benzo[*a*]pyrene in mouse skin (sodium arsenite at 10 mg/l, 10 weeks; Fischer et al., 2005).

DMA^V and MMA^V were not mutagenic in the Ames test, but a number of studies have shown that they can cause chromosomal aberrations and mutations at cytotoxic (high micromole per litre) concentrations (ATSDR, 2007; EFSA, 2009).

In subcellular and cellular systems, MMA^{III} and DMA^{III} induced DNA strand breaks and oxidative base lesions generally at lower concentrations than were required for inorganic arsenic and the pentavalent metabolites (EFSA, 2009). $DMMTA^{V}$ induced aneuploidy, structural chromosomal aberrations and abnormalities of spindle organization and centrosome integrity, starting at micromole per litre (≥10 µmol/l) concentrations (Ochi et al., 2008).

Oral administration of DMA^{V} to mice caused DNA strand breaks in the lung (1500 mg/kg bw, a single dose; Yamanaka et al., 1989; Yamanaka & Okada, 1994) and increased the urinary level of 8-hydroxy-2α-deoxyguanosine (8-OHdG) lesions (50 mg/kg bw, a single dose; Yamanaka et al., 2001) and the 8-OHdG DNA levels in the lung and liver (400 mg/l in drinking-water, 4 weeks; Yamanaka et al., 2001), but not in the bladder, skin, spleen or kidney. In contrast, DMA^{V} administered to rats significantly increased the level of 8-OHdG in the bladder (200 mg/l in drinking-water, 2 weeks or 20 days; Wei et al., 2002; Kinoshita et al., 2007) and kidney (10 mg/kg bw, 4 weeks, every 5 days; Vijayaraghavan et al., 2001). Following an intraperitoneal injection, DMA^{V} induced aneuploidy (300 mg/kg bw, a single injection), but no chromosomal aberrations, in mouse bone marrow cells (Kashiwada, Kuroda & Endo, 1998) and an increase of *lacZ* mutations in the lung, but not in the bladder or bone marrow, in Muta™Mouse (10.6 mg/kg bw per day, 6 days; Noda et al., 2002). After TMAO exposure (200 mg/l in drinking-water, 15 days; Kinoshita et al., 2007), a significant increase in 8-OHdG was observed in the rat liver.

The major underlying mechanisms of the genotoxic effects of arsenic compounds include the rapid induction of oxidative DNA damage and DNA repair inhibition and slower changes in DNA methylation patterns, aneuploidy and gene amplification. Gene amplification, altered DNA methylation and aneuploidy lead to altered gene expression and genomic instability. Inhibition of DNA repair leads to co-mutagenicity as well. These effects are consistent with the experimental animal carcinogenicity data, in which arsenite is a transgenerational carcinogen, with exposure being present during many cell generations, and with co-carcinogenicity (EFSA, 2009; IARC, in press).

There is very limited information relating to the genotoxicity of other arsenic compounds. One paper has been identified relating to the genotoxicity of arsenosugars. The trivalent and pentavalent arsenosugars that were investigated were not mutagenic in *Salmonella* strain TA104 (Andrewes et al., 2004). Arsenobetaine (AB) at concentrations up to 10 mg/ml did not induce mutations in bacterial or mammalian cell assays and did not induce sister chromatid exchanges or metabolic cooperation in V79 Chinese hamster cells. Unlike inorganic and methylated arsenic species, AB had no synergistic or antagonistic effects on the action of benzo[*a*]pyrene and TPA (Jongen et al., 1985).

2.2.5 Reproductive and developmental toxicity

As discussed in EFSA (2009), inorganic arsenic has been shown to be embryotoxic and teratogenic in experimental animals; however, most studies have used high parenteral arsenic dosing, which might have involved maternal toxicity

(Golub, Macintosh & Baumrind, 1998; Wang et al., 2006). Recently, experimental studies without maternal toxicity have shown fetal growth retardation, neurotoxicity and alteration in pulmonary structure following oral dosing at relevant exposure levels, often in the form of arsenate (Wang et al., 2006; Hill, Wlodarczyk & Finnell, 2008). Using a mouse model, in utero and early postnatal exposures to arsenic (100 µg/l or less in drinking-water in the form of arsenite) were found to alter airway reactivity to methacholine challenge in 28-day-old pups (Lantz et al., 2009). The functional changes were correlated with protein and gene expression changes as well as morphological structural changes around the airways.

During its development, the brain is particularly vulnerable, and fetal arsenic exposure and exposure soon after birth cause neurotoxicity, resulting in behavioural changes (Rodriguez, Jimenez-Capdeville & Giordano, 2003; Wang et al., 2006). Rats exposed to high concentrations of arsenite (37 mg/l) in drinking-water from GD 15 until 4 months of age showed increased spontaneous locomotor activity and alterations in a spatial learning task compared with control rats (Rodriguez et al., 2002). The latter effects were also found in rats exposed from PND 1. Exposure of pregnant rats and offspring to high inorganic arsenic (sodium arsenite at 100 mg/l in drinking-water from GD 6 to PND 42) also caused alterations in learning and memory behaviour and some reflex responses (Xi et al., 2009).

Exposure of mouse dams to relatively low levels of arsenic (50 µg/l as arsenate) during pregnancy and lactation resulted in changes in the neuroendocrine markers associated with depression and altered behaviour indicative of depression (learned helplessness and immobility during forced swim) in affected adult C57BL/6J mouse offspring (Martinez et al., 2008). The results suggested that perinatal arsenic exposure may disrupt the regulatory interactions between the hypothalamic–pituitary–adrenal axis and the serotonergic system in the dorsal hippocampal formation in a manner that predisposes affected offspring towards depressive-like behaviour.

Neural tube defects have been observed in experimental studies, with a dose-related increase at inorganic arsenic doses of 4.8–14.4 mg/kg bw per day administered to mice by oral gavage as sodium arsenate (Hill, Wlodarczyk & Finnell, 2008).

In summary, studies in experimental animals demonstrate that in utero exposure to inorganic arsenic via oral administration to the dam causes neural tube defects, fetal growth retardation and neurotoxicity, including alterations in locomotor activity and spatial learning and changes in neuroendocrine markers associated with depressive-like behaviours in the offspring. Inhibition of arsenic methylation has been shown to increase its developmental toxicity (EFSA, 2009).

Little information exists on early-life toxicity of DMA^V and MMA^V. Developmental toxicity studies of orally administered DMA^V and MMA^V in the Sprague-Dawley rat and New Zealand White rabbit have shown an absence of dose-related effects at exposure levels that were not maternally toxic. MMA^V at doses of 0, 10, 100 and 500 mg/kg bw per day (rat) and 0, 1, 3, 7 and 12 mg/kg bw per day (rabbit) and DMA^V at doses of 0, 4, 12 and 36 mg/kg bw per day (rat) and 0, 3, 12 and 48 mg/kg bw per day (rabbit) were administered by oral gavage daily

during organogenesis (GDs 6–15 in rats and GDs 7–19 in rabbits), and the litters were examined at maternal sacrifice (GD 20 in rats; GD 29 in rabbits). After treatment with MMA^V, both maternal toxicity and fetal toxicity were observed at the highest doses of 500 mg/kg bw per day (rat) and 12 mg/kg bw per day (rabbit), but no treatment-related developmental toxicity was found at the lower doses. There was no evidence of teratogenicity associated with MMA^V treatment. With DMA^V, maternal toxicity and developmental toxicity were observed in the rat at 36 mg/kg bw per day. In the rabbits at 48 mg/kg bw per day, there was marked maternal toxicity, culminating in maternal death or abortion, and there were no surviving fetuses for evaluation. There was no treatment-related maternal or developmental toxicity in the rat or rabbit at 12 mg/kg bw per day or below (Irvine, Boyer & DeSesso, 2006).

Groups of 12 time-mated pregnant Sprague-Dawley rats were given AB in aqueous solution by oral gavage at doses of 0, 0.1, 1.0 and 10 mg/kg bw per day from GD 8 until sacrifice on GD 20 (6 dams), PND 13 (3 dams plus pups) and PND 21 (3 dams), at which time pups were weaned and allowed to reach 90 days of age without further dosing. Reproductive and developmental parameters were monitored. There were no differences in maternal body weight or organ weights or in sex ratio or litter size of the offspring. In the pups, there were no treatment-related differences in body weight or organ weights. Preliminary analysis indicated a small, significant increase in crown–rump length in the pups of the highest dose group. In male pups, preputial separation was delayed slightly by the low dose of AB, and in females, vaginal opening was delayed by both the low and high doses of AB. A small advancement in the day of eye opening was also observed. Clinical chemistry and haematology showed some minor differences (Cooke, 2009).

2.2.4 Special studies

(a) Immunotoxicity

EFSA (2009) described studies demonstrating effects of arsenicals on the immune system. Arsenate at concentrations of 0.5, 5 and 50 mg/l in drinking-water administered to female mice for 12 weeks resulted in decreased production of nitric oxide and superoxide in stimulated peritoneal macrophages (Arkusz et al., 2005). In male mice, 3 weeks of exposure to arsenite in drinking-water (0.5, 2.0 and 10 mg/l) resulted in immunosuppression of the humoral response, suppressing both the primary and secondary immune responses (Blakley, Sisodia & Mukkur, 1980). In day-old chicks, inorganic arsenic at 3.7 mg/l in drinking-water for up to 60 days suppressed the cellular and humoral immune response (Aggarwal et al., 2008). Suppression of the immune system has also been reported in zebrafish embryos exposed to inorganic arsenic at 2 and 10 µg/l in egg water for several days (Nayak, Lage & Kim, 2007) and in mice given arsenite at 10 or 100 µg/l in drinking-water or at 10 µg/kg in food for 5–6 weeks (Kozul et al., 2009). In male mice exposed to arsenite at 0.1, 1.0 and 50 µg/l in drinking-water for 5 weeks, there was a decrease in expression of transcripts involved in the immune response (Andrew et al., 2007).

Oral administration of MMA^V to nestling finches at 4–72 mg/kg bw per day for 20 days resulted in no effects on immune function. No further studies were found

regarding immune function or immunological or lymphoreticular effects following oral exposure to organic arsenic. No histological alterations were observed in immunological tissues following exposure of rats and mice to high doses of DMA^V (7.8 and 94 mg/kg bw per day), MMA^V (67.1 and 72.4 mg/kg bw per day) or roxarsone (4 and 43 mg/kg bw per day) (ATSDR, 2007).

In addition, Singh et al. (2010) investigated the adverse health effects of inorganic arsenic administered in the diet as sodium arsenite at low (0.05 mg/kg) and high (5 mg/kg) doses in Swiss male albino mice, alone and in combination with jaggery (a natural sweetener made from sugarcane juice) feeding (250 mg/mouse), consecutively for 180 days. Arsenic treatment resulted in substantially reduced total antioxidant levels, inhibition of pro-inflammatory cytokine activity, induction of DNA single-strand breaks and necrotic and degenerative changes in bronchiolar epithelium with emphysema and thickening of alveolar septa in the lung, in a dose-dependent manner, compared with the groups treated with both arsenic and jaggery. The authors concluded that chronic exposure to arsenic induced dose-dependent toxicity via oxidative stress with immunotoxicity and pathomorphological lesions to the respiratory system and that jaggery feeding antagonized the arsenic-induced negative effects.

(b) Neurotoxicity

A number of studies in rats and mice have reported no symptoms of overt systemic toxicity from inorganic arsenic (ATSDR, 2007; EFSA, 2009), but more subtle neurobehavioural effects have been observed (Rodriguez, Jimenez-Capdeville & Giordano, 2003). In rats, the most consistent change in behaviour after high oral inorganic arsenic administration (10 and 20 mg/kg bw per day by gavage for 2–4 weeks) was a decrease in locomotor activity. Additionally, rats showed a delay in the execution of various task tests reflecting learning and memory after oral exposure to arsenic (Rodriguez et al., 2001, 2002). Effects on locomotor activity, grip strength and rota rod performance were also observed recently in rats exposed orally to arsenite at 20 mg/kg bw per day for 28 days (Yadav et al., 2009). Mice were exposed to arsenic trioxide at 1 and 4 mg/l in the drinking-water subchronically for 60 days, and significant dose-dependent neurobehavioural changes associated with memory (Morris Water Maze test) were observed. In addition, the critical gene expression profiles related to the Creb-dependent phase of cerebellar long-term depression were analysed by GeneChip and showed downregulated expression of Ca^{2+}/calmodulin-dependent protein kinase IV (*Camk4*). Finally, antioxidants such as taurine and vitamin C did not prevent the downregulation of *Camk4*, indicating that such downregulation may be via an oxidation-independent mechanism (Y. Wang et al., 2009). Additionally, rats exposed to inorganic arsenic in drinking-water at 68 mg/l for 3 months showed a significant decrease in their spatial memory, whereas neurons and endothelial cells presented pathological changes, and the gene expression of aspartate receptors in the hippocampus was downregulated. These effects were not seen at 2.72 or 13.6 mg/l (Luo et al., 2009).

In mice, inorganic arsenic in drinking-water (0.05–5 mg/l, 4 months) led to sex-dependent alterations in dopaminergic markers, spontaneous locomotor

activity and downregulation of the antioxidant capacity of the brain (Bardullas et al., 2009).

Dietary organoarsenicals, including AB and arsenocholine (AC), have not been associated with peripheral or central neurotoxicity. MMA^{V} did not result in clinical signs of neurotoxicity or brain lesions following chronic dietary exposure of rats at doses up to 70.4 mg/kg bw per day or of mice at doses up to 67.1 mg/kg bw per day (Arnold et al., 2003). A similar outcome for DMA^{V} was reported; no clinical signs or histological alterations were observed after chronic exposure to 7.6 or 42.6 mg/kg bw per day (Arnold et al., 2006). Hippocampal slices of young (14–21 days old) and adult (2–4 months old) rats were treated with MMA^{V} and MMA^{III}, and evoked synaptic field potentials from the Schaffer collateral–CA1 (the excitatory cornu ammoni, a specific anatomic area in the hippocampus) synapse were measured under control conditions and during and after 30 and 60 min of application of the arsenic compounds. MMA^{V} had no effect on the synapse functions either in slices from adult rats or in those from young rats, whereas MMA^{III} strongly depressed the synaptic transmission at concentrations of 50/25 µmol/l (adult/young rats) and long-term potentiation amplitudes at concentrations of 25/10 µmol/l (adult/young rats). In contrast, application of MMA^{III} at 1 µmol/l led to an enhancement of the long-term potentiation amplitude in young rats, which was interpreted as an enhancing effect on *N*-methyl-D-aspartate receptors and a lack of blocking effect on α-amino-3-hydroxy-5-methylisoxazole-4-propionate receptors. These impairments of the CA1 synapse were interpreted as being more likely caused by the action of methylarsonite on post-synaptic glutamatergic receptors and may be jointly responsible for dysfunctions of cognitive effects in arsenic toxicity (Krüger et al., 2009).

A recent study reported a link between disruption of the synthesis and assembly of myelin, an essential element for neural transmission, and a deficient production of methylated compounds in an in vivo model of prolonged arsenic exposure. Adult female Wistar rats exposed to arsenic (3 and 36 mg/l in drinking-water) from gestation throughout lactation and development until 1, 2, 3 and 4 months of age suffered myelin damage reflected as empty spaces in fibre tracts. The 3 mg/l (approximately 0.4 mg/kg bw per day) group did not present myelin damage during the first 2 months, with only moderate alterations in the third and fourth months. By contrast, animals exposed to 36 mg/l (approximately 4 mg/kg bw per day) showed moderate to severe damage to nerve tracts from the first month of age. The myelin alterations were followed by significantly lower levels of dimethyl arginine in the third and fourth months of age and exposure, compared with the controls, suggesting that myelin composition is a target of arsenic through interference with arginine methylation and that disturbances in nervous transmission through myelinated fibres are an important component of arsenic neurotoxicity (Zarazúa et al., 2010).

(c) Cardiovascular effects

Arsenate and arsenite have been shown to alter cardiovascular response in studies in rats and rabbits. Rats given arsenite or arsenate at 50 mg/l in drinking-water for 200 days showed an elevation in blood pressure up to day 80, with the

effects of arsenite being more marked than those of arsenate. The most common marker of hypertension, the angiotensin-converting enzyme (ACE), showed no significant change in either arsenic group, whereas cytochrome P450 4A (CYP4A) was highly expressed in both groups. The authors concluded that CYP4A might be more important than ACE in contributing to arsenic-induced hypertension (Yang et al., 2007; EFSA, 2009).

Sodium arsenite (50 µg/ml as arsenic) administered in drinking-water to rats (18 months) or rabbits (10 months) was associated with decreased cardiac stroke volume and output and increased vascular resistance (IPCS, 2001). Changes in blood cell counts, enzymes associated with haem synthesis and anaemia have been reported in a number of studies. The lowest arsenite doses (administered in drinking-water) associated with altered haemotocrit were 0.9 mg/kg bw per day in rats and 0.7 mg/kg bw per day in guinea-pigs (ATSDR, 2007).

Unlike inorganic arsenic, MMA^V and DMA^V have not been found to cause cardiovascular effects (ATSDR, 2007; EFSA, 2009).

(d) Nephrotoxicity

A short-term study in which Kunming mice were treated for 60 days with arsenic trioxide at 1, 2 or 4 mg/l in drinking-water showed pathological changes, such as cellular swelling, tubular dilatation and lymphocytic infiltration, as well as a significant increase in the level of 8-OHdG expression ($P < 0.01$) in the kidney tissues, suggesting that these changes may be related to arsenic-induced increases in oxidative stress (Li et al., 2010). A dose-dependent increase in renal damage and stronger immunoactivity of 8-OHdG were observed, mainly concentrated in the Bowman's capsule and renal tubules.

2.3 Observations in humans

2.3.1 Biomarkers of exposure

Biomarkers for assessing the exposure to arsenic from all sources are arsenic concentrations in urine, blood, hair and nails (Klaassen, 2001; Hughes, 2006). Perhaps the most commonly used biomarker is measurement of total arsenic in urine; ingested arsenic compounds are excreted with a short half-time of a few days (Buchet, Lauwerys & Roels, 1981; Vahter, 2002; Hughes, 2006). However, exposure to arsenic in fish or seafood commodities that contain organic arsenic in the form of AB has been observed to vastly increase the measurement of total arsenic in urine (Arbouine & Wilson, 1992; Buchet, Pauwels & Lauwerys, 1994; Heitland & Koster, 2008). Thus, measurement of total arsenic in urine may lead to an overestimation of exposure if ingestion of AB is not taken into account (Caldwell et al., 2009; Sirot et al., 2009a). Intake of certain seafood, such as mussels that contain DMA^V or seaweed containing arsenosugars, can also interfere with the interpretation of exposure when total arsenic is measured in urine (Hakala & Pyy, 1995; Ma & Le, 1998).

Urine samples may vary in dilution owing to differences in fluid intake; thus, urinary arsenic concentrations may be normalized to urinary specific gravity or, in some instances, to creatinine concentration (ACGIH, 2008; Nermell et al., 2008).

Because of the organic arsenic in fish, shellfish and seaweed and the need for determination of the level of inorganic arsenic in urine, specific measurements of inorganic arsenic and its methylated metabolites in urine are preferred (Buchet, Lauwerys & Roels, 1981; Farmer & Johnson, 1990; Hakala & Pyy, 1995; Verdon et al., 2009). High-throughput analytical methods developed for the population biomonitoring programme of the United States Centers for Disease Control and Prevention can provide determination of seven separate arsenic species in human urine: AB, AC, TMAO, arsenate, arsenite, MMA^{V} and DMA^{V} (Verdon et al., 2009). Together, arsenate and arsenite constitute excreted total inorganic arsenic, whereas MMA^{V} and DMA^{V} constitute total excreted methylated metabolites using standard analytical methods. Urinary concentrations of inorganic arsenic and methylated metabolites in the general population vary in different locations given differences in arsenic concentrations in primary foodstuffs and drinking-water, among other exposure sources. Inorganic arsenic and methylated metabolite concentrations in the urine of the general population are about 10 µg/l in European countries, approximately 9 µg/l in the USA (Caldwell et al., 2009) and up to 50 µg/l in Japan (Foa et al., 1984, 1987; Aizawa & Takata, 1990; Aitio, Hakala & Pyy, 1997; Klaassen, 2001). A reference value of 15 µg/l is reported for German children (Schulz et al., 2009).

AB, an organic arsenic compound not readily bioavailable, is excreted in urine following dietary exposure principally via ingestion of fish and seafood commodities. AB accounts for an increasing median percentage of total arsenic in urine as total arsenic in urine increases (Caldwell et al., 2009). For example, for urine samples with a total arsenic concentration below 20 µg/l, AB accounts for 16.2% of the total arsenic in the urine; for urine samples with a total arsenic concentration of 20–49 µg/l, AB accounts for 43.4% of the total; and for urine samples with a total arsenic concentration above 50 µg/l, AB accounts for 62.7% of the total.

A number of studies have indicated a roughly 1:1 ratio between the sum of the concentrations of inorganic arsenic, MMA and DMA in urine and the concentration of inorganic arsenic in drinking-water, where arsenic intake from water exceeds that from food (Hopenhayn-Rich et al., 1996; Calderon et al., 1999; Concha, Nermell & Vahter, 2006; Lindberg et al., 2006, 2008; Vahter et al., 2006). Accordingly, if drinking-water arsenic levels are low relative to those in food, the ratio of the sum of inorganic arsenic, MMA and DMA in urine to that in water may be greater than 1 (EFSA, 2009).

Following exposure, arsenic is cleared rapidly from the blood; for low and intermittent environmental or occupational exposures, arsenic blood concentration generally has not been considered a reliable indicator of exposure (NRC, 1999; ACGIH, 2008). In the instance of chronic high exposure to inorganic arsenic, however, it appears that arsenic in blood reaches a steady state and therefore may well reflect exposure in these circumstances (Hall et al., 2006, 2007).

Intake of arsenic compounds results in accumulation of arsenic in hair and nails due to binding to sulfhydryl groups in keratin; measurement of arsenic in hair and nails is considered a reasonable reflection of exposure over a period of the previous months (NRC, 1999; Hughes, 2006; ATSDR, 2007). Arsenic contamination of hair and nail samples due to adsorption from external sources is not distinguished from arsenic from internal sources using standard analytical methods (Hindmarsh, 2002; Hughes, 2006). More recent analytical work on hair has shown that arsenic from internal sources resides at the periphery of the strand (Nicolis et al., 2009). Hair can adsorb relatively more exogenous arsenic (Mandal, Ogra & Suzuki, 2003); therefore, nails are the preferred sample, although either can be contaminated from contact with exogenous sources, including water or soil. Significant correlations have been observed between exposure to arsenic in drinking-water and arsenic in hair (Kurttio et al., 1998) and toenails (Karagas et al., 2000; Slotnick et al., 2007; Slotnick, Meliker & Nriagu, 2008). A regression model that used total daily arsenic exposure from food and drinking-water explained the most variability in toenail arsenic concentrations ($R^2 = 0.71$) when the median daily arsenic dose was 1.0 µg/kg bw per day from food and 0.1 µg/kg bw per day from drinking-water (Kile et al., 2007a). Arsenic measured in toenails at 3- to 6-year intervals has been shown to yield a consistent correlation with arsenic in water, indicating stability of the measurement over time (Garland et al., 1993; Karagas et al., 2001a). Generally, the principal compound in hair and nails is inorganic arsenic; measurement of total arsenic in hair and nails is considered useful as a biomarker of exposure.

Toenail arsenic concentrations between 0.07 and 0.45 µg/g reflect arsenic water concentrations between 1 and 100 µg/l ($r = 0.65$, $P < 0.0001$); a toenail arsenic concentration of 0.326 µg/l approximates a concentration of 50 µg/l in water. The correlation of toenail arsenic with drinking-water arsenic at water concentrations above 1 µg/l is $r = 0.64$ (Karagas et al., 2000). Toenail arsenic concentrations were correlated with a food frequency questionnaire ($r = 0.33$, $P < 0.0001$), but not with published food content information (MacIntosh et al., 1997).

2.3.2 Biomarkers of effect

A number of biomarkers of effect have been reported; however, none are attributed specifically to arsenic. Urine proteomics have been applied to identify an increased level of human β-defensin-1 (HBD-1) in urine of highly exposed men (arsenic concentration in drinking-water >500 µg/l), but not women (Hegedus et al., 2008). HBD-1 was also 1 of 33 proteins identified in urine of eight patients with blackfoot disease typical of the high-arsenic areas of south-western Taiwan, China (Tan et al., 2008). It has been suggested that urine proteomics be further explored as a promising arsenic biomarker of effect (Navas-Acien & Guallar, 2008). Biomarkers of effect that include those for oxidative stress and damage related to arsenic exposure, such as urinary excretion of 8-OHdG, have been recently reviewed (De Vizcaya-Ruiz et al., 2009). Malondialdehyde levels in urine are increased in people who have been chronically exposed to arsenic and is thought to be a useful biomarker of effect (Wang et al., 2009a). Some additional nonspecific biomarkers of effect, such as high pulse pressure, increased carotid

artery intima-medial thickness, proteinuria, presence of transforming growth factor-alpha (TGFα) in urine and increased serum level of Clara cell protein, have been correlated with arsenic exposure and proposed as nonspecific biomarkers of chronic effect (Chen et al., 2010b).

2.3.3 Clinical observations

Signs and symptoms of acute illness may include anorexia, hepatomegaly, cardiac arrhythmia, respiratory tract symptoms, peripheral neuropathy and gastrointestinal, cardiovascular and haematopoietic effects (Klaassen, 2001). Other acute symptoms include muscular cramps, facial oedema and cardiac abnormalities. The fatal dose of ingested arsenic trioxide for humans ranged from 1 to 3 mg/kg bw (Vallee, Ulmer & Wacker, 1960).

Chronic exposure may lead to dose-related neurotoxicity, including sensory changes and paraesthesia, as well as progressive peripheral neuropathy. Clinical effects, including liver injury, peripheral vascular and cardiovascular effects, diabetes and cancer (see section 2.3.4), have been observed following chronic environmental or occupational exposure to various forms of arsenic. Arsenicosis is a term ascribed to a multisystem disorder, including skin manifestations, related to long-term chronic exposure to high concentrations of arsenic, principally in drinking-water (Ghosh et al., 2008; Sengupta, Das & Datta, 2008). Predominant clinical manifestations are related to cutaneous involvement, such as pigmentary changes, hyperkeratosis and skin cancers (Bowen disease, squamous cell carcinoma and basal cell epithelioma), as well as other clinical effects on the circulatory, neurological, haematological, respiratory and renal systems.

2.3.4 Epidemiological studies

(a) Cancer

(i) Skin cancer

The classification of arsenic as a carcinogen was originally based on evidence of skin cancers in patients treated with arsenic-containing solutions and in occupational settings (IARC, 1987). Subsequently, ecological studies in the blackfoot disease–endemic region of Taiwan, China, where high exposures to arsenic in drinking-water occurred, indicated a causal relationship with skin cancer alone (Tseng et al., 1968). These studies and others from the region confirmed the relationship (IARC, 2004). Studies at lower levels of arsenic exposure in drinking-water have been conducted in the USA and Denmark to examine increased risk for non-melanoma skin cancer (NMSC).

Skin cancer case–control studies

Analysis of NMSC data using alternative statistical approaches in a case–control study in New Hampshire, USA, indicated that for squamous cell carcinoma (SCC), a two-segment regression model identified a maximum likelihood change point of 0.105 µg of arsenic per gram of toenails (95% confidence interval [CI]

0.068–0.115), after which the increasing trend of 0.61% increase in risk of SCC associated with a 1% increase in toenail arsenic was statistically significant (Karagas, Stukel & Tosteson, 2002). For SCC, the 95% CI fell within the exposure range of the control group, and both the quadratic and two-segment models produced relatively consistent results. The change point for SCC was at arsenic concentrations corresponding to about 1–2 µg/l in water, with the 95% CI spanning from below 1 µg/l up to 10–20 µg/l. The two-segment regression analysis could not be estimated reliably for basal cell carcinoma (BCC). The authors pointed out that "change points" need to be interpreted with caution, as they rely on the appropriate model fit as well as statistical precision.

A case–control study in Iowa, USA, examined risk of melanoma skin cancer in relation to arsenic exposure and found a significantly increased trend for risk of melanoma with elevated toenail arsenic concentration, particularly among those with self-reported prior skin cancer diagnosis (Beane Freeman et al., 2004). A study limitation is that melanoma cases were compared with colon cancer controls.

Skin cancer cohort study

A prospective cohort study on the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort was conducted in Denmark using a geographic information system (GIS) to estimate individual exposure to arsenic in drinking-water, which ranged from 0.05 to 25.3 µg/l (mean 1.2 µg/l). After adjustment for enrolment area, no significant increase in NMSC was found.

Results of key studies are summarized in Table 3.

(ii) Bladder cancer

Significant associations between exposure to high levels of ingested arsenic in drinking-water and bladder cancer have been observed in ecological studies from Chile, Argentina and Taiwan, China, and case–control studies in Taiwan, China (IARC, 2004). A number of more recent bladder cancer studies of populations exposed to drinking-water arsenic concentrations at or below 100 µg/l have used total arsenic toenail concentration as an exposure biomarker, as it may integrate exposure from all routes and reflect exposure over a longer period than either blood or urinary levels of arsenic (see section 2.3.1).

Bladder cancer ecological study

An ecological study was conducted on all 44 counties in Idaho, USA, grouping counties into three categories of exposure based on groundwater arsenic measurements (Han et al., 2009). In total, 3530 bladder cancer cases (960 cases in 23 Low counties, defined as <2 µg/l in groundwater; 1895 cases in 16 Intermediate counties, defined as 2–10 µg/l; and 675 cases in 5 High counties, defined as >10 µg/l) were included in the study. After adjustment for race, sex, population density, smoking prevalence and body mass index, no relationship between arsenic level in groundwater and cancer incidence was shown.

Table 3. Epidemiological case–control studies on skin cancer in humans in relation to ingested inorganic arsenic exposure below 100 µg/l in drinking-water[a]

Design Study population Reference(s)	Outcome definition	Population size (*n*)	Arsenic exposure	Results		Additional information
Ecological study South-west Taiwan, China Tseng et al. (1968)	Skin cancer prevalence	40 421 (428 skin cancers)	Concentration in water (µg/l)	Prevalence rate (/1000)		Used in earlier risk assessments with extrapolation to lower levels of exposure
			<300	2.6		
			300–600	10.1		
			>600	21.4		
Case–control study New Hampshire, USA Karagas et al. (2001b); Karagas, Stukel & Tosteson (2002)	Histologically confirmed incident BCC and SCC	BCC/SCC/ controls	Concentration in toenail (µg/g)	OR (95% CI)		Maximum likelihood estimate of the point at which the dose–response began to increase for SCC by 0.61% with a 1% increase in toenail arsenic: 0.105 µg/g (95% CI = 0.093–0.219). In total, 587 BCC cases and 284 SCC cases
				BCC	SCC	
		281/155/263	0.009–0.089	1.00 (reference)	1.00 (reference)	
		156/64/136	0.090–0.133	1.01 (0.76–1.35)	0.93 (0.64–1.34)	
		92/33/73	0.134–0.211	1.06 (0.74–1.51)	0.98 (0.61–1.58)	
		22/14/26	0.212–0.280	0.72 (0.40–1.31)	1.10 (0.55–2.21)	
		10/5/11	0.281–0.344	0.75 (0.31–1.81)	1.00 (0.33–3.01)	
		26/13/15	0.345–0.81	1.44 (0.74–2.81)	2.07 (0.92–4.66)	
Case–control study Iowa, USA Beane Freeman et al. (2004)	Histologically confirmed incident melanoma of the skin	Cases/ controls	Concentration in toenail (µg/g)	OR (95% CI) (*P* for trend = 0.001)		Estimated 12% equal to or above 10 µg/l in the population, highest level 80 µg/l. Note: finding was regarded
		52/82	≤0.020	1.0		
		58/83	0.021–0.039	1.0 (0.6–1.6)		

Design Study population Reference(s)	Outcome definition	Population size (*n*)	Arsenic exposure	Results				Additional information
		95/82	0.04–0.083	1.7 (1.1–2.7)				as preliminary because controls were colon cancer cases. In total, 363 melanoma cases and 373 controls (colon cancer)
		121/82	≥0.084	2.1 (1.4–3.3)				
Cohort study Denmark Baastrup et al. (2008)	First NMSC	1010 NMSC cases, 147 melanomas, cohort size = 57 053		Adjusted analysis		Further adjustment for area of enrolment		GIS analysis based on "Diet, Cancer and Health" cohort, exposure range 0.05–25.3 µg/l (mean = 1.2 µg/l). No designation of histological type of NMSC; most could be BCC
			Time-weighted average exposure from water (µg/l)	NMSC	Melanoma	NMSC	Melanoma	
				P-value = 0.99	*P*-value = 0.80	*P*-value = 0.85	*P*-value = 0.14	
				0.88 (0.81–0.94)	0.89 (0.73–1.07)	0.99 (0.94–1.06)	0.80 (0.59–1.08)	
			Cumulative exposure (5 mg)	*P*-value = <0.0001	*P*-value = 0.35	*P*-value = 0.35	*P*-value = 0.32	
				0.95 (0.92–0.97)	0.80 (0.59–1.08)	0.99 (0.97–1.01)	0.96 (0.89–1.04)	

OR, odds ratio

[a] Excludes Knobeloch, Zierold & Anderson (2006) study of skin cancer (no histological type specified) based on self-report; excludes Guo et al. (2001) ecological study.

Source: Adapted from Table 33 in EFSA (2009).

Bladder cancer case–control studies

Case–control studies in Utah, USA (Bates, Smith & Cantor, 1995), showed a statistically significant trend for smokers for cumulative exposure to arsenic in water (arsenic concentrations 0.5–160 µg/l). In Finland (Kurttio et al., 1999), an increase was also seen in smokers with relatively short latency at drinking-water concentrations up to 64 µg/l.

Three case–control studies have found increased risk for bladder cancer principally in ever smokers at moderately high arsenic exposures. Steinmaus et al. (2003) showed excess bladder cancer risk for smokers with a 40-year lag period and a median arsenic exposure of 177 µg/day, but not for shorter lag times or for never smokers. Karagas et al. (2004) likewise found an elevated odds ratio (OR) for bladder cancer (OR 2.17, 95% CI 0.92–5.11) for toenail arsenic category above 0.330 µg/g compared with below 0.06 µg/g. Among never smokers, a significant association was not found. Bates et al. (2004) found no evidence of bladder cancer associations with exposure estimates based on arsenic concentrations in drinking-water; however, when well water consumption was used as the exposure measure, time window analyses suggested that use of well water with arsenic levels above 50 µg/l more than 50 years before the interview was associated with increased bladder cancer risk in ever smokers only (OR 2.5, 95% CI 1.1–5.5).

A case–control study of incident bladder cancer risk conducted in Finland in which toenail arsenic (0.02–17.5 µg/g) was used as a biomarker of exposure found no association between inorganic arsenic concentration and bladder cancer risk (OR 1.13, 95% CI 0.70–1.81, for the highest versus the lowest tertile) (Michaud et al., 2004).

Bladder cancer cases (n = 832) in a case–control study in which individual exposure to arsenic was determined in home drinking-water and toenail samples were evaluated for survival with a median duration of follow-up of 9.3 years (Kwong et al., 2010). Comparisons of survival time with various percentiles of arsenic exposure were conducted—for example, lowest quartile exposure (0.057 µg/g toenail or 0.11 µg/l drinking-water) versus highest quartile exposure (0.12 µg/g toenail or 0.74 µg/l drinking-water). Results showed that overall survival was significantly prolonged for the highest arsenic exposure group using either measure of exposure after adjustment for age, sex, smoking status, stage, grade and therapy.

Bladder cancer cohort studies

A cohort study of 8086 subjects conducted in north-eastern Taiwan, China, found a nonsignificant increase in relative risk (RR) for exposure between 10.1 and 50 µg/l in several multivariate-adjusted models with an approximately 5-year follow-up (Chiou et al., 2001). A subsequent study at 12 years of follow-up was conducted (Chen et al., 2010a). Forty-five incident urinary cancer cases were ascertained through linkage with a national cancer registry and showed a significant positive trend with increasing arsenic concentration in drinking-water. For exposures above 100 µg/l, the RR was increased 5-fold, whereas the risk was elevated but not significant for low exposure (<100 µg/l).

A cohort standardized mortality ratio (SMR) study conducted in Utah, USA, on 2203 deceased individuals found no excess risk for bladder cancer (drinking-water arsenic range 14–166 µg/l) in this predominantly Mormon population (Lewis et al., 1999). Exposure misclassification is a consideration, and the number of bladder cancer cases observed was small ($n = 5$).

A prospective cohort study of 57 053 persons was conducted using the Danish Cancer Registry to identify cancer cases, including bladder cancer cases (n = 214 cases) (Baastrup et al., 2008). Individual exposure to arsenic was estimated to range between 0.05 and 25.3 µg/l. No significant association was found between exposure to arsenic and risk for a number of cancers, including bladder cancer.

Literature reviews on arsenic and bladder cancer have been conducted by Cantor & Lubin (2007) and Mink et al. (2008). It is conjectured that inconsistencies in arsenic bladder cancer study results may be related to low statistical power to detect modest effects at lower levels of exposure, among other factors. In general, bladder cancer risks at lower levels of exposure (e.g. 100 µg/l) appear to be below predictions based on high-exposure studies from Taiwan, China, and other high-exposure areas (Steinmaus et al., 2003).

Results of key studies are summarized in Table 4. As shown in Table 4, six bladder cancer case–control studies evaluated RR for never smokers and ever smokers. Of those, two studies (Bates, Smith & Cantor, 1995; Kurttio et al., 1999) showed significantly increased RR for ever smokers with cumulative arsenic exposure. One study (Bates et al., 2004) showed significantly increased RR after 50 years of arsenic exposure in ever smokers only, and three studies (Steinmaus et al., 2003; Karagas et al., 2004; Michaud et al., 2004) found non-significant increases in trend for RR for ever smokers only. Chiou et al. (2001), Chen et al. (2010a) and Baastrup et al. (2008) reported RR adjusted for age, sex and smoking in multivariate models. Of those studies, only Chen et al. (2010a) reported a significant trend ($P < 0.0001$) for RR with increasing arsenic concentrations.

(iii) Lung cancer

Exposure to arsenic at high concentrations in drinking-water has been shown to be associated with lung cancer in studies from Japan, Chile, Argentina, the USA and Taiwan, China (IARC, 2004). There are fewer studies at drinking-water exposures at and below 100 µg/l.

Lung cancer ecological study

An ecological study was conducted on all 44 counties in Idaho, USA, in which counties were grouped into three categories of exposure based on groundwater arsenic measurements (Han et al., 2009). A total of 9291 lung and bronchus cancer cases (2471 cases in 23 Low counties, defined as <2 µg/l in groundwater; 4910 cases in 16 Intermediate counties, defined as 2–10 µg/l; and 1910 cases in 5 High counties, defined as >10 µg/l) were included in the study. After adjustment for race, sex, population density, smoking and body mass index, no relationship between arsenic level in groundwater and lung and bronchus cancer incidence was shown.

Table 4. Epidemiological studies on bladder cancer and arsenic exposure informing dose–response at arsenic levels below 100 µg/l in drinking-water[a]

Design Study population Reference(s)	Outcome definition	Population size (*n*)	Smoking status	Arsenic exposure	Results: OR/RR (95% CI)	Additional information
Case–control study Utah, USA Bates, Smith & Cantor (1995)	Histologically confirmed bladder cancer	Bladder cancer cases =177; controls = 266 Cases/controls		Cumulative exposure (mg)	All subjects	Range 0.5–160 µg/l; recorded daily total fluid intake in litres. Statistically significant trend observed for ever smokers with 10–19 years' exposure, but not for shorter or longer exposure or for any exposure period for never smokers
		14/47		<19	1.00	
		21/36		19–<33	1.56 (0.8–3.2)	
		17/39		33–<53	0.95 (0.4–2.0)	
		19/38		>53	1.41 (0.7–2.9)	
				(mg/l)-years, latency 10–19 years	All subjects	
		18/42		<33	1.00	
		16/42		33–<53	0.69 (0.3–1.5)	
		16/40		53–<74	0.54 (0.3–1.2)	
		21/36		≥74	1.00 (0.5–2.1)	
					10–19 years' exposure	
		9/23	Never smoked	<8	1.00	
		8/19		8–<10	0.99 (0.3–2.9)	
		6/20		10–<13	0.67 (0.2–2.2)	

Design Study population Reference(s)	Outcome definition	Population size (*n*)		Smoking status	Arsenic exposure	Results: OR/RR (95% CI)		Additional information
		6/17			≥13	0.79 (0.2–2.6)		
		8/21		Ever Smoked	<8	1.00		
		12/19			8–<10	1.36 (0.5–3.9)		
		12/19			10–<13	1.57 (0.5–4.5)		
		17/18			≥13	2.92 (1.1–8.0)		
						P for trend < 0.05		
Case–control study Finland Kurttio et al. (1999)	Bladder cancer	Cases			Concentration in water (μg/l)	Short latency	Long latency	Maximum = 64 μg/l, and 1% exceeded 10 μg/l
		Short latency	Long latency					
		23	26		<0.1	1.00	1.00	Bladder cancer cases = 61, controls = 275
		19	18		0.1–0.5	1.53 (0.75–3.09)	0.81 (0.41–1.63)	
		19	17		0.5–64	2.44 (1.11–5.37)	1.51 (0.67–3.38)	
					(log) continuous	1.37 (0.95–1.96)	0.96 (0.59–1.55)	
		Smoker	Never/ ex-smoker		Concentration in water (μg/l)	Smoker	Never/ex-smoker	
		8	8	See results	<0.1	1.00	1.00	
		3	4		0.1–0.5	1.10 (0.19–6.24)	0.95 (0.25–3.02)	
		7	5		0.5–64	10.3 (1.16–92.6)	0.87 (0.25–3.02)	

Design Study population Reference(s)	Outcome definition	Population size (*n*)		Smoking status	Arsenic exposure	Results: OR/RR (95% CI)		Additional information
Case–control study Nevada, California, USA Steinmaus et al. (2003)	Primary bladder cancer	5-year lag	40-year lag		Cumulative exposure from water (mg)	5-year lag	40-year lag	Bladder cancer cases = 181, controls = 238
		58/63	130/189	Ever smokers	<6.4	1.00	1.00	
		46/79	6/8		6.4–82.8	0.69 (0.40–1.18)	1.06 (0.34–3.33)	
		48/66	16/11		>82.8	0.76 (0.44–1.30)	2.25 (0.97–5.20)	
		8/38	23/92	Never Smokers	<6.4	1.00	1.00	
		11/32	3/5		6.4–82.8	1.55 (0.51–4.72)	2.65 (0.49–14.24)	
		10/49	3/22		>82.8	0.83 (0.28–2.49)	0.50 (0.12–2.05)	
Case–control study New Hampshire, USA Karagas et al. (2004)	Incident TCC (96%)	Never smoker	Ever smoker	See results	Toenail arsenic (µg/g)	Never smoker	Ever smoker	Maximum likelihood estimate change point of 0.326 µg/g (95% CI 0.121–0.446), which equates to approximately 50 µg/l, with a 1.1% increase in ORs for 1% increase in toenail arsenic concentration
		15/41	75/121		0.009–0.059	1.00	1.00	
		20/56	99/105		0.060–0.086	0.85 (0.38–1.91)	1.53 (1.02–2.29)	
		22/48	66/109		0.087–0.126	1.18 (0.53–2.66)	1.02 (0.66–1.56)	
		11/29	37/67		0.127–0.193	1.10 (0.42–2.90)	1.00 (0.60–1.67)	
		3/14	18/18		0.194–0.277	0.49 (0.12–2.05)	1.78 (0.86–3.67)	
		0/3	3/10		0.278–0.330	—	0.50 (0.1–1.88)	
		0/8	14/11		0.331–2.484	—	2.17 (0.92–5.11)	
		7/4			0.331–2.484, <15 years	3.09 (0.80–11.96)		

Design Study population Reference(s)	Outcome definition	Population size (*n*)		Smoking status	Arsenic exposure	Results: OR/RR (95% CI)		Additional information
		7/6			0.331–2.484, ≥15 years	1.86 (0.57–6.03)		above change point ($P = 0.10$) TCC cases = 383, controls = 641
Case–control study Argentina Bates et al. (2004)	Incident transitional bladder cell cancer cases	Never smoker	Ever smoker		Concentration in water (µg/l)	Never smoker	Ever smoker	Possible latency effects: statistically significant associations among smokers with more than 50 years of exposure: 51–60 years: OR = 2.65 (1.2–5.8) 61–70 years: OR = 2.54 (1.0–6.4) for well water use TCC cases = 114, controls = 114
		22/37	65/45		0–50	1.00	1.00	
		2/4	7/4		51–100	1.05 (0.2–6.9)	1.29 (0.3–5.0)	
		3/5	10/8		101–200	1.10 (0.2–6.3)	0.96 (0.3–3.0)	
		1/4	2/6		>200	0.58 (0.1–6.2)	0.17 (0.0–1.0)	

Design Study population Reference(s)	Outcome definition	Population size (*n*)			Smoking status	Arsenic exposure	Results: OR/RR (95% CI)			Additional information
Case–control study Finland Michaud et al. (2004)	All cases of bladder cancer as defined by the Finnish Cancer Registry	Years of smoking Cases				Concentration in toenail (μg/g)	Years of smoking			Male smokers aged 50–60, range 0.02–17.5 μg/g Choice of the concentration intervals was based on tertiles or quartiles Total bladder cancer cases = 280, controls = 280
		≤35	36–45	>45			≤35	36–45	>45	
		16	57	11		0.017–0.070	1.0	1.0	1.0	
		21	50	18		0.071–0.137	1.14 (0.45–2.93)	0.90 (0.53–1.53)	1.46 (0.52–4.13)	
		30	60	17		>0.137	1.30 (0.55–3.06)	1.16 (0.69–1.95)	2.30 (0.77–6.88)	
		65/74				<0.050	1.0			
		71/73				0.050–0.105	1.09 (0.68–1.74)			
		73/73				0.106–0.161	1.13 (0.71–1.80)			
		71/73				>0.161	1.13 (0.70–1.81)			
							P trend = 0.65			
Cohort study North-east Taiwan, China Chiou et al. (2001); Chen et al. (2010a)	Area endemic for arseniasis	Number of cases/person-years of observation				Concentration in well water (μg/l)	All urinary cancers			Chen et al. (2010a) is a follow-up study to Chiou et al. (2001). Adjusted for age, sex,
		5/26 609				<10.0	1.0			
		8/24 247				10–49.9	1.66 (0.53–5.21)			

Design Study population Reference(s)	Outcome definition	Population size (*n*)	Smoking status	Arsenic exposure	Results: OR/RR (95% CI)		Additional information
		5/10 359		50–99.9	2.42 (0.69–8.54)		smoking and duration of drinking well water. Duration of the study: 12-year follow-up Sample size: 8086 (*n* = 45 urinary cancers, *n* = 8 urothelial cancers)
		8/10 416		100.0–299.9	4.15 (1.32–12.91)		
		11/7799		≥300	7.80 (2.64–23.1) *P* for trend < 0.001		
				Concentration in well water (µg/l)	Urothelial carcinoma		
		2/26 609		<10.0	1.0		
		2/24 247		10.1–49.9	1.54 (0.20–12.0)		
		2/10 359		50.1–99.9	3.44 (0.45–26.5)		
1/10 416			100.0–299.9	1.69 (0.14–20.0)			
1/7799			≥300	2.40 (0.20–28.4) *P* for trend = 0.504			
Cohort study Denmark Baastrup et al. (2008)	First bladder cancer	214 bladder cancer cases out of total sample size of 57 053			IRR (95% CI)		GIS analysis based on "Diet, Cancer and Health" cohort of 57 053, exposure range 0.05–25.3 µg/l (mean = 1.2 µg/l)
				Time-weighted average exposure (µg/l)	Adjusted analysis	Further adjustment for area of enrolment	
					P-value = 0.75	*P*-value = 0.93	
					1.01 (0.93–1.11)	1.00 (0.91–1.11)	

Design Study population Reference(s)	Outcome definition	Population size (*n*)	Smoking status	Arsenic exposure	Results: OR/RR (95% CI)		Additional information
				Cumulative exposure	*P*-value = 0.55 1.0 (0.98–1.04)	*P*-value = 0.69 1.01 (0.98–1.04)	

IRR, incidence rate ratio; TCC, transitional cell carcinoma
[a] Excludes Lewis et al. (1999), Han et al. (2009) and Kwong et al. (2010).
Source: Adapted from Table 34 in EFSA (2009).

Lung cancer case–control studies

A hospital-based case–control study in Chile found evidence of a significant exposure-related increase in lung cancer with an OR of 3.9 (95% CI 1.2–12.3) beginning at an average arsenic water concentration of 30–49 µg/l (Ferreccio et al., 2000). There was evidence of synergy between cigarette smoking and ingestion of arsenic in drinking-water. Potential control selection bias in this study is a limitation due to complex recruitment of hospital-based control groups in which the target distribution of control groups between hospitals was not achieved. Controls for the highest exposure category (<400 µg/l) were overrepresented, leading to underestimation of ORs, whereas for the 100–300 µg/l exposure category, controls were markedly underrepresented, leading to bias towards overestimation of ORs. The authors stated that it is possible that some underascertainment of cases would have occurred in the same cities in which controls were underselected. Because of the above issues and the availability of a more recent study with a prospective cohort study design (Chen et al., 2010b), the above case–control study was not selected as a pivotal study upon which to model lung cancer risk.

In a case–control study, newly diagnosed lung cancer cases among 2503 residents in south-western Taiwan, China, and 8088 in north-eastern areas in Taiwan, China, were followed up for an average of 8 years (C.L. Chen et al., 2004). A significant trend for increased lung cancer risk was observed, with a synergistic effect of ingested arsenic and cigarette smoking on lung cancer.

Arsenic exposure was estimated by average concentrations for each of 64 districts in a clinic-based case–control study conducted in Bangladesh (Mostafa, McDonald & Cherry, 2008). ORs were increased with mean arsenic concentration, but were significant only for exposures to arsenic above 100 µg/l for both male and female smokers; no significant trends for lung cancer risk with arsenic exposure were seen in non-smokers. A study limitation was selection of patients with suspicious lung lesions on chest X-ray as controls.

A case–control study using toenail arsenic as a biomarker of exposure conducted in the USA found evidence of an exposure-related risk of small cell carcinoma and SCC of the lung for toenail arsenic concentrations of and above 0.114 µg/g compared with below 0.05 µg/g (OR 2.75, 95% CI 1.00–7.57) and for individuals with chronic lung disease, but no association for lung cancers overall (Heck et al., 2009). Toenail arsenic concentration was positively associated with number of fish servings per week.

Lung cancer cohort studies

An SMR cohort study conducted in Utah, USA, on 2203 deceased individuals found no excess risk for respiratory tract cancer (drinking-water arsenic concentration range 14–166 µg/l) in this predominantly Mormon population (Lewis et al., 1999); 34 respiratory tract cancer cases were observed.

A prospective cohort study of 57 053 persons was conducted in Denmark to identify cancer cases, including primary lung cancer cases (n = 402 cases) (Baastrup et al., 2008). Individual exposure to arsenic was estimated to range

between 0.05 and 25.3 µg/l. No significant association was found between exposure to arsenic and risk for a number of cancers, including lung cancer.

A prospective cohort study of 6888 residents (n = 178 incident lung cancer cases) with 11 years of follow-up in north-eastern Taiwan, China, showed a significant exposure–response trend of lung cancer risk at 100–300 µg/l (RR 1.54, 95% CI 0.97–2.46), but not between 10 and 100 µg/l (Chen et al., 2010b). In total, 3901 water samples were collected for arsenic analysis from individual wells (85.1% of 4586 households) during the personal home interview. A synergistic effect between cigarette smoking was observed for squamous and small cell lung carcinomas, but not for adenocarcinomas.

Results of key studies are summarized in Table 5. Four lung cancer studies considered the effect of smoking in combination with that of arsenic exposure via drinking-water (Ferreccio et al., 2000; C.L. Chen et al., 2004, 2010b; Mostafa, McDonald & Cherry, 2008). Studies by Ferreccio et al. (2000) and Mostafa, McDonald & Cherry (2008) were of case–control design, whereas those by C.L. Chen et al. (2004, 2010b) were cohort studies. In general, exposed smokers exhibited higher risk for lung cancer than never smokers.

(iv) Other cancers

Cancers at other sites implicated in exposure to arsenic, which include prostate, liver and kidney, have fewer studies and less conclusive results (IARC, 2004). An excess of prostate cancer was found in a study in Utah, USA (SMR 1.5, 95% CI 1.7–1.9) (Lewis et al., 1999); however, no excess of prostate cancer was seen in another study in Australia (Hinwood, Jolley & Sim, 1999). A recent study conducted in Chile found an approximately 25-year latency pattern for kidney cancer mortality following a 13-year period of high exposure (>850 µg/l) in drinking-water (Yuan et al., 2010). A recent IARC assessment found the evidence “limited” for cancers of the kidney, liver and prostate (Straif et al., 2009; IARC, in press).

(b) Effects other than cancer

(i) Skin lesions

Epidemiological studies in different regions of the world have consistently demonstrated a strong association between long-term inorganic arsenic ingestion and skin lesions, typically in the form of hyperkeratosis, hyperpigmentation or hypopigmentation. These studies have been extensively reviewed by NRC (2001) and ATSDR (2007). More recently, human studies relating to low-level inorganic arsenic exposure (<100 µg/l in drinking-water) have been reported, and the European Food Safety Authority (EFSA) has summarized them in its scientific opinion (Section 8.3.3.2 and Table 36 of EFSA, 2009). The observations of skin lesions following low-level exposure have suggested that these characteristic dermal changes are sensitive indications of the toxic effects of inorganic arsenic.

Table 5. Epidemiological studies on lung cancer in humans in relation to ingested inorganic arsenic exposure[a]

Design Study population Reference	Outcome definition	Population size (*n*)	Smoking status	Arsenic exposure	Results	Additional information
Case–control study Chile Ferreccio et al. (2000)	Lung cancer	Cases = 151, controls = 419		Average concentration in water 1930–1994 (µg/l)	OR age and sex adjusted	Potential control selection bias. Hospital-based study; two control groups: i) excludes cancers of liver, skin, kidney, bladder or prostate; ii) shared control group for bladder cancer study; excludes cardiovascular disease, skin and neurological diseases
			Total	0–10	1.00	
				10–29	1.6 (0.5–5.3)	
				30–49	3.9 (1.2–12.3)	
				50–199	5.2 (2.3–11.7)	
				200–400	8.9 (4.0–19.6)	
				Peak years average concentration in water 1958–1970 (µg/l)	OR age and sex adjusted	
				0–10	1.00	
				10–29	0.3 (0.1–1.2)	
				30–59	1.8 (0.5–6.9)	
				60–89	4.1 (1.8–9.6)	
				90–199	2.7 (1.0–7.1)	
				200–399	4.7 (2.0–11.0)	
				400–699	5.7 (1.9–16.9)	
				700–999	7.1 (3.4–14.8)	

Design Study population Reference	Outcome definition	Population size (*n*)	Smoking status	Arsenic exposure	Results	Additional information
				Average concentration in water 1930–1994 (μg/l)	OR age and sex adjusted	
			Never smoked	≤49	1.00	
				50–199	5.9 (1.2–40.2)	
				≥200	8.0 (1.7–52.3)	
			Ever smoked	≤49	6.1 (1.31–39.2)	
				50–199	18.6 (4.13–116.4)	
				≥200	32.0 (7.22–198.0)	
Case–control study Taiwan, China C.L. Chen et al. (2004)	Newly diagnosed lung cancer	2503 in south-west, 8088 in north-east (*n* = 139 lung cancer cases)		Average concentration in well water (μg/l)	Multivariate-adjusted RR (95% CI)	
			Overall	<10	1.00	
				10–99	1.09 (0.63–1.91)	
				100–299	2.28 (1.22–4.27)	
				300–699	3.03 (1.62–5.69)	
				≥700	3.29 (1.60–6.78)	
				Unknown	1.10 (0.60–2.03)	
			Non-smoker	<10	1.00	
				10–699	1.24 (0.53–2.91)	

Design Study population Reference	Outcome definition	Population size (*n*)	Smoking status	Arsenic exposure	Results	Additional information
				≥700	2.21 (0.71–6.86)	
			<25 pack-years[b]	<10	2.55 (0.68–9.52)	
				10–699	5.50 (1.96–15.5)	
				≥700	6.28 (1.53–25.7)	
			≥25 pack-years	<10	3.80 (1.29–11.2)	
				10–699	5.93 (2.19–16.1)	
				≥700	11.10 (3.32–37.2)	
Case–control study Bangladesh Mostafa, McDonald & Cherry (2008)	Primary lung cancer	Cases = 3223, controls = 1588		Average concentration in well water (µg/l)	OR	Clinic-based study; people drank from tube wells and lived in a village for 10 years; controls = patients referred for lung cytology and found not to have cancer
			Overall	0–10	1.00	
				>100	Men (all): 1.45 (1.16–1.80)	
					Women (smokers): 2.64 (0.65–10.73)	
			Non-smoker	0–≤10	1.00	No significant trends in non-smokers
				11–≤50	0.90 (0.62–1.33)	
				51–≤100	1.10 (0.62–1.96)	
				101–400	0.94 (0.62–1.41)	
			Smoker	0–≤10	1.00	

Design Study population Reference	Outcome definition	Population size (*n*)	Smoking status	Arsenic exposure	Results	Additional information
				11 –≤50	1.25 (0.96–1.62)	
				51–≤100	1.37 (0.92–2.03)	
				101–400	1.65 (1.25–2.18)	
Case–control study USA		Cases/controls		Average concentration in toenail (μg/g)	OR (95% CI)	
Heck et al. (2009)	All lung cancer	65/69		<0.05	1.00	
		58/66		0.05–<0.0768	1.34 (0.71–2.53)	
		58/44		0.0768–<0.1137	1.10 (0.55–2.20	
		58/44		≥0.1137	0.89 (0.46–1.75)	
	Small cell and squamous cell	65/17		<0.05	1.00	
		58/24		0.05–<0.0768	2.99 (1.12–7.99)	
		58/13		0.0768–<0.1137	1.86 (0.62–5.58)	
		57/21		≥0.1137	2.75 (1.00–7.57)	
	Lung disease:					
	No	52/57		<0.05	1.00	
		121/164		≥0.05	1.02 (0.62–1.69)	
	Yes	17/8		<0.05	1.31 (0.45–3.84)	
		33/9		≥0.05	4.78 (1.87–12.2)	

Design Study population Reference	Outcome definition	Population size (*n*)	Smoking status	Arsenic exposure	Results		Additional information
Cohort study Millard County, Utah, USA Lewis et al. (1999)	Respiratory tract cancer mortality	28 cases in men, 6 cases in women		Concentration in water, (μg/l)-years	SMR Women	Men	Mormon population abstains from smoking; median drinking-water concentration of towns ranged from 14 to 166 μg/l
				<1000	0.44	0.32	
				1000–4999	0.66	0.96	
				>5000	0.22	0.44	
Cohort study Denmark Baastrup et al. (2008)	Primary lung cancer	402 cases out of total sample size of 57 053			0.99 (0.92–1.07)		See notes on bladder cancer table (Table 4)
Cohort study North-eastern Taiwan, China Chen et al. (2010b)	Incident lung cancer (11-year follow-up)	6888 (*n* = 178 lung cancer cases)		Average concentration in well water (μg/l)	Multivariate-adjusted RR (95% CI)		No apparent increase in lung cancer risk observed between 10 and 100 μg/l Increased risk for squamous cell and small cell carcinoma lung cancer (but not adenocarcinoma) between 100 and 300 μg/l (RR 2.25, 95% CI 1.43–3.53) Individual well water arsenic
			Overall	<10	1.00		
				10–49.9	1.10 (0.74–1.63)		
				50–99.9	0.99 (0.59–1.68)		
				100–299.9	1.54 (0.97–2.46)		
				≥300	2.25 (1.43–3.55)		
			Non-smoker	<10	1.00		
				10–99.9	1.22 (0.64–2.32)		
				≥100	1.32 (0.64–2.74)		

Design Study population Reference	Outcome definition	Population size (*n*)	Smoking status	Arsenic exposure	Results	Additional information
			<25 pack-years	<10	2.14 (0.79–5.79)	concentrations measured
				10–99.9	1.52 (0.56–4.15)	Personal interview included smoking history and information to estimate latency, recency and cumulative arsenic exposure
				≥100	5.30 (2.19–12.8)	
			≥25 pack-years	<10	4.08 (1.83–9.10)	
				10–99.9	4.19 (1.92–5.14)	
				≥100	8.17 (3.74–17.9)	

[a] Excludes Han et al. (2009) ecological study.
[b] Packs per day × duration.
Source: Adapted from Table 35 in EFSA (2009).

In most epidemiological studies, the prevalence or odds ratio of skin lesions was associated with inorganic arsenic exposure in a dose-dependent manner. In three large-scale drinking-water studies conducted in Bangladesh (Ahsan et al., 2006; Rahman et al., 2006) and India (Guha Mazumder et al., 1998), males seemed to be more sensitive than females to inorganic arsenic–related skin lesions. Recent findings from the Health Effects of Arsenic Longitudinal Study in Bangladesh suggested that smoking, body mass index and the nutritional status of folate and selenium could influence the susceptibility to inorganic arsenic–induced skin lesions (Chen et al., 2009). Metabolism may also play a role in the dermal effects of arsenic. Elevated fractions of excreted monomethylarsenic species (MMA^{III} + MMA^{V}) and the concentration of urinary MMA^{III} have been linked to a higher risk of arsenic-related skin lesions (EFSA, 2009). Genetic polymorphism of arsenic metabolic enzymes, such as GST-1 and methylenetetrahydrofolate reductase (Ahsan et al., 2007), as well as arsenic (As^{III}) methyltransferase (Valenzuela et al., 2009), may contribute to individual variations in arsenic metabolic capacity. Epidemiological studies with larger sample size are needed to confirm the effects of the above-mentioned risk-modifying factors.

Table 6 summarizes selective large-scale epidemiological studies relating low-level drinking-water arsenic exposure to skin lesions. Ecological studies and studies with small sample sizes are not listed. A more complete study list can be found in the EFSA opinion (Table 36 of EFSA, 2009). The studies of Rahman et al. (2006) and Ahsan et al. (2006) include low-level inorganic arsenic exposure and also analysed the risk of skin lesions in males and females separately. They provide useful dose–response information that the Committee considered as a possible basis for a reference point.

Guha Mazumder et al. (1998) conducted a cross-sectional study in West Bengal, India, in which keratosis and hyperpigmentation were analysed separately. Water arsenic level was strongly related to the age-adjusted prevalence of both types of skin lesion. Calculation by dose per body weight showed that men had roughly 2–3 times the prevalence of both keratosis and hyperpigmentation compared with women ingesting the same dose of arsenic. However, the questionable disease diagnosis and the possibility of other sources of arsenic exposure have limited the validity of this study.

Rahman et al. (2006) reported a case–control study conducted in Matlab, Bangladesh, to study the dose–response relationship between skin lesions and inorganic arsenic level in drinking-water. Among residents aged 4 years and older, 504 cases were identified, and 1830 randomly selected controls were recruited. Inorganic arsenic exposure, represented by the level in drinking-water (μg/l) and cumulative arsenic exposure (μg/l × years), was measured for each participant. The OR for skin lesions, both in males and in females, increased along with arsenic exposure, with a trend of $P < 0.0001$.

Table 6. Selective large-scale cross-sectional and case–control studies relating low-level drinking-water arsenic exposure to skin lesions

Design Study population Reference	Population size (*n*)		Arsenic exposure (total arsenic in well water, µg/l)	Results (OR* or % case prevalence**)				Additional information
Cross-sectional study West Bengal, India Guha Mazumder et al. (1998)	Keratosis F: 48/4093 (cases/total) M:108/3590 (cases/total)	Hyperpigmentation F: 127/4093 (cases/total) M: 234/3590 (cases/total)		Keratosis		Hyperpigmentation		A combination of high-exposure and reference exposure areas Possible misdiagnosis of cases (EFSA, 2009)
				F	M	F	M	
			<50	0**	0.2**	0.3**	0.4**	
			50–99	0.4	1.5	0.8	3.2	
			100–149	1.2	1.6	5.7	11.0	
			150–199	2.3	4.7	5.1	7.8	
			200–349	2.0	4.9	6.5	13.1	
			350–499	2.7	9.0	9.5	15.7	
			500–799	3.1	8.9	5.3	13.8	
			>800	8.3	10.7	11.5	22.7	
Case–control study Matlab, Bangladesh Rahman et al. (2006)	F: 272/833 (cases/controls) M: 232/997 (cases/controls)			F		M		High-arsenic exposure area The controls were randomly selected from the same study area
			<10	Ref*		Ref*		
			10–49	1.66		3.25		
			50–149	3.06		2.28		
			150–299	4.08		5.41		
			>300	6.88		9.56		

Table 6 (contd)

Design Study population Reference	Population size (*n*)	Arsenic exposure (total arsenic in well water, µg/l)	Results (OR* or % case prevalence**)		Additional information
Cross-sectional study Araihazar, Bangladesh Ahsan et al. (2006)	F: 130/6562 (cases/total) M: 584/4876 (cases/total)	(Time-weighted) 0.1–8.0 8.1–40.0 40.1–91.0 91.1–175.0 175.1–864.0	F Ref* 1.59 2.82 2.53 4.81	M 3.61 6.88 11.30 14.04 19.04	Area of a full range of exposure
Cross-sectional study Inner Mongolia, China Xia et al. (2009)	622/11 416 (cases/total)	0–5 5.1–10 10.1–20 20.1–50 50.1–100 100.1–300 >300	Ref* 2.52 2.83 3.94 6.03 8.83 7.94		Low to moderate arsenic exposure area Did not analyse males and females separately

F, female; M, male; Ref, reference population

Ahsan et al. (2006) reported the dose–response effect of arsenic on the risk of skin lesions from a cross-sectional study conducted in Araihazar, Bangladesh. From a population exposed to the full dose range of inorganic arsenic (0.1–864 µg/l), 11 746 participants were interviewed and examined individually for skin lesions. Exposure was estimated for each participant based on well water arsenic concentration, cumulative exposure and urinary arsenic concentration. Consistent dose–response effects were observed for all three arsenic exposure measures. Compared with drinking-water containing less than 8.1 µg/l of arsenic, drinking-water containing inorganic arsenic concentrations of 8.1–40.0, 40.1–91.0, 91.1–175.0 and 175.1–864.0 µg/l was associated with adjusted prevalence ORs of skin lesions of 1.91, 3.03, 3.71 and 5.39, respectively. Males were found to be more susceptible than females to inorganic arsenic–related skin lesions.

Xia et al. (2009) recently reported a United States Environmental Protection Agency (USEPA)–supported cross-sectional study in Inner Mongolia, China. Drinking-water seemed to be the only significant source of exposure to inorganic arsenic in this area (Heng et al., 1999). With a low inorganic arsenic concentration in well water (mean 37.9 µg/l; median 21.0 µg/l), 5% of the 12 334 residents surveyed had skin lesions characteristic of arsenic exposure. Skin lesions were strongly associated with well water arsenic level. Compared with the reference population, which consumed drinking-water with an arsenic level below 5 µg/l, there was an elevated prevalence among those with exposures to drinking-water with arsenic concentrations as low as 5–10 µg/l. In this study, the risks in males and females were not analysed separately.

(ii) Developmental effects

Effects of arsenic on fetal development

The information contained in this summary relies heavily on the 2009 EFSA evaluation, as there were no new studies reported in the open literature since the EFSA report (EFSA, 2009).

In spite of the prevalence of inorganic arsenic exposure, there are only a few studies on fetal development in relation to inorganic arsenic exposure reported in the scientific literature. Epidemiological studies suggest that there is an association between pregnant women's exposure to elevated arsenic concentrations in drinking-water and increased risk of spontaneous abortion, stillbirth, preterm birth, neonatal death, birth defects and fetal loss (Hopenhayn-Rich et al., 2000; Ahmad et al., 2001; Milton et al., 2005; Kwok, Kaufmann & Jakariya, 2006; von Ehrenstein et al., 2006; Rahman et al., 2007). Studies in Chile and Taiwan, China, showed that infants born to women who drank water with elevated inorganic arsenic concentrations during pregnancy had significant reduction in birth weights (Hopenhayn et al., 2003; Yang et al., 2003; Huyck et al., 2007).

A recent longitudinal study by Rahman et al. (2009) showed a significant negative association between birth weight or head and chest circumferences and urinary arsenic concentrations in the low exposure range (<100 µg/l in urine), where birth weight decreased by 1.7 g for each microgram per litre of maternal urinary

arsenic concentration. However, in a study carried out in Mongolia for which inorganic arsenic levels in maternal drinking-water of up to 100 µg/l were measured, no adverse birth outcomes or significant increases in neonatal death rate were observed (Myers et al., 2010).

Effects of arsenic on child health and development

Prenatal and post-weaning exposure of infants to inorganic arsenic may affect child health and development and result in infant mortality as a result of its effects on fetal growth and immune function. Cohort studies found that infants born to mothers who consumed drinking-water with arsenic concentrations of 164–275 µg/l during pregnancy had significantly increased mortality during the first year of life; the dose–response relationship indicated that the increased risk of infant mortality started at arsenic concentrations of about 50 µg/l in water. The increase in infant mortality may be attributable to arsenic-related mechanisms, such as growth retardation and impaired immune function (Soto-Pena et al., 2006; Ferrario et al., 2008; Raqib et al., 2009).

Recent cross-sectional studies conducted in Bangladesh (Wasserman et al., 2004, 2007) and India (von Ehrenstein et al., 2007) reported links between inorganic arsenic exposure through drinking-water and neurobehavioural deficits in schoolchildren, although the studies did not include many children and held little information on exposure early in life. In another cross-sectional study, chronic exposure to arsenic and lead was found to be associated with impaired neuropsychological development in children living in the vicinity of a smelter in Mexico, compared with children living in an area with lower, although still elevated, arsenic exposure, but similar lead exposure (Calderon et al., 2001). In a similar study conducted in Taiwan, China, Tsai et al. (2003) observed impaired development of cognitive function among adolescents due to long-term inorganic arsenic exposure.

The evidence for a link between inorganic arsenic and neurobehavioural deficits in schoolchildren, provided by the current studies, and the notion that arsenic is a developmental neurotoxicant is bolstered by the earlier evidence of severe clinical effects caused by inorganic arsenic contamination, at concentrations of 4–7 mg/l, of milk powder used for preparation of infant formula in Japan in 1955. Follow-up of the children exposed to contaminated milk powder revealed neurological diseases, neurobehavioural dysfunction and decreased cognitive skills (Yamashita et al., 1972; Dakeishi, Murata & Grandjean, 2006; Grandjean & Murata, 2007). However, a longitudinal study conducted in Bangladesh reported that problem-solving ability and motor development were not related to prenatal inorganic arsenic exposure (Tofail et al., 2009).

Taken together, these studies provide some evidence for neurobehavioural effects of inorganic arsenic exposure during childhood, at exposure levels occurring in areas with elevated concentrations in drinking-water. More longitudinal studies are warranted to evaluate the most critical windows of exposure, the type of effects and dose–response relationships.

(iii) Cardiovascular disease

The cardiovascular effects following non-therapeutic oral exposure to inorganic arsenic have been investigated in a large number of studies. As reviewed by Navas-Acien et al. (2005) and EFSA (2009), the cardiovascular outcomes from chronic drinking-water exposure include blackfoot disease, increased mortality or prevalence of coronary heart disease, peripheral arterial disease, myocardial infarction and stroke. Recent studies have begun to investigate other cardiovascular end-points, such as blood pressure and the duration of the electrocardiogram QT interval.

Although the association between blackfoot disease and inorganic arsenic exposure has been confirmed by many studies, blackfoot disease is reported only in an area along the south-western coast of Taiwan, China, where arsenic contamination in well water is very high (170–880 µg/l) (NRC, 2001).

Among studies based on disease mortality or prevalence, many were conducted in the blackfoot disease–endemic area in Taiwan, China, and unanimously showed a positive association between cardiovascular end-points and inorganic arsenic exposure. Y. Yuan et al. (2007) reported on a study conducted in Chile, which showed that young adult men aged 30–49 years had the highest risk for acute myocardial infarction. These men were born during the high-exposure (~700 µg/l) period, with probable exposure in utero and in early childhood. From a population-based cohort study conducted in Bangladesh, Sohel et al. (2009) reported that the mortality rate of cardiovascular disease was associated with inorganic arsenic level in drinking-water in a dose-dependent manner ($P < 0.001$). Compared with the reference population, which was exposed to drinking-water with an average inorganic arsenic level below 10 µg/l, those exposed to inorganic arsenic levels of 10–49, 50–149, 150–299 and 300+ µg/l had an adjusted hazard ratio of 1.03 (95% CI 0.82–1.29), 1.16 (95% CI 0.96–1.40), 1.23 (95% CI 1.01–1.51) and 1.37 (95% CI 1.07–1.77), respectively. Although this study provided dose–response information at low-level exposure, the definition of cardiovascular disease was not specified, making it difficult to compare with other studies. Studies conducted in the USA (reviewed by Navas-Acien et al., 2005; EFSA, 2009) and Spain (Medrano et al., 2010) also included populations with low-level arsenic exposures. However, they all reported no or weak associations. Owing to the inconsistent results and unstandardized outcome definitions among different studies, the relationships between inorganic arsenic exposure and cardiovascular prevalence and mortality are not very convincing.

Recently, there have been a number of studies investigating the relationship between arsenic exposure and cardiovascular end-points such as blood pressure. In a cross-sectional study conducted in Bangladesh, baseline blood pressure of 10 910 participants was used to derive an association with the time-weighted well water arsenic concentration. The authors found that inorganic arsenic exposure was positively associated with systolic hypertension and high pulse pressure, and the associations were more pronounced among participants with lower intake levels of folate and the B vitamins. No apparent association was observed between inorganic arsenic exposure and general hypertension (Chen et al., 2007). A dose-dependent

association between inorganic arsenic exposure and systolic blood pressure was also reported in another cross-sectional study with 8790 women of reproductive age in Inner Mongolia, China (Kwok et al., 2007). Compared with the reference population (inorganic arsenic exposure <20 µg/l), the adjusted population mean systolic blood pressure rose 1.88 (95% CI 1.03–2.73) mmHg (0.25 [95% CI 0.14–0.36] kPa), 3.90 (95% CI 2.52–5.29) mmHg (0.52 [95% CI 0.36–0.71] kPa) and 6.83 (95% CI 5.39–8.27) mmHg (0.91 [95% CI 0.72–1.1] kPa) as the drinking-water arsenic concentration increased from 21–50 µg/l to 51–100 µg/l to greater than 100 µg/l, respectively.

There are four population-based studies using the end-point of the duration of corrected QT interval (QT_c) from individual electrocardiograms. They all reported a positive association between high inorganic arsenic exposure and a prolonged QT_c (Ahmad et al., 2006; Mumford et al., 2007; Yildiz et al., 2008; C.H. Wang et al., 2009). However, the data at low levels of exposure are limited for a dose–response evaluation.

(iv) Neurotoxicity

The information contained in this summary relies heavily on the 2009 EFSA evaluation, as there were no new studies reported in the open literature since the EFSA report (EFSA, 2009).

Effects of arsenic on the peripheral nervous system

Exposure to arsenic may affect both the central and peripheral nervous systems, but the most frequent neurological manifestation of inorganic arsenic is peripheral neuropathy. Acute exposure of humans to inorganic arsenic is commonly associated with peripheral neuropathy with both axonopathy and demyelination. Chronic exposure to inorganic arsenic compounds may lead to peripheral and central neurotoxicity. Early events may include paraesthesia followed by muscle weakness. In the periphery, both motor and sensory neurons are affected.

Unlike acute exposure, chronic inorganic arsenic exposure was not found to be consistently associated with peripheral neuropathy. An earlier study indicated that no dose–response relationship existed between daily arsenic ingestion from well water with levels up to 5 mg/l and peripheral neuropathy (Kreiss et al., 1983). However, two more recent studies (Hafeman et al., 2005; Tseng et al., 2006) reported positive associations between cumulative inorganic arsenic exposure from well water and parameters for peripheral neuropathy (nerve conduction velocity, vibrotactile threshold). In its 1999 assessment, the United States National Research Council concluded that there was no consistent evidence of peripheral neuropathy in humans exposed to inorganic arsenic in drinking-water at levels below 1 mg/l (NRC, 1999). However, recent studies indicate that adverse neurosensory effects of chronic arsenic exposure occur at concentrations well below 1 mg/l drinking-water (Hafeman et al., 2005; Otto et al., 2007).

Peripheral neurotoxicity of organic arsenic compounds is not well documented. Apart from the occasional report of peripheral neuropathies in syphilitic and trypanosomiasis patients, resulting from use of arsenic in the forms of

arsphenamine and melarsoprol as therapeutic agents, no overt human peripheral neurotoxicity has been observed from exposure to the dietary organic arsenic compounds, such as AB and AC. Similarly, the neurotoxicity of the various arsenic metabolites (e.g. MMA and DMA) has never been decisively established on a clinical level.

Effects of arsenic on the central nervous system

Several reports indicate that arsenic encephalopathy occurs following acute exposure to inorganic arsenic–containing fumes or after ingestion of inorganic arsenic and that the severity of the symptoms is related to the ingested dose (ATSDR, 2007). However, there are no reports of overt encephalopathy resulting from chronic ingestion of arsenic at low dosages. The central nervous system is more subtly affected on a neurobehavioural level, as evidenced by impairment of cognitive functions, such as learning, memory, hand–eye coordination and attentive processes.

Earlier studies indicated that syphilis patients treated with the organic arsenic compounds arsphenamine and melarsoprol developed acute conditions called arsphenamine encephalitism and severe reactive arsenical encephalopathy, respectively. Beyond these therapeutically used organic arsenic compounds, no overt human central neurotoxicity has been observed as a result of exposure to the dietary organic arsenic compounds, such as AB and AC. Similarly, neurotoxicity of the various arsenic metabolites (e.g. MMA and DMA) has never been decisively established on a clinical level.

Summary

In summary, available epidemiological studies indicate a relationship between high-level oral exposures to inorganic arsenic and sensitive end-points for peripheral and central neurotoxicity. Moreover, exposures of the developing central nervous system and probably the peripheral nervous system, including in utero, may lead to serious health effects later in life. Therefore, longitudinal studies are necessary to better establish the relationship between exposure in a specific time frame during development and neurotoxic effects.

(v) Diabetes

The effect of oral exposure to inorganic arsenic on abnormal glucose metabolism and diabetes was recently reviewed in the EFSA opinion (EFSA, 2009), and no new studies have been published since. In general, studies conducted in Bangladesh and Taiwan, China, indicated an extra risk of diabetes among high-exposure populations. However, many of these studies lacked adjustment for body mass index. In studies of general populations with low to moderate exposures, none of them showed a positive association. Using data from the United States National Health and Nutrition Examination Survey (NHANES), Navas-Acien et al. (2009) reported an increased prevalence of type II diabetes for those with higher (80th percentile) versus those with lower (20th percentile) urinary arsenic levels, adjusted for the organic arsenic species, AB. However, using the same data, Steinmaus et

al. (2009) reported no association when AB was subtracted from total arsenic to reflect the inorganic exposure. In conclusion, the relationship between arsenic exposure and diabetes remains uncertain.

(vi) Other effects

In a small-scale study conducted in India, the immunoresponse to concanavalin A, a potent mitogen, was examined in patients with inorganic arsenic–induced skin lesions and in unexposed controls. T cell proliferation and cytokine levels were significantly lower ($P < 0.001$) in exposed individuals than in the unexposed (Biswas et al., 2008). The same group also reported significantly ($P < 0.001$) impaired macrophage functions, such as loss of cell adhesion capacity and decrease in nitric oxide production and phagocytic capacity, in arsenic-exposed individuals ($n = 70$) compared with the unexposed ($n = 64$) (Banerjee et al., 2009).

3. ANALYTICAL METHODS

3.1 Sample preparation for total arsenic determination

Sample digestion can be achieved by wet or dry mineralization. Wet digestion is the technique most widely used in food, because it requires less time than methods based on dry ashing. The systems most commonly utilized in the laboratory currently are the high-pressure asher, which can attain temperatures of over 320 °C, and the microwave-assisted digestion (MAE) systems, in which the temperatures do not go above 260 °C, because the Teflon material used in most of the systems starts to melt at that temperature (Goessler & Pavkov, 2003). Nitric acid is the oxidant most often used, although combinations of various acids are also common. Generally, the acid is combined with hydrogen peroxide, which enhances the digestion yield as a result of an extra oxidation.

A major problem presented by the MAE system is the complete decomposition of some organoarsenical species. AB, TMAO and tetramethylarsonium ion (TMA^+) are resistant to the attack of oxidizing agents and require high temperatures to break the arsenic–carbon bonds (≥300 °C), which cannot be achieved in MAE systems (Fecher & Ruhnke, 1998). This leads to an underestimation of the total arsenic concentration in samples containing these species when the detection method used after MAE digestion is based on hydride generation (HG): HG–atomic absorption spectrometry (HG-AAS) or HG–atomic fluorescence spectrometry (HG-AFS). Duarte et al. (2009) used a microwave-induced combustion method, generating adequate recoveries in the quantification in seafood by flow injection–HG-AAS.

At present, there are various official methods for the determination of total arsenic in foods based on digestion of samples by wet mineralization (USEPA, 1996; European Committee for Standardization, 2004, 2005b, 2009).

Dry ashing involves oxidation of organic compounds in open systems at elevated temperatures by air oxygen. An advantage of these methods is the possibility of handling relatively large amounts of samples. The main drawback with

regard to wet digestion is that the process requires more time. The use of ashing aid reagents (MgO, $Mg(NO_3)_2$ or mixtures of both) avoids the losses of arsenic due to the formation of volatile compounds and also accelerated mineralization of samples. Dry ashing mineralization is used in several official methods (AOAC, 1990; European Committee for Standardization, 2005a).

3.2 Sample preparation for arsenic species determination

The extractants most commonly used are polar solvents, such as methanol, water and methanol/water mixtures, nitric acid, tetramethylammonium hydroxide, trifluoroacetic acid, phosphoric acid, sodium hydroxide and enzyme mixtures at neutral pH.

Certain considerations must be taken into account when developing extraction methods for arsenic species. First of all, it is necessary to study whether transformations take place in the arsenic species during the extraction and storage of the extract obtained. Also, an extractant may give very different efficiencies for the same type of food, and even optimal results in certified reference materials may not be reproduced in food products purchased from retail outlets (Heitkemper et al., 2001). Application of the method to cooked food may also alter the extraction efficiency. Finally, mass balance calculations should form part of the quality control performed to select the extraction method (Schaeffer et al., 2005). The more polar or ionic organoarsenic species (AB, DMA, MMA, TMAO, TMA^+, arsenosugars) are easily extractable, even with the less aggressive methods, but As^{III} is difficult to extract because covalent bonds are formed with the sulfhydryl groups of proteins. The extraction of arsenolipids requires non-polar solvents such as hexane.

From the toxicological point of view, special attention must be paid to the separation of As^{III} and As^{V} from the other species, as at present they are the main focus of attention in health institutions and regulating organizations. Methods for a selective inorganic arsenic extraction have been described. Muñoz, Vélez & Montoro (1999) developed a quantitative extraction with chloroform followed by back-extraction with hydrochloric acid and determination by dry-ashing HG-AAS or inductively coupled plasma mass spectrometry (ICP-MS). This method has been applied effectively to a wide variety of foods (Muñoz et al., 2000, 2002; Almela et al., 2006; Rose et al., 2007; Jorhem et al., 2008).

Many techniques have been used to assist arsenic species extraction. Mechanical agitation has been widely used in food samples. A recent study by van Elteren et al. (2007) shows the variability in extraction from the certified reference material IAEA-140/TM (*Fucus* sp.) using different methanol/water ratios assisted by a mechanical agitation. None of the conditions assayed achieved quantitative extraction of the arsenic species. Some acids have been used for extraction of arsenic species. Trifluoroacetic acid has been effectively applied at high temperatures for arsenic speciation in rice (Williams et al., 2005), vegetables (Nam et al., 2006) and baby food products (Vela & Heitkemper, 2004). The use of nitric acid (0.3 mol/l) at 80 °C also allows quantitative extraction in *Hizikia fusiforme* (Hamano-Nagaoka et al., 2008).

Bath or focused probe sonication does not always improve the results obtained with simple mechanical agitation (Caruso, Heitkemper & B'Hymer, 2001; Nam et al., 2006; Salgado, Quijano Nieto & Bonilla Simón, 2006). However, ultrasound-assisted extraction with enzymatic solutions achieves satisfactory efficiencies in rice and meat (Sanz, Muñoz-Olivas & Cámara, 2005a,b). Another technique that has been used in recent years is accelerated solvent extraction, with possibilities of working with pressure and with high extraction temperatures, conditions that cannot be attained in sonication. The use of accelerated solvent extraction in fish products (methanol/water, methanol/acetic acid, 100 °C) and carrots (water, 100 °C) allows quantitative extractions in some food matrices (McKiernan et al., 1999; Vela, Heitkemper & Stewart, 2001; Wahlen et al., 2004).

With regard to MAE, many applications of this methodology have been described in recent years. Larsen et al. (2005) applied MAE and an alkaline alcoholic mixture to seafood samples, although the method was unsuitable for fatty fish. MAE has been applied to seaweed, with satisfactory recoveries, using as extractants water, nitric acid (2%) and methanol/water (Tukai et al., 2002; Salgado, Quijano Nieto & Bonilla Simón, 2006; Foster et al., 2007). A suitable extraction of arsenic species from vegetables and cereals using MAE has been achieved in the presence of protein extraction solution (Rahman, Chen & Naide, 2009), enzyme mixture (Guzmán Mar et al., 2009; Rahman, Chen & Naide, 2009) or water (Narukawa et al., 2008). Finally, the use of a sequential extraction procedure in MAE improved the arsenic extraction efficiency in samples in which extraction is difficult (seaweed, plant and animal digestive tissue) (Tukai et al., 2002; Foster et al., 2007).

3.3 Separation of arsenic species

The nature of the food to be analysed determines which arsenic species are present and, consequently, the chromatographic separation selected and its complexity. A number of reviews (Guerin, Astruc & Astruc, 1999; Gong et al., 2002; McSheehy et al., 2003; Francesconi & Kuehnelt, 2004; Niegel & Matysik, 2010) provide an overview of the various chromatographic conditions used for arsenic speciation analysis. High-performance liquid chromatography (HPLC) is the separation technique that has been most commonly used.

The foods in which the largest number of speciation studies has been conducted are vegetables, cereals and aquatic products. In the majority of vegetables and cereals, the major species are As^{III}, As^{V}, MMA and DMA, which can be separated without difficulty in anion exchange columns using isocratic elution over a very variable pH range (generally between 5 and 7) and with various kinds of mobile phase (particularly phosphates or carbonates).

A considerable number of arsenic species coexist in aquatic food products (freshwater fish, marine fish, shellfish and algae). Generally, to avoid overlapping, misidentification and errors in the quantification, it is best to use multidimensional chromatography. Two different chromatographic columns, anion and cation exchange, placed in line (Nischwitz & Pergantis, 2006) or connected by a column switching system (Suñer et al., 2001) permit good resolution of a considerable number of species with one chromatographic run. Other systems have been carried

out off-line, using different columns in two (Kirby et al., 2004) or three chromatographic runs (Schaeffer et al., 2005). An interesting development in HPLC systems is the high-speed separation method using micro-HPLC columns. Only one application of this system for speciation of arsenic in foods has been described (Wangkarn & Pergantis, 2000).

Often the complexity of the arsenic profile and the presence of the unknown species make it necessary to perform a structural identification of the peaks eluted from the HPLC by electrospray ionization mass spectrometry (ESI-MS) or tandem mass spectrometry (ESI-MS/MS) (McSheehy et al., 2001; Sloth, Larsen & Julshamn, 2005; Nischwitz & Pergantis, 2006). In addition, it is necessary to take account of another factor, the non-quantitative elution of arsenic injected in the column (Raab et al., 2003; Soeroes et al., 2005).

3.4 Detection systems

The detection systems most commonly used for the determination of total arsenic and its species in foods are AAS, AFS, inductively coupled plasma atomic emission spectrometry (ICP-AES) and ICP-MS:

- *Atomic absorption spectrometry (AAS):* HG-AAS is one of the techniques most commonly used for the detection of arsenic and its species in foods. HG-AAS allows good preconcentration and chemical separation of the arsenic from potential matrix interferences and has the advantage of being cheaper in terms of both equipment and maintenance. For speciation of the organoarsenic species that do not generate hydrides or that do so with low efficiency, post-column derivatization after their separation is required. This process is performed by means of on-line thermo-oxidation (microwave, heated bath) or photo-oxidation (UV light) using an oxidant, generally potassium persulfate. Although its limits of detection (LODs) are slightly higher than those obtained by ICP-MS, they are suitable for quantification of arsenic species in foods (Koch et al., 2007; Signes et al., 2007).
- *Atomic fluorescence spectrometry (AFS):* As in the case of AAS, combination with HG increases sensitivity and reduces matrix effects. In comparison with detection by AAS, AFS offers advantages in terms of linearity and LODs. In recent years, HG-AFS has been used extensively for detection of arsenic species. For the organoarsenical species, thermo-oxidation or photo-oxidation is necessary prior to HG-AFS. Gómez-Ariza et al. (2000) conducted a comparative study of ICP-MS and AFS for arsenic speciation in which they showed that LODs and linear range were comparable. AFS equipment is less expensive and easier to handle than that for ICP-MS, and therefore it is an excellent alternative for detecting arsenic species.
- *Inductively coupled plasma atomic emission spectrometry (ICP-AES):* This technique has a larger working range, but its instrumental LODs are not good enough for the determination of arsenic in many food samples, and it suffers from various matrix interferences. Research into the determination of arsenic by ICP-AES has basically followed a combination of the technique of HG with ICP. The LODs are at least an order of magnitude lower than those obtained with conventional nebulization. Arsenic speciation studies in seafood products using

HPLC-ICP-AES have shown that this technique is suitable for the determination of major compounds, such as AB in marine organisms.

- *Inductively coupled plasma mass spectrometry (ICP-MS):* With this methodology, sub-nanogram per gram LODs are achieved without the need for preconcentration and derivatization. Another advantage of this technique is the wide linearity range, which can be extended by several orders of magnitude. One of its main disadvantages is the high cost of instrumentation and maintenance and the spectral interferences. The chloride ion present in food samples combines with the plasma gas to form $^{40}Ar^{35}Cl^{+}$, creating polyatomic interferences. Only ICP-MS equipped with a high-resolution mass analyser (sector field system) can improve the separation of these signals, but this equipment is very expensive. One technology introduced to eliminate these polyatomic interferences is the use of collision/reaction cells; however, the gas used in these cells can cause other interferences (Dufailly, Noël & Guérin, 2008). HG prior to ICP-MS was used not only to reduce the interferences but also to improve the LODs.

HPLC-ICP-MS is the hyphenated technique most commonly used for the analysis of arsenic species in foods. LODs below 1 µg/l for the various arsenic species are achieved with single quadrupole instruments. An appropriate choice of chromatographic conditions can also help to avoid this interference, eluting $^{40}Ar^{35}Cl^{+}$ with a retention time different from that of the arsenic species.

Recently, HPLC coupled to MS or MS/MS has been used as the sole technique for identification and quantification of a great variety of arsenic species (Van Hulle et al., 2002; Kato, Nagashima & Shiomi, 2004; Nischwitz & Pergantis, 2005; Ninh, Nagashima & Shiomi, 2006). Near-infrared spectroscopy is also a valuable non-destructive technique that offers low cost and speed of analysis, combining applied spectroscopy and statistics. The potential of near-infrared spectroscopy for screening the inorganic arsenic contents of rice and red crayfish has been assessed (Font et al., 2004, 2005). Other non-destructive methodologies are the X-ray spectroscopic methods, such as X-ray near-edge spectroscopy, X-ray fluorescence and particle-induced X-ray emission. Lombi et al. (2009), using X-ray absorption near-edge spectroscopy, identified and quantified arsenic–glutathione complexes [$As(Glu)_3$], not observable by routine HPLC-ICP-MS analysis because of dissociation of the complex during extraction and analysis.

4. EFFECTS OF PROCESSING

Although there has been little research on the effects of preparation or preservation processes applied to food products on arsenic content, some quantitative and qualitative changes in arsenic have been shown. The effects of processing on arsenic contents and its species in foods have been reviewed in a recent publication (Devesa, Vélez & Montoro, 2008).

Studies on vegetables show that total arsenic contents are much higher in potato and carrot skin (Helgesen & Larsen, 1998; Muñoz et al., 2002; Roychowdhury et al., 2002) than in food that has been peeled. Similar results have

been shown in samples of beetroot and garlic, with concentrations of arsenic in the skin 5 and 70 times greater, respectively, than the levels in the edible part (Muñoz et al., 2002). It has also been described that dehusking/polishing rice reduces total arsenic contents (Signes et al., 2008a). The hepatopancreas of some crustaceans has total arsenic contents equal to or greater than those of muscle (Sekuli, Sapunar & Bažuli, 1993; Devesa et al., 2002), and it also accumulates a greater inorganic arsenic content (Devesa et al., 2002); therefore, its removal may also produce a decrease in the arsenic content.

With regard to washing, studies have concentrated on rice washing, a usual practice in some regions. Various studies (Sengupta et al., 2006; Mihucz et al., 2007; Signes et al., 2008b) show that washing rice with water (5–6 times) and disposing of the water before cooking can eliminate up to 23% of the arsenic. Mihucz et al. (2007) found that As^{III} was the arsenic species with the highest removal.

Among the treatments prior to consumption, cooking is the most studied. Quantitative changes after cooking may be due to an increase in the concentration of arsenic correlating with a decrease in weight or to a decrease in arsenic resulting from solubilization. In fish and shellfish, these changes are significant only for a few of the product/treatment combinations (Dabeka et al., 1993; Devesa et al., 2001a; Ersoy et al., 2006; Perelló et al., 2008). There have been studies confirming the transfer of AB, DMA, As^{V} and arsenosugars into the broth during the process of boiling and steaming crustaceans and bivalves (Devesa et al., 2001a; Lai et al., 2004). For algae, processes such as baking do not alter the arsenic content; however, soaking and boiling can reduce the inorganic arsenic content by up to 82% (Hanaoka et al., 2001a; Laparra et al., 2004; Almela et al., 2005; Ichikawa et al., 2006; Rose et al., 2007). Regarding studies on vegetables and manufactured cereal products, boiling can cause the loss of up to 60% (She & Kheng, 1992; Cubadda et al., 2003). The most detailed studies have been conducted on rice samples, for which boiling produces a loss of arsenic. However, a large volume of water is needed in order to remove substantial quantities of total arsenic (35%) and inorganic arsenic (45%) (Raab et al., 2009).

Studies on qualitative changes after cooking treatments are very sparse. In fish and shellfish, it has been shown that treatments in which the surface of the food reaches temperatures above 150 °C (baking, frying or grilling) can lead to the appearance of TMA^{+} (Devesa et al., 2001b, 2005; Hanaoka et al., 2001b). The elucidation of this phenomenon in standards of arsenic species has confirmed that TMA^{+} can be generated by decarboxylation of AB (van Elteren & Šlejkovec, 1997; Devesa et al., 2001c).

Cooking with water that contains arsenic deserves a separate mention. Most of the studies report changes in the contents of total arsenic and show that cooking with polluted water increases the arsenic concentration to values that depend on the amount of water, the concentration of arsenic in the water and the cooking time (Bae et al., 2002; Del Razo et al., 2002; Roychowdhury et al., 2002; Díaz et al., 2004; Ackerman et al., 2005; Torres-Escribano et al., 2008). Very few studies have attempted to quantify arsenic species in food cooked in these conditions. They all

show that inorganic arsenic is the major species (Díaz et al., 2004; Smith et al., 2006; Torres-Escribano et al., 2008).

There are no studies that evaluate contents of total arsenic or its chemical forms before and after subjecting food to preservation processes similar to those applied in the food industry, in commerce or in the home. Concerning freezing processes, Edmonds & Francesconi (1988) considered the possible decomposition of AB in frozen fish. However, their conclusions that the content of AB in fish decreases upon freezing were not obtained by analysing the product before and after freezing, so the possibility that the difference in AB concentrations in fish before and after freezing was due to the size or source of the raw material cannot be excluded. In contrast, the possibility that the decrease in AB was due to its solubilization during the defrosting process also cannot be ruled out. Among preserved foods, canned seafood products have been studied the most, with reported arsenic concentrations lower than those present in raw products of the same animal species (Vélez & Montoro, 1998; Muñoz et al., 2000; Ikem & Egiebor, 2005). It has been shown that there is a transfer of AB and DMA to the brine (Vélez, Ybáñez & Montoro, 1997).

Kato, Nagashima & Shiomi (2004) conducted a study on fish sauces purchased in retail outlets, prepared by fermentation of raw fish for a long period of time. They compared the arsenic composition of the fish sauces with that of the same fresh fish and observed differences with regard to the predominant species (DMA in sauces and AB in fresh product). The authors suggested that AB was transformed to DMA by bacterial action during manufacturing. A later study (Rodriguez, Raber & Goessler, 2009) on the same type of fermented fish sauces showed that AB was the predominant species; therefore, the authors concluded that there was no transformation during the fermentation. The discrepancies between the two studies might be due to differences in the fermentation process (conditions, inoculum, time).

Van Elteren & Šlejkovec (1997) studied the effect of gamma irradiation (100–10 kGy) on the stability of arsenic species, showing a partial decomposition of AB, DMA and MMA. The gamma ray doses used in commercial foods are lower (5 kGy) than those assayed, so these changes may not occur in the products purchased by consumers.

5. PREVENTION AND CONTROL

Arsenic sources such as mining and some pesticides and wood preservatives may contribute to human exposure and should be controlled in order to prevent environmental contamination. However, the great majority of exposure occurs through naturally contaminated groundwater—through drinking-water, water used in food preparation or water used to irrigate food crops, particularly rice. Paddy rice may also contain relatively high levels of arsenic at low soil arsenic levels due to the high availability of arsenic in flooded soils.

5.1 Strategies for reducing arsenic exposure from water

The ideal solution is to use alternative sources of water that are low in arsenic. However, it is important that this does not result in risk substitution—for example, if the alternative water source, although low in arsenic, increases exposure to waterborne pathogens and results in acute gastrointestinal infections, which are a major source of mortality and morbidity in many parts of the world (Howard, 2003). This is important for most alternative water sources other than water from tube wells. Water safety frameworks should be used during planning, installation and management of all new water points, especially ones based on surface water and very shallow groundwater, to minimize risks from faecal and other non-arsenic contamination. Screening for arsenic and other possible chemical contaminants of concern that can cause problems with health or acceptability, including fluoride, nitrate, iron and manganese, is also important to ensure that new sources are acceptable. Occasional screening may also be required after a source is established to ensure that it remains safe.

Where there are large urban supplies, resources are often available to treat water to remove arsenic or to exploit alternative low-arsenic sources, such as surface water that can be treated to avoid microbiological and other hazards. These low-arsenic sources can be used to blend with higher-arsenic sources to lower the concentration to acceptable levels while still retaining the resource.

Many of the major problems lie in rural areas, where there are many small supplies, sometimes down to the household level. At this level, water availability and financial and technical resources are all limited. There are several available approaches, but there is a basic requirement for education. In particular, there is a need to understand the risks of high arsenic exposure and the sources of arsenic exposure, including the uptake of arsenic by crops from irrigation water and the uptake of arsenic into food from cooking water.

A number of approaches have been successfully used in rural areas, including source substitution and the use of both high- and low-arsenic sources blended together. These sources may be used to provide drinking-water and cooking water or to provide water for irrigation. High-arsenic water can still be used for bathing and clothes washing or other requirements that do not result in contamination of food. However, it is important to remember that there may be other contaminants present as well as arsenic, and so it is important to determine whether other contaminants of concern are present.

Low-cost approaches that have been developed to lower exposure to arsenic where contamination of groundwater is a problem include the following:

- alternative sources, including dug wells that are properly protected to prevent microbiological contamination and rainwater harvesting, which may be possible for at least some months of the year, with steps taken to minimize contamination;

- surface ponds, which require appropriate steps to minimize microbial and chemical contamination and also require treatment to ensure microbial safety before drinking;
- identifying high- and low-arsenic tube wells by painting them different colours and sharing wells (spatial variability in groundwater arsenic contamination in Argentina, Chile and the river deltas of South and South-east Asia is very high, so there are mixtures of arsenic-contaminated and arsenic-uncontaminated wells in most villages);
- sinking new wells into low-arsenic strata. This requires significant technical support to ensure that low arsenic levels are known and can be exploited without other problems arising. Deeper groundwater aquifers can be used to develop community water supplies, which generally succeed where there is community involvement in their establishment and operation;
- removal of arsenic by low-cost village or household treatment systems, usually using absorptive media, such as elemental iron, iron or aluminium oxides and carbon. Shallow groundwater that is anoxic (e.g. in South and South-east Asia) is generally high in dissolved iron, so a pretreatment step involving the formation and precipitation of iron hydroxide, which will then adsorb arsenic, is advantageous. Many household treatment systems in Bangladesh and West Bengal, India, may fail prematurely because of high levels of phosphate, which competes with inorganic arsenic species for adsorption, in the water. Safe disposal of arsenic-contaminated wastes should also be considered.

In areas where there is observable arsenicosis, there is usually no problem in persuading the local population to follow arsenic mitigation measures, even though they often require significant extra effort. Involvement of individuals and communities in the planning, implementation and management of the mitigation strategy is a key factor for successful intervention. Studies in Bangladesh have shown that most rural households prefer sharing of uncontaminated wells or filtration of low-arsenic surface water through sand to treatment of groundwater (Howard, 2003; Johnston, Hanchett & Khan, 2010).

Where arsenic levels are lower and the adverse effects of arsenic exposure are less obvious, there will be a much greater requirement for education in order for mitigation measures to be carried out effectively over an extended time period. More information can be found in sources such as Howard (2003), JICA/AAN (2004) and WHO (in preparation).

5.2 Strategies for reducing arsenic exposure from foods

General strategies for reducing human exposure to arsenic from foods include reducing arsenic uptake into food crops, increasing the proportion of less toxic organic forms relative to inorganic arsenic in food crops and reducing the arsenic content of foods by processing, preparation or cooking methods. These strategies are discussed briefly below.

5.2.1 Reducing arsenic uptake into food crops

(a) Soil amendments

Because arsenic is toxic to plants, various soil amendments aimed at counteracting its toxicity have been investigated, and these should also lower arsenic concentrations in plants. Selection of amendments has been based on our understanding of the factors that regulate arsenic solubility and speciation in soils and plant uptake of arsenic.

(i) Phosphate

As an essential nutrient, phosphate additions to soils are generally needed for crop production purposes. Arsenate, the major arsenic species in aerobic soils, is a close chemical analogue of phosphate, and these two oxyanions exhibit similar chemical behaviour. Plant uptake of arsenate is via the phosphate transport system and is competitive with plant uptake of phosphate (Meharg & MacNair, 1992; Abedin, Feldmann & Meharg, 2002), suggesting that addition of phosphate to soil will reduce arsenic uptake by plants. However, phosphate and arsenate also compete for adsorption sites in soils, especially iron (Fe^{III}) oxides and oxyhydroxides (hereafter termed oxides), and phosphate addition will displace some adsorbed arsenate. Thus, phosphate addition can either decrease or increase plant uptake of arsenate, depending on the effect of its addition on the ratio of phosphate to arsenate in soil solution. Most studies of plant uptake of arsenic from soils show that phosphate additions increase plant tissue arsenic concentration for crops grown in aerobic soils (e.g. Jiang & Singh, 1994; Cao & Ma, 2004) and either have no effect on or increase arsenic concentrations in vegetative tissues and grains of paddy rice (Hossain et al., 2009). Very large additions of phosphate, which have sometimes been used to leach arsenic from surface soil, would likely reduce plant uptake of arsenic. However, this strategy is undesirable, as it just creates a different environmental pollution problem.

(ii) Silicate

This element is required in large amounts by rice, where the straw may contain as much as 15% on a dry weight basis. Uptake of arsenite, the major inorganic arsenic species in flooded or reduced soils, is by the same aquaporin channel and is competitive with uptake of silicate (Ma et al., 2008). Two studies show a reduction in rice grain arsenic with silicate addition (Bogdan & Schenk, 2008; Li et al., 2009), but they appear to have been carried out in soil with marginal to deficient levels of silicate for rice. While silicate addition would be expected to lower arsenite uptake in this circumstance, it may not do so under conditions of silicate sufficiency.

(iii) Iron- or manganese-containing materials

Soil additions of iron or manganese salts and inexpensive iron metal grits that will generate oxides sometimes reduce arsenic concentrations in vegetable crops (Warren et al., 2003; Hartley & Lepp, 2008) and paddy rice (Hossain et al.,

2009; Ultra et al., 2009). There are several challenges to this approach, which suggest that it may not be very viable: 1) these materials also reduce phosphorus availability, requiring increased phosphorus additions, which, in turn, increase arsenic solubility; 2) freshly precipitated oxides are initially amorphous but reorganize to crystalline phases with much lower adsorption capacity; and 3) other soil constituents, including silicate, humic substances and simpler organic acids, also complex with oxide surfaces, reducing their capacity for complexing arsenate. These factors are more problematic for aerobic soils, where iron oxides are not as subject to the dissolution and reprecipitation cycles that occur in a rice paddy.

(b) Inoculation with arbuscular mycorrhizal (AM) fungi

Infection of root systems with AM fungi can increase nutrient acquisition by plants, especially phosphorus, which can lead to downregulation of the high-affinity phosphate uptake transport system and reduce arsenic uptake. This was recently reported for barley (Christophersen, Smith & Smith, 2009). Here, an AM–inorganic phosphorus transport system compensated for reduced direct root uptake of phosphate and did not transport arsenate. Unfortunately, other studies of AM inoculation have shown inconsistent results and have usually not been carried out to crop maturity, so there is often no information on arsenic levels in edible plant parts. AM infection significantly lowered arsenic concentrations in tobacco leaves from 22.1 mg/kg to between 14.3 and 18.0 mg/kg, depending on the AM species, with essentially no effect on phosphorus concentration or biomass production (Hua et al., 2009). In this case, AM infection lowered soil pH and increased arsenic adsorption by crystalline iron oxides, which was thought to be the main explanation for the observed result. In maize, AM infection reversed arsenic toxicity and increased phosphorus uptake, but it increased leaf tissue arsenic concentration with one AM species and reduced it with a second species (Bai et al., 2008). More work is needed to establish whether inoculation with AM fungi can have practical value. It should also be recognized that AM infection is not considered important to phosphorus nutrition of crops in well-fertilized soils and does not apply at all to paddy rice.

(c) Varietal selection

Varietal differences in arsenic uptake have been reported for rice (Norton et al., 2009a). However, emerging information is showing that the environment is more important than genetics as a determinant of rice grain arsenic concentration (Ahmed, 2009; Norton et al., 2009b). In a study in Bangladesh, Ahmed (2009) found that 70–80% of the variability in rice grain arsenic was explained by the environment, 10% by genetics and 10–20% by the interaction between genetics and the environment, in a study across nine environments, two seasons and 38 varieties. A few varieties had consistently high or low grain arsenic concentrations across environments, so that limited recommendations could probably be made to farmers, and low-arsenic varieties can be used in breeding programmes in Bangladesh. As reported by others (Duxbury et al., 2003; Williams et al., 2005), strong seasonal effects on grain arsenic were observed, with the mean arsenic concentration in the monsoon season rice varieties (0.154 mg/kg) being approximately half that of the

dry, winter season varieties (0.288 mg/kg). Highly photoperiod-sensitive aromatic Indica varieties had the lowest grain arsenic concentrations, consistent with a market basket survey in which aromatic rice from India and Pakistan contained significantly lower levels of arsenic than did rice from the USA or Europe (Zavala & Duxbury, 2008).

Other research has shown that rice varieties from different countries vary in their tolerance of toxicity from inorganic arsenic, with tolerance decreasing in the order China > USA > Bangladesh (Ahmed, 2009). Chinese rice varieties are also much more tolerant, compared with USA varieties, of monosodium methane arsonate (Yan et al., 2005), which was formerly used on cotton in some current USA rice production areas. Tolerance of inorganic arsenic was associated with higher grain arsenic concentrations, but increased proportions of DMA^V, in rice grain in a greenhouse study with many Bangladeshi and two USA rice varieties (Ahmed, 2009). Tolerance was also associated with the amount of oxygen diffusing from roots in a greenhouse study with varieties grown in China (Mei, Ye & Wong, 2009). In the latter case, grain and straw arsenic concentrations were also lower with increasing tolerance, but grain arsenic levels for the five most tolerant varieties were all about 1 mg/kg when arsenic was added to soil at the very high rate of 100 mg/kg. These results indicate that exclusion of arsenic from rice may play some role in tolerance of arsenic toxicity, but may not adequately protect against high grain arsenic levels.

(d) Growing rice under less reduced conditions

Growing rice "more aerobically" lowers the solubility of arsenic and can reduce grain arsenic concentrations substantially (Table 7). A challenge to this approach is that yields of rice are generally reduced to unacceptable levels, perhaps averaging about 30% under "aerobic" (or less reducing) conditions. On the positive side, much effort is currently being directed towards "aerobic" rice production methods as water availability is becoming physically and economically limited (Tuong & Bouman, 2003). Partial drainage of fields, either periodically or throughout rice growth (Xie & Huang, 1998), and growing rice on raised beds (Duxbury & Panaullah, 2007) have been used to reduce arsenic toxicity, and these practices also reduce the arsenic content of rice grain and straw (Table 7). Greenhouse studies have shown greater potential for reduction in grain and straw arsenic concentrations than has so far been realized in the field (Table 7). Except for the study by Xu et al. (2008), yield decreases under "aerobic" conditions were found when arsenic was not toxic, but yield increases were found where arsenic toxicity was mitigated.

5.2.2 Increasing the proportion of organic arsenic in food crops

There are only a few reports of arsenic speciation in vegetables, where it is largely inorganic (Muñoz et al., 2002; Signes-Pastor et al., 2008), with variable distribution between arsenite and arsenate (Smith et al., 2009).

Table 7. Effect of growing rice under flooded and less reducing conditions on grain yield and arsenic concentrations in grain and straw

Study	Soil total arsenic concentration (mg/kg)	Grain yield		Arsenic concentration (mg/kg)			
				Grain		Straw	
Duxbury & Panaullah (2007)		(Mg/ha)					
Arsenic gradient in Bangladeshi farmer's field from 20 years of use of irrigation water		Fld.	Aer.	Fld.	Aer.	Fld.	Aer.
Aer. is raised beds	12	8.9	7.8	0.54	0.26	7.3	1.1
	26	8.1	8.2	0.53	0.28	9.7	1.2
	40	6.4	7.0	0.38	0.34	9.9	3.2
	58	3.0	5.2	0.34	0.36	11.5	3.9
Xu et al. (2008)		(g/pot)					
Greenhouse, non-rice soil		Fld.	Aer.	Fld.	Aer.	Fld.	Aer.
As^{III} or As^{V} added							
Aer. is 70% field capacity	Control 15	8.0	9.2	1.0	0.09	13	1
	+ As^{III} 25	6.0	8.0	2.5	0.18	26	3
	+ As^{V} 25	6.2	10.2	2.2	0.15	30	2
Xie & Huang (1998)		(Mg/ha)					
Arsenic-contaminated field site, China		Fld.	Aer.	Fld.	Aer.	Fld.	Aer.
Aer. is maintaining moist conditions after a few days of flooding, Eh ~260	Control 68	5.5	6.6	0.65	0.49	48 (flag leaf)	18 (flag leaf)

Table 7 (contd)

Study	Soil total arsenic concentration (mg/kg)	Grain yield			Arsenic concentration (mg/kg)					
					Grain			Straw		
Y.J. Zavala & J.M. Duxbury (unpublished)		(g/plant)								
Greenhouse, non-rice soil		Fld.	A1	A2	Fld.	A1	A2	Fld.	A1	A2
Aer. is water table at 10 cm (A1) or 20 cm (A2)	7	95	75	45	0.35	0.20	0.01	7.3	2.0	0.1
Arao et al. (2009)		(g/pot)								
Greenhouse, arsenic- and cadmium-contaminated rice soils		Fld.	B1	B2	Fld.	B1	B2	Fld.	B1	B2
Aer. is flooded from transplanting to heading (B1) or 3 weeks before heading (B2)	Soil A 25	36	31	27	0.95	0.30	0.11	28	26	25
	Soil B 48	46	40	36	1.7	0.59	0.17	42	31	38

Aer., “aerobic” or less reducing; Eh, redox potential; Fld., flooded

Arsenic speciation in rice grain varies considerably, with DMA^V comprising from 1% to 90% (Schoof et al., 1999; Heitkemper et al., 2001; Ackerman et al., 2005; Williams et al., 2005; Smith et al., 2008; Zavala et al., 2008). Strong positive relationships between either DMA^V or inorganic arsenic in grain and total grain arsenic have been found (Zavala et al., 2008; Zhu et al., 2008; and when data from Torres-Escribano et al., 2008, were plotted), leading to classification of rice into DMA^V and inorganic arsenic types (Zavala et al., 2008). Differences in speciation in grain also appear to be associated with differences in speciation in other plant parts. In greenhouse-grown rice, where grain was dominated by DMA^V with some arsenite, the major species in stems and leaves was arsenite, with some arsenate and DMA^V, whereas roots contained only arsenite and arsenate (Smith et al., 2008). In contrast, field-grown rice from West Bengal, India, contained predominantly arsenite in grain and arsenate in straw (Sanz et al., 2007). It has recently been shown that DMA^V is preferentially mobilized to rice grain (Carey et al., 2010), explaining why grain can be dominated by DMA^V when there are only low to moderate levels of DMA^V in foliar tissue. What is not yet known is whether DMA^V is synthesized by rice or is taken up as such from soil. In the former case, current varieties with the DMA^V "trait" could be more widely used, and this trait could be incorporated into preferred local varieties and even into other food crops. If DMA^V is coming from soil, strategies to increase DMA^V in soil could be investigated.

5.2.3 Reducing the arsenic content of foods by preparation or cooking methods

Preparation and cooking methods can both increase and decrease arsenic levels in foods. For foods that are cooked by boiling, it is important to use water that has low arsenic levels. Arsenic concentrations in foods may be decreased as much as 60% when the arsenic concentration in water is low and excess water is discarded (Díaz et al., 2004; Devesa, Vélez & Montoro, 2008). However, if cooking water is contaminated with arsenic, adsorption by the food may occur, leading to elevated arsenic levels. Foods that absorb a lot of water, such as dry beans and rice, are especially vulnerable to increases in arsenic concentrations. The traditional method of cooking rice in West Bengal, India—namely, washing rice until the water is clear (5–6 times), followed by cooking in about 6 times the amount of water and discarding excess water—reduced grain arsenic concentration by 56–58% when cooking water contained arsenic at less than 3 µg/l (Sengupta et al., 2006). Approximately equal amounts of arsenic were removed by the washing and cooking steps. However, the same cooking method increased arsenic concentrations in cooked rice by 2- to 4-fold when cooking water had an arsenic concentration twice as high as that in rice over a range of concentrations. Other studies confirm these results (Bae et al., 2002; Roychowdhury et al., 2002; Ackerman et al., 2005; Laparra et al., 2005). Soaking and boiling the seaweed *Hizikia fusiforme* reduced the arsenic concentration up to 82%, but had no effect on other species of red and green seaweed (Laparra et al., 2003; Devesa, Vélez & Montoro, 2008).

The peelings of root vegetables contain 2–7 times higher arsenic concentrations than the peeled root vegetables (Muñoz et al., 2002), but constitute a small fraction of the total weight. Consequently, peeling does not change the arsenic concentration by much. Polishing of brown rice removes arsenic associated

with the bran, so that white rice contains less arsenic than brown rice (Zavala & Duxbury, 2008). In one study, grain arsenic concentration was reduced by an average of 27% (range 18–40%) when 7% of the grain mass was removed, which also selectively removed inorganic arsenic, so further reducing the grain toxicity hazard (Sun et al., 2008). In a village-level study in Bangladesh, parboiling and polishing rice reduced grain arsenic concentration by an average of 19% (range 5–31%) (Duxbury et al., 2003).

6. LEVELS AND PATTERNS OF CONTAMINATION IN FOOD COMMODITIES

6.1 Arsenic content of food

Data on total arsenic contents of foods for evaluation in the present monograph were obtained from the literature and from submissions to the Committee by Brazil, France, Japan and Singapore. The total number of analytical results (single or composite) evaluated was 17 498. Table 8 summarizes the ranges of total arsenic concentrations by food category, based on results with quantified values (minimum to maximum). The highest total arsenic concentrations have been found in seaweed, fish and shellfish, mushrooms and fungi, rice and some meat products. The levels in the remaining food products usually do not exceed 1 mg/kg. In some food groups, the number of non-detectable/non-quantifiable results was important ($n = 9081$) and influences the derivation of mean concentrations. This was the case with milk products (66%), meat and meat products (74%), eggs and egg products (65%), bakery wares (70%), cereals other than rice (80%) and vegetables other than mushrooms (86%).

Table 9 summarizes the ranges of levels of inorganic arsenic obtained from the literature and from data submitted by Japan, France and Singapore (minimum to maximum).

Levels of inorganic arsenic in foods and beverages do not usually exceed 0.1 mg/kg, with mean values generally less than 0.03 mg/kg. However, seaweed, rice and some fish and shellfish products have higher inorganic arsenic levels. Food crops grown in arsenic-contaminated soils can have higher inorganic arsenic levels. In the seaweed *Hizikia fusiforme*, inorganic arsenic is more than 50% of total arsenic, with levels usually ranging from 30 to 130 mg/kg. In other seaweed species, inorganic arsenic is less than 15% of total arsenic, with levels normally below 2 mg/kg. The proportion of inorganic arsenic in rice varies from 17% to 100% of total arsenic and in vegetables from 33% to 74%. For fish and fish products, the proportion of inorganic arsenic usually does not exceed 10% of the total arsenic, but was found to reach 15% in some shellfish samples.

Table 8. Summary of available data on total arsenic concentrations in food products[a]

Food category	*n*	*n* < LOR	Concentration range (mg/kg)
Dairy products and analogues			
Milk and milk powder	284	65	0.001–0.15
Milk products	92	61	0.010–0.35
Fats and oils	39	0	0.003–0.18
Meat and meat products			
Meat	4977	4124	0.004–0.78
Offal	2074	1096	0.009–0.45
Meat products	50	20	0.003–3.25
Eggs and egg products	171	111	0.003–0.04
Confectionery products	186	61	0.002–1.13
Sweeteners	138	21	0.003–0.26
Bakery wares	71	49	0.002–0.25
Beverages			
Alcoholic beverages (except rice distilled spirits)	462	64	0.001–0.05[b]
Rice distilled spirits	8	2	0.050–1.64[b]
Non-alcoholic beverages	120	16	0.001–0.26[b]
Vegetables/fruits/nuts/seaweed			
Fruits	966	800	0.005–2.20
Vegetables (except mushrooms and fungi)	2503	2164	0.001–1.27
Mushrooms and fungi	302	60	0.011–5.79
Nuts and oilseeds	70	15	0.005–0.88
Dried seaweeds	953	3	0.114–236
Cereals and cereal products			
Cereals (except rice)	410	325	0.007–0.43
Rice	1693	0	0.002–1.83
Breakfast cereals	17	10	0.017–0.27
Pasta	19	9	0.003–0.18
Fish and shellfish			
Marine fish	1409	0	0.10–62

Table 8 (contd)

Food category	*n*	*n* < LOR	Concentration range (mg/kg)
Shellfish	171	0	0.090–66
Freshwater fish	238	0	0.060–4.72
Baby food products	75	5	0.001–4.66

LOR, limit of reporting (detection or quantification limit)

[a] Results presented for detected values only (samples in which arsenic was not detected were assigned a concentration of 0).

[b] Data expressed as mg/l.

Sources:

Data submissions: Brazil, Japan, France, Singapore

Literature sources: Bruno, Campos & Curtiust (1994); Cervera, Lopex & Montoro (1994); Pedersen, Mortersen & Larsen (1994); Berti et al. (1998); Sancho et al. (1998); Herce-Pagliai et al. (1999, 2002); Segura, Madrid & Cámara (1999); Viñas, Pardo-Martínez & Hernández-Córdoba (1999); Wangkarn & Pergantis (1999); Bhandari & Amarasiriwardena (2000); Demirözü-Erdinç & Saldamli (2000); López-Alonso et al. (2000, 2007); Moreno et al. (2000); Queirolo et al. (2000); Simsek et al. (2000); Šinigoj-Ganik & Doganoc (2000); Zaidi et al. (2000); Chen et al. (2001); Martínez et al. (2001); Matusiewicz & Mikoajczak (2001); Pardo-Martínez et al. (2001); Wyrzykowska et al. (2001); Carbonell-Barrachina et al. (2002, 2003); D'Ilio et al. (2002); Galani-Nikolakaki, Kallithrakas-Kontos & Katsanos (2002); Karadjova & Venelinov (2002); Kilic, Kenduzler & Acar (2002); Malmauret et al. (2002); Muñoz et al. (2002, 2005); Ronda et al. (2002); Roychowdhury et al. (2002); Vázquez-Moreno et al. (2002); Barbaste, Medina & Perez-Trujillo (2003); Cava-Montesinos et al. (2003, 2004); Coelho et al. (2003); Cubadda et al. (2003); Delgado-Andrade et al. (2003); Jureša & Blanuša (2003); Li et al. (2003); Meharg & Rahman (2003); Miranda et al. (2003); Roychowdhury, Tokunaga & Ando (2003); Viñas et al. (2003a,b); Waheed, Zaidi & Ahmad (2003); Wei et al. (2003); Bordajandi et al. (2004); Castiñeira et al. (2004); Y.-H. Chen et al. (2004); Díaz et al. (2004); Erdogan, Celik & Erdogan (2004); Jos et al. (2004); Julshamn et al. (2004); Laparra et al. (2004); Terrab, Hernanz & Heredia (2004); Zarcinas et al. (2004); Al Rmalli et al. (2005); Dugo et al. (2005); Karadjova et al. (2005); Liu, Probsta & Liao (2005); Patel et al. (2005); Pérez-Carrera & Fernández-Cirelli (2005); Soeroes et al. (2005); Tašev, Karadjova & Traje (2005); Williams et al. (2005, 2007); Almela et al. (2006); Catarino et al. (2006); Falcó et al. (2006); Hirata, Toshimitsu & Aihara (2006); van Overmeire et al. (2006); Weeks et al. (2006); Burger et al. (2007); Chanthai et al. (2007); El-Hadri, Morales-Rubio & de la Guardia (2007); Maduabuchi et al. (2007); Ohno et al. (2007); Pérez et al. (2007); Rose et al. (2007); Signes et al. (2007); Beni, Diana & Marconi (2008); Bronkowska et al. (2008); Cheung, Leung & Wong (2008); Donadini, Spalla & Beone (2008); Fu et al. (2008); Gülda et al. (2008); Hamano-Nagaoka et al. (2008); Jorhem et al. (2008); Lin et al. (2008); Meharg et al. (2008); Pellerano et al. (2008); Pisani, Protano & Riccobono (2008); Torres-Escribano et al. (2008); Zavala et al. (2008); Zhu et al. (2008); Ayar, Sert & Akin (2009); Baeyens et al. (2009); Besada et al. (2009); Caldas et al. (2009); Gonzálvez et al. (2009); Laoharojanaphand et al. (2009); Nardi et al. (2009); Raab et al. (2009); Roberge et al. (2009); Signes-Pastor et al. (2009); Sun et al. (2009); Uluozlu et al. (2009); Waegeneers et al. (2009a,b).

Table 9. Summary of available data on inorganic arsenic concentrations in food products[a]

Food product	*n*	*n* < LOD	Concentration range (mg/kg)
Dried seaweed	539	4	0.1–130
Rice	837	0	0.01–0.51
Fish and fish products	325	1	0.001–1.2
Vegetables	36	1	0.008–0.61

[a] Results presented for detected values only (samples in which arsenic was not detected were assigned a concentration of 0).

Sources:

Data submissions: Japan, France, Singapore

Literature sources: Suñer et al. (1999); Storelli & Marcotrigiano (2001); Almela et al. (2002, 2006); Muñoz et al. (2002); Williams et al. (2005); Rose et al. (2007); Jorhem et al. (2008); Sloth & Julshamn (2008); Torres-Escribano et al. (2008); Zavala et al. (2008); Besada et al. (2009).

Besides inorganic forms, there are a variety of organoarsenic species in foods. In meat, speciation studies are sparse (Zbinden, Andrewy & Blake, 2000; Pizarro et al., 2003; Polatajko & Szpunar, 2004; Sanz, Muñoz-Olivas & Cámara, 2005b; Sánchez-Rodas, Gómez-Ariza & Oliveira, 2006), and they show differences in the profile of arsenic species. DMA has been detected as the major species in many of the samples analysed, and AB and MMA have also been found. The presence of nitarsone, a phenylarsonic acid used as a coccidiostat, has also been reported (Sánchez-Rodas, Gómez-Ariza & Oliveira, 2006).

The greatest variety of arsenic species in vegetables has been detected in mushrooms, food matrices that contain AB, MMA, TMAO, DMA, AC and TMA^+ (Šlejkovec et al., 1997; Larsen, Hansen & Gössler, 1998; Soeroes et al., 2005; Smith, Koch & Reimer, 2007). For other vegetables, MMA has been found in carrot, radish and potato (Signes-Pastor et al., 2008), and MMA and DMA have been found in chard and aubergine (Reyes et al., 2008). Arsenic species found in fish and fish products include AB, arsenosugars, MMA, DMA, AC, TMA^+, TMAO, dimethylarsionylethanol (DMAE), trimethylarsoniopropionate (TMAP), arsenolipids and thioarsenic compounds. AB is the major species (80–90%), except in some kinds of shellfish, where arsenosugars are the major species found. In seaweeds, arsenosugars are the major species, with smaller amounts of DMA, arsenolipids and thioarsenic compounds. The valencies of MMA and DMA in food have not been determined.

6.2 Occurrence of arsenic in water

Arsenic is found widely in the earth's crust in oxidation states of –3, 0, +3 and +5, often as sulfides or metal arsenides or arsenates. In water, it is mostly present as arsenate (+5), but in anaerobic conditions, it is likely to be present as arsenite (+3). It is usually present in natural waters at concentrations below 1–2 µg/l. However, in waters, particularly groundwaters, where there are sulfide mineral deposits and sedimentary deposits derived from volcanic rocks, the concentrations can be significantly elevated. Groundwater environments that are prone to naturally high levels of arsenic (above the World Health Organization [WHO] drinking-water guideline value of 10 µg/l; WHO, 2008) are generally characterized by low rates of flushing and a large volume of young sediments (Smedley & Kinniburgh, 2002). These are mostly associated with shallow aquifers. High arsenic concentrations can be present under both reducing and oxidizing conditions. Amini et al. (2008) modelled the probability that arsenic concentrations would be above 10 µg/l in shallow groundwater for reducing and high pH/oxidizing conditions in many parts of the world. This provides a means of identifying areas potentially at risk of having drinking-water with high arsenic concentrations and prioritizing where investigations should be conducted (Table 10). Often the greatest problems are with supplies to small communities or household wells, where there are only limited resources for finding alternative supplies or for installing and maintaining treatment.

Table 10. Predicted arsenic contamination of groundwater in different countries

Country/region	Condition	% area[a]
Cambodia	Reducing	45.8
Amazon basin[b]	Reducing	37.6
Estonia	Reducing	37.2
Bangladesh	Reducing	35.4
Lithuania	Both	35.0
Finland	Unknown	34.7
Congo	Reducing	30.1
Viet Nam	Reducing	15.8
Russian Federation	Both	14.8
Cameroon	Both	14.0
Myanmar	Both	9.2
Nigeria	Oxidizing	9.0
Poland	Both	8.8
USA	Both	8.3
China, Province of Taiwan	Reducing	8.2

Country/region	Condition	% area[a]
Hungary	Reducing	7.4
Ukraine	Oxidizing	7.0
Zambia	Oxidizing	7.0
India	Both	6.4
Angola	Oxidizing	5.5
Ethiopia	Oxidizing	5.3
Argentina	Oxidizing	4.9
Romania	Reducing	3.5
Belarus	Oxidizing	3.3
Nepal	Reducing	3.2
China	Both	2.5
Kenya	Oxidizing	2.4
Greece	Unknown	0.1

[a] % area in each country with probability of arsenic contamination $P > 0.75$.
[b] Average values for Peru, Brazil and Colombia.
Source: Amini et al. (2008).

Arsenic contamination of groundwater is widespread, and there are a number of regions where arsenic contamination of drinking-water is important. Exposure via water can be very variable, with high and low arsenic sources present in close proximity, and there is also variation with depth of the well. This means that assessment of the probability of wells in an area being contaminated is not easy to judge without data on individual wells. Areas affected include southern Asia (e.g. Bangladesh, India), South-east and East Asia (e.g. China, including Taiwan, Mongolia, Viet Nam), the Americas (e.g. Argentina, Canada, Chile, Mexico, USA) and Europe (e.g. Finland, Hungary, Romania). Concentrations can vary widely, and contaminated water that is used for drinking and food preparation can contain concentrations of inorganic arsenic up to several hundred micrograms per litre, although more normally the concentration would be between 10 and 200 µg/l. Extensive surveys in West Bengal, India (Chakraborti et al., 2009), and Bangladesh (Kinniburgh & Smedley, 2001) reported that 42–50% of household wells contained arsenic concentrations above 10 µg/l and 25% contained concentrations above 50 µg/l. More data on the proportion of samples of shallow groundwater in Asian countries, showing different concentration ranges, are given in Table 11. These data should be considered illustrative, because the sampling was not necessarily systematic.

Table 11. Distribution of arsenic concentrations in shallow groundwater in Asian countries

Country and sampling area	No. of samples	% of samples in concentration range (µg/l)					
		<10	10–50	50–100	100–200	200–300	>300
Bangladesh – national[a]	3 534	58	17	9	7	4	5
India – West Bengal[b]	135 555	50	25	19	8	3	3
Nepal – Terai[c]	12 949	73	22	4	1	<1	<1
Viet Nam/Cambodia – Mekong Delta[d]	352	63	11	4	8	3	11
Viet Nam – Red Delta[e]							
- Private wells, wet season	68	9	35	16	22	6	12
- Private wells, dry season	68	56	13	16	6	4	4
- Hanoi city supply wells, raw water	8	0	25	38	25	13	0
- Hanoi city supply wells, treated water	8	0	50	50	0	0	0

[a] Kinniburgh & Smedley (2001).
[b] Chakraborti et al. (2004, 2009).
[c] Shrestha, Whitney & Shrestha (2004).
[d] Buschmann et al. (2007, 2008).
[e] Berg et al. (2001, 2007).

7. FOOD CONSUMPTION AND DIETARY EXPOSURE ESTIMATES

Dietary exposure estimates for arsenic were reported by the Committee at its twenty-seventh meeting and were not revised at the thirty-third meeting. Only values for total arsenic were given for several European countries, the USA, Canada and the Republic of Korea; these ranged from 10 to 200 µg/day from food (0.17–3.33 µg/kg bw per day, assuming a 60 kg body weight). Estimated dietary exposures to total arsenic from water ranged from 15 to 750 µg/day (0.25–12.5 µg/kg bw per day), the range reflecting normal arsenic concentrations in water (10 µg/l) and elevated arsenic concentrations (500 µg/l), assuming consumption of 1.5 litres of water a day. The Committee at its twenty-seventh meeting noted that water and seafood were the major sources of total arsenic, with other foods making minor contributions.

In the majority of studies on dietary arsenic exposure, available results were reported for total arsenic rather than for inorganic arsenic, which was of more interest for the evaluation. Results available for total arsenic are discussed below, with more focus given to the available estimates of inorganic arsenic dietary exposure. In the earlier studies that report inorganic arsenic dietary exposures, set

conversion factors were used to estimate inorganic arsenic dietary exposures from total arsenic dietary exposures, rather than analytical values.

Many of the early studies, total diet studies in particular, did not include consumption of water, and only one mentioned dietary supplements. They are therefore likely to underestimate total and inorganic arsenic dietary exposures.

At the present meeting, the Committee considered dietary exposure estimates submitted by China, Japan, Australia and New Zealand, published total diet studies and other reports in the literature.

7.1 Arsenic levels used in dietary exposure estimates

The main factors influencing arsenic content in food are the water supply, type of food and food preparation methods.

Reported arsenic levels in water from different countries were given in section 6.2. Arsenic levels in water used in the dietary exposure estimates evaluated are given in Table 12, with the high consumption or maximum amount of water drunk reported.

As noted in section 6, total arsenic levels are higher in fish and seafood commodities than in most other foods, but the arsenic is mainly organic. Levels vary a great deal with species, region and level of water contamination (Cheung, Leung & Wong, 2008). Total arsenic levels tend to be higher in marine fish than in freshwater fish (Larsen & Francesconi, 2003), except for fish from areas with geothermal waters (Whyte et al., 2009). Individual concentrations can be assigned to the correct fish species for the purpose of estimating dietary exposure only if food consumption records are sufficiently detailed. However, more often, a mean concentration is derived for a broad food group such as fish or shellfish, thus losing some accuracy in the dietary exposure estimate.

Rice tends to be a major source of inorganic arsenic in the diet, particularly in Asian countries, where it is a staple food. Speciation of arsenic in rice varies between different regions, with a higher inorganic content in rice grown in Asia compared with the USA (Williams et al., 2005; Meharg et al., 2009). Enhanced arsenic assimilation in rice also results in elevated concentrations compared with other grains (Williams et al., 2007).

The level of inorganic arsenic in the food consumed also depends on food processing and preparation methods. Water can be a major source of inorganic arsenic in food if the food is produced by irrigation with arsenic-contaminated water and/or from food preparation and cooking with contaminated water (see section 6).

The fact that water consumption and water used in cooking are not always included in dietary exposure estimates means that exposure will be underestimated where water has not been included. It also makes direct comparison of reported total and inorganic dietary exposures from different studies difficult.

There are numerous reports of total arsenic levels used in reported dietary exposure estimates, particularly from total diet and duplicate diet studies.

Table 12. Total arsenic levels in water used in dietary exposure estimates

Country or region (references)	Sample number	Mean level (mg/kg)	Median level (mg/kg)	Maximum level (mg/kg)	Water legislation limit (mg/kg)	Maximum amount of water consumed (litres/day)	Comment
Europe (EFSA, 2009)	15 365	0.0013 LB 0.0022 UB	0.000 LB 0.001 UB	0.47	0.01	2.4 95th percentile	Scenarios assume water is 50%, 70% or 100% inorganic
USA (Meliker et al., 2006)	12 520 homes, 1300 communal sources		0.0004 DW 0.0004 cooking	0.099 DW	0.01	4.25 DW 0.97 cooking 2.36 beverages 5.31 coffee	Analytical values used in dietary exposure estimates
USA (Schoof et al., 1999; NRC, 2001; Tsuji et al., 2007)	4	0.0018 total 0.0008 inorganic			0.01	1.9–2.2 DW 95th percentile 1.3–1.7 food processing 95th percentile	Water sampled in one state Two-day averaged water consumption over four regions
Canada (Health Canada, 2006)		0.0018		0.580	0.01		Levels higher in groundwater than in surface water
Bangladesh (Watanabe et al., 2004)				0.001–0.6	0.05	3 mean 6 maximum	Watanabe et al. (2004) study: rural communities using tube wells, 38 participants

Table 12 (contd)

Country or region (references)	Sample number	Mean level (mg/kg)	Median level (mg/kg)	Maximum level (mg/kg)	Water legislation limit (mg/kg)	Maximum amount of water consumed (litres/day)	Comment
Australia (NHMRC, 2004; FSANZ, 2009a)					0.007	2.2 90th percentile	
New Zealand (MOH, 2008; FSANZ, 2009b)					0.01	2.0 90th percentile	

DW, drinking-water; LB, lower bound; UB, upper bound

The 2009 EFSA review used 100 857 results from European countries reported in a 2008 data call to derive total arsenic levels for 15 major food groups, statistically adjusting mean levels for the proportion of individual foods in each food group for use in the dietary exposure assessment (Table 13; EFSA, 2009). These included previously reported values in Europe for total diet studies and from a previous Scientific Cooperation on Questions relating to Food (SCOOP) project (Leblanc et al., 2000; SCOOP, 2004; COT, 2008).

Table 13. Mean adjusted total arsenic content of foods used in the EFSA (2009) dietary exposure estimates[a]

Food group	Total arsenic lower bound mean level (mg/kg)	Total arsenic upper bound mean level (mg/kg)
01. All cereal & cereal products	0.0671	0.0848
01.A Cereal-based dishes	0.0157	0.0283
01.B Cereal & cereal products	0.0825	0.1017
02. Sugar products and chocolate	0.0135	0.0320
03. Fats (vegetable and animal)	0.0063	0.0245
04. All vegetables, nuts, pulses[b]	0.0121	0.0212
04.A Vegetable soups	0.0050	0.0110
04.B Vegetables, nuts, pulses[b]	0.0122	0.0213
05. Starchy roots and tubers	0.0031	0.0142
06. Fruits[b]	0.0051	0.0155
07. Juices, soft drinks and bottled water	0.0030	0.0068
07.A Fruit and vegetable juices[b]	0.0048	0.0129
07.B Soft drinks	0.0044	0.0132
07.C Bottled water	0.0023	0.0041
08. Coffee, tea, cocoa[b]	0.0034	0.0051
09. Alcoholic beverages	0.0055	0.0151
09.A Beer and substitutes	0.0054	0.0161
09.B Wine and substitutes	0.0061	0.0110
09.C Other alcoholic beverages	0.0085	0.0155
10. All meat and meat products, offal	0.0044	0.0138
10.A Meat and meat products	0.0042	0.0137

Table 13 (contd)

Food group	Total arsenic lower bound mean level (mg/kg)	Total arsenic upper bound mean level (mg/kg)
10.B Edible offal and offal products	0.0044	0.0139
10.C Meat-based preparations	0.0121	0.0185
11. All fish and seafood	1.6136	1.6159
11.A Seafood and seafood products	5.5537	5.5545
11.B Fish and fish products	1.4426	1.4549
11.C Fish-based preparations	1.1524	1.1573
12. Eggs	0.0042	0.0117
13. Milk and milk-based products	0.0044	0.0139
13.A Milk and dairy-based drinks	0.0026	0.0104
13.B Dairy-based products	0.0068	0.0184
13.C Cheese	0.0065	0.0188
14. Miscellaneous/special dietary products	0.3993	0.4187
14.A Miscellaneous products	0.2449	0.2658
14.B Foods for special dietary uses	0.4383	0.4573
15. Tap water	0.0013	0.0022

[a] Adjusted mean for whole food category obtained by applying relevant sampling adjustment factor to food subcategories to correct for unbalanced proportion of samples analysed in these subcategories in relation to their actual dietary contribution; non-adjusted means for whole food categories where means not reported for subcategories.

[b] Calculated mean values include conversion to fresh mass by applying various dilution factors.

Source: EFSA (2009).

Total arsenic levels for some foods in other countries reported prior to 2004, mainly from total diet studies, were summarized in the review of arsenic in food by Uneyama et al. (2007) and are not reported here. Arsenic levels from some of the more recent studies on dietary exposure are given in Table 14 for seafood and rice and some other foods, with inorganic arsenic levels given where reported.

Inorganic levels are high in a few rarely consumed foods, such as seaweed, particularly hijiki seaweed, and edible algae; these foods were included in the miscellaneous food group in the European estimates (EFSA, 2009), but dealt with separately in a study in the United Kingdom (FSA, 2004a). In Japan, seaweed is a more important part of the diet and can make a significant contribution to dietary exposures, particularly for people with high consumption of these food items (Uneyama et al., 2007; Ogawa & Kayama, 2009).

Table 14. Mean total and inorganic arsenic content for rice, seafood and some other foods used in dietary exposure estimates other than in the EFSA (2009) report

Country/region (reference)	Food group	Amount consumed (g/day)	Total arsenic mean level (mg/kg)	Inorganic arsenic mean level (mg/kg)
Australia (FSANZ, 2003, 2009a)	White rice (ww)	125 90th percentile (2009 estimate)	0.03–0.06 (LB–UB, 2003 estimate) 0.109 (2009 estimate)	
	Infant mixed cereal (2003 estimate)		0–0.07	
	Seafood (2009 estimate)	180 oysters 206 lobsters 232 fish 90th percentile	0.29 salmon 0.42 fish 0.70 crustaceans 0.335 lobsters 2.40 oysters 11.40 crabs	
Bangladesh (Rahman et al., 2008)	Rice from Bangladesh grown under different soil and water conditions, highest value when soil treated with arsenic at 40 mg/kg	400–650	0.05 (SD 0.02)	
Bangladesh (Williams et al., 2005)			0.13	

Table 14 (contd)

Country/region (reference)	Food group	Amount consumed (g/day)	Total arsenic mean level (mg/kg)	Inorganic arsenic mean level (mg/kg)
Bangladesh, China, Egypt, France, India, Italy, Japan, Spain, Thailand, USA (Meharg et al., 2009)	Rice (India lowest arsenic level; USA, France highest arsenic level)	15 mean France 18 mean USA 218 mean China 445 mean Bangladesh (FAO food balance sheet data)	Mean 0.15 (range 0.05–0.28) Median 0.13 (range 0.04–0.25) Maximum 0.82	Mean range 0.03–0.11 Median range 0.03–0.12 Maximum 0.38
Belgium (Baeyens et al., 2009)	Fish (19 species) Seafood (4 species)	14.7 mean 4.0 mean	12.83 (SD 12.01) 21.57 (SD 20.88)	0.132 (SD 0.075) 0.198 (SD 0.068)
China, Hong Kong Special Administrative Region (Cheung, Leung & Wong, 2008)	Fish – ponds Fish – freshwater Fish – marine	142 high consumer	0.70–3.44 0.24–2.13 0.93–8.11	Assumed 10% inorganic
China, Province of Taiwan (Schoof et al., 1998)	Rice Yam	225 ww 500 ww	0.120–0.150 dw 0.081 dw	0.083–0.110 dw 0.058 dw
China, Province of Taiwan (Lin, Wong & Li, 2004)	Rice	178 ww	0.08 (0.05 polished–0.12 unpolished)	
	Seafood	24	1.66 (0.8–3.17) oysters 1.55 (0.51–3.76) mussels	
China, Province of Taiwan (DOH, 2009)	Rice sampled in 1993, 1997	130–365 per capita (highest 1972, lowest 2007)	0.22 unpolished 0.24 polished	
United Kingdom (Meharg et al., 2008)	Infant rice food (17 samples)	20 g serving, up to 3 servings per day	Median 0.22 (range 0.12–0.47)	Median 0.11 (range 0.06–0.16)

Table 14 (contd)

Country/region (reference)	Food group	Amount consumed (g/day)	Total arsenic mean level (mg/kg)	Inorganic arsenic mean level (mg/kg)
United Kingdom (FSA, 2004a)			*As sold*	*As sold*
	Seaweed – hijiki		110.0	77.0
	Seaweed – others[a]		24.0–50.0	<0.3
			As prepared	*As prepared*
	Seaweed – hijiki		16.0	11.0
	Seaweed – others		3.0–4.0	<0.3
USA (Schoof et al., 1999 [selection of foods with higher levels given only]; Batres-Marquez & Jensen, 2005; Tsuji et al., 2007)	Rice	*Rice*	0.303 (SE 0.061) ww	0.074 (SE 0.0096) ww
	Bread (flour)	11 dw	0.039 (SE 0.006)	0.011 (SE 0.0026)
	Watermelon	USA average	0.042 (SE 0.003)	0.009 (SE 0.0005)
	Saltwater finfish	115 dw	2.369 (SE 1.311)	0.0005 (SE 0.0002)
	Freshwater finfish	Asian, Pacific Islander groups	0.160 (SE 0.132)	0.001 (SE 0.0003)
	Tuna	average in USA	0.512 (SE 0.131)	0.001 (SE 0)
	Shrimp		1.890 (SE 0.566)	0.0019 (SE 0.0003)
	Beef		0.052 (SE 0.110)	0.0004 (SE 0.0002)
	Chicken		0.086 (SE 0.006)	0.0009 (SE 0.0001)
	Pork		0.014 (SE 0.001)	0.0006 (SE 0.0000)
USA (Meliker et al., 2006)	Seaweed	Median 0.0 Maximum 2.2		Median 0.36 Maximum 0.57

dw, dry weight; FAO, Food and Agriculture Organization of the United Nations; LB, lower bound; SD, standard deviation; SE, standard error; UB, upper bound; ww, wet weight

[a] Arame, wakame, kombu, nori.

7.1.1 Conversion factors from total arsenic to inorganic arsenic

In studies in which inorganic arsenic levels are not measured or the LOD is too high to measure inorganic arsenic accurately, conversion factors are often used to estimate inorganic arsenic levels from the total arsenic results for use in estimating dietary exposure. However, the factors used vary from study to study (Table 15). Prior to recent studies that have reported measured inorganic arsenic levels accurately in a wide variety of foods as well as fish and seafood commodities, it was common to assume that inorganic arsenic levels for all foods were up to 10% of total arsenic levels, on the assumption that this was the worst case for conversion for fish and seafood commodities, the major contributors to total arsenic dietary exposures.

7.2 Dietary exposure estimates

7.2.1 Estimates of total arsenic dietary exposure

A comprehensive review of total arsenic content and dietary exposure estimates from total diet studies from the 1970s to 2002 was given in Uneyama et al. (2007), with reported total arsenic dietary exposures across many different countries: for Europe, from 0.001 µg/day for Portugal to 458 µg/day for Spain; for Asia, from 27 µg/day for Japan to 658 µg/day for India; for the USA and Canada, from 6 to 137 µg/day; for New Zealand, 55 µg/day; and for South America, from 7 µg/day for Brazil to 394 µg/day for Mexico.

Estimates of dietary exposure to total arsenic for the whole population derived from individual dietary records for 19 European countries were reported in 2009 and are summarized in Table 16. For Europe, mean total arsenic dietary exposures ranged from 0.45 to 4.58 µg/kg bw per day, and 95th-percentile exposures from 1.75 to 11.22 µg/kg bw per day.

Estimates derived from individual records reported elsewhere in the scientific literature are given in Table 17. Total arsenic dietary exposure estimates (including water) for the USA, Australia and New Zealand were lower than those for Europe, although arsenic levels for individual foods were used in the estimates, rather than for wide food groups, as in the European estimates: USA mean 0.39 µg/kg bw per day (tap water included) (Xue et al., 2010); Australia/New Zealand mean 0.5–0.7 µg/kg bw per day (tap water included), 95th percentile 0.8–1.0 µg/kg bw per day (FSANZ, 2009a,b). Those reported for countries with high-rice diets and/or arsenic-contaminated water were much higher: Japan mean 3.82–4.73 µg/kg bw per day (Tsuda et al., 1995); Bangladesh mean 0.91 µg/kg bw per day in an area with no detected arsenic in the drinking-water (Kile et al., 2007b), 10.30–13.48 µg/kg bw per day in rural areas with contaminated tube well water (Watanabe et al., 2004); Chile mean 2.18–23.3 µg/kg bw per day in an area with high arsenic levels in the river water used as drinking-water (Díaz et al., 2004).

Table 15. Reported conversion factors from total arsenic to inorganic arsenic

Data source	Food	No. of samples	Mean % inorganic	Comments
Uneyama et al. (2007)	Vegetable and cereal	21	84.0 (70–100)	Conversion factors extracted from literature values and applied to total arsenic dietary exposures for a variety of total diet studies
	Fish	133	4.2 (0–50)	
	Crustaceans, other seafood	97	2.2 (0–12)	
	Seaweed (except hijiki)	40	3.3 (0–20)	
	Hijiki	15	61.0 (30–82)	
	Meat, dairy	not sampled	100 (assumed value)	
EFSA (2009)	Fish	170	2.0	Standard ratios for fish and seafood commodities used in EFSA assessment regardless of total arsenic concentration, as proportion inorganic decreases as total arsenic concentration increases (Sirot et al., 2009a) For all other foods, EFSA assessment for inorganic arsenic assumes 50%, 70% or 100% inorganic scenarios
	Seafood products	219	3.5	
			Standard ratio	
	Fish		0.015 or 0.03 mg/kg	
	Seafood products		0.05 or 0.10 mg/kg	
	Rice	200	50–60 (30–90 reported in literature)	
	Cereal products and vegetables		30–100 (Schoof et al., 1999; Muñoz et al., 2002; Díaz et al., 2004)	
	Tea		29–88 (C. Yuan et al., 2007)	
	Edible algae		60	

Table 15 (contd)

Data source	Food	No. of samples	Mean % inorganic	Comments
Yost, Schoof & Aucoin (1998)	Milk and dairy products		26	Single samples, duplicates
	Meat		100	
	Poultry		41	
	Fish saltwater		1	
	Fish freshwater		15	
Leblanc et al. (2000)	All foods		10	Based on worst-case scenario for fish and seafood commodities, assuming most inorganic arsenic will derive from fish and seafood commodities, which were major sources of total arsenic

Table 16. Dietary exposure to total arsenic for Europe, individual dietary records

Country	Number of subjects	Mean[b] (µg/kg bw per day)	95th percentile (µg/kg bw per day)	Comments
Europe (summary over all countries)[a]		0.45 minimum LB 0.94 median LB 4.31 maximum LB 0.65 minimum UB 1.22 median UB 4.58 maximum UB	1.75 minimum LB 3.16 median LB 10.96 maximum LB 1.97 minimum UB 3.38 median UB 11.22 maximum UB	Foods assigned mean analytical values for Europe (100 867 results, sampling adjustment factors used in each food category) Differences in dietary exposure due to different food consumption patterns in each country Includes drinking-water
Austria	2123	0.88–1.14 LB–UB	4.15–4.40 LB–UB	24 h recall, 2005–2006
Belgium	1723	0.91–1.19 LB–UB	2.79–3.11 LB–UB	2 × 24 h recall, 2004–2005
Bulgaria	853	0.86–1.08 LB–UB	3.89–4.16 LB–UB	24 h recall, 2004
Czech Republic	1751	0.87–1.16 LB–UB	2.74–3.01 LB–UB	2 × 24 h recall, 2003–2004
Denmark	3159	0.94–1.22 LB–UB	2.10–2.44 LB–UB	7-day pre-coded diary with open fields, 2000–2004
Estonia	2010	0.86–1.10 LB–UB	3.97–4.20 LB–UB	24 h recall, 1997
Finland	2007	0.98–1.21 LB–UB	3.16–3.38 LB–UB	2 × 24 h recall (one interview, consecutive days), 2007
France	1195	1.61–1.88 LB–UB	3.97–4.25 LB–UB	7-day dietary record, 2006–2007
Germany	3550	1.05–1.36 LB–UB	2.41–2.78 LB–UB	2 × 24 h recall, 2005–2007
Great Britain	1724	1.07–1.07 LB–UB	2.89–3.18 LB–UB	7-day dietary record, 2000–2001

Table 16 (contd)

Country	Number of subjects	Mean[b] (µg/kg bw per day)	95th percentile (µg/kg bw per day)	Comments
Hungary	927	0.60–0.84 LB–UB	1.75–1.97 LB–UB	3-day dietary record, 2003–2004
Iceland	1075	1.46–1.75 LB–UB	4.75–5.17 LB–UB	Not available
Ireland	1372	0.98–1.27 LB–UB	2.25–2.65 LB–UB	7-day dietary record, 1997–1999
Italy	1544	2.11–2.37 LB–UB	6.54–6.74 LB–UB	3-day dietary record, 2005–2006
Netherlands	4285	0.79–1.07 LB–UB	2.42–2.69 LB–UB	2 × 24 h recall, 2003
Norway	2321	4.31–4.58 LB–UB	10.96–11.22 LB–UB	Not available
Poland	2692	0.93–1.25 LB–UB	3.58–3.91 LB–UB	24 h recall, 2000
Slovakia	2208	0.45–0.65 LB–UB	2.15–2.48 LB–UB	24 h recall, 2006
Sweden	1088	2.53–2.82 LB–UB	6.46–6.80 LB–UB	7-day dietary record, 1997–1998

LB, lower bound; UB, upper bound

[a] EFSA Concise European Food Consumption Database, 19 countries; individual dietary records, body weights, whole population; arsenic levels reported in 2008.

[b] Except where otherwise indicated.

Source: EFSA (2009)

Table 17. Other estimates of dietary exposure to total arsenic, individual records

Country (reference)	Data source	Mean (µg/kg bw per day)	90th/95th percentile (µg/kg bw per day)	Comments
Australia (FSANZ, 2009a)	Food consumption from 1995 NNS, consumers were whole population 2+ years (all were arsenic consumers) Arsenic levels from TDS and other sources	*Tap water not included* 0.5–0.6 mean 0.1–0.2 median *Tap water included* 0.6–0.7 mean 0.3–0.3 median	*Tap water not included* 0.6–0.7 90th percentile *Tap water included* 0.8–1.0 90th percentile	Range lower to upper bound Assumed inorganic arsenic level at Australian drinking-water guideline, maximum of 7 µg/l, 100% inorganic
Bangladesh (Watanabe et al., 2004)	24 h recall, FFQ and interviews, 38 participants for water consumption study, 230 samples for food recall/FFQ	13.48 males 10.30 females		Assumed 50 kg bw to convert to per kg bw Tube well water, assumed arsenic level of 0.10 mg/l
Bangladesh (Kile et al., 2007b)	Duplicate diets × 6 days, 47 women from longitudinal study on arsenic and biomarker response	0.91 mean background (arsenic not detected in drinking-water)	0.96 median food only 1.36 median food + water	Average 50 kg bw Inorganic fraction of duplicate diets was 81 ± 13.9% Rice main contributor from diet, little seafood consumed, as inland community Tube well water arsenic level 0.0016 mg/l median, range from 0 to 0.45 mg/l
Chile (Díaz et al., 2004)	24 h recall in 1999, 50 participants, foods prepared as consumed prior to analysis (results in Muñoz et al., 2002)	0.63–1.1 mean food 2.18–23.3 mean food + water		Assumed 60 kg bw to convert to per kg bw Range of values due to different analysed water content at two sampling periods (0.041–0.572 mg/l)

Table 17 (contd)

Country (reference)	Data source	Mean (µg/kg bw per day)	90th/95th percentile (µg/kg bw per day)	Comments
France (Leblanc et al., 2000)	Duplicate diet method, only breakfast and lunch meals provided out of home analysed	1.82		Total dietary exposure derived by assuming total = breakfast + 2 × lunch values, drinking-water not included Assumed 60 kg bw
France (Sirot et al., 2009a)	996 participants, FFQ for fish and seafood commodities plus mean consumption from French national survey for other foods, fish and seafood commodities analysed	11.04 males 13.53 females	25.14 males 95th percentile 33.00 females 95th percentile	Frequent fish and seafood commodity consumers (>2 meals per week) from coastal area Includes drinking-water
Japan (Tsuda et al., 1995)	3 × duplicate diets, 79 women, Shiga Prefecture	4.73 (SD 3.46) 1991 3.82 (SD 2.00) 1992	na	Assumed 55 kg bw, drinking-water not included
Japan (Ogawa & Kayama, 2009)	2007 diet history of women and 10-year-old children in fishing and rice-growing communities Analysed composite values for rice, vegetables, seaweed, fish	24.10 fishermen's wives 23.57 rice farmers' wives 19.71 10-year-old children (TDS for whole population 4.91–4.96 reported in 2008)	*95th percentile* 78.00 fishermen's wives 68.86 rice farmers' wives 68.86 10-year-old children *Maximum* 159.57 fishermen's wives 148.86 rice farmers' wives 114.00 10-year-old children	Assumed 50 kg bw Range lower to upper bound Lower-bound non-detects = 0, upper-bound non-detects = ½ LOQ Dietary exposure for high consumers of edible algae, seaweed, fish and shellfish

Table 17 (contd)

Country (reference)	Data source	Mean (µg/kg bw per day)	90th/95th percentile (µg/kg bw per day)	Comments
New Zealand (FSANZ, 2009b)	Food consumption from 1997 NNS adults (all were arsenic consumers) Arsenic levels from TDS and other sources	*Tap water not included* 0.4–0.5 mean 0.1–0.2 median *Tap water included* 0.5–0.6 mean 0.2–0.3 median	*Tap water not included* 0.6–0.7 90th percentile *Tap water included* 0.8–0.9 90th percentile	Range lower to upper bound Assumed inorganic arsenic level at WHO drinking-water guideline, maximum of 10 µg/l
USA (Xue et al., 2010)	USA TDS analytical values for total arsenic used from 1991–2004, with conversion factors from Schoof et al. (1999) NHANES 2003–2004 1-day data used for food consumption	0.36 food 0.03 water	1.40 food 95th percentile 0.11 water 95th percentile	SHEDS – Dietary model, probabilistic model, included food and water consumption (recipes used to convert food to raw agricultural commodities)

FFQ, food frequency questionnaire; LOQ, limit of quantification; na, not available; NNS, National Nutrition Survey; TDS, total diet study

For communities where seafood is a major component of the diet, higher total arsenic dietary exposure estimates were reported. For a coastal community in France, a mean exposure of 11.04–13.53 µg/kg bw per day and a 95th-percentile exposure of 25.14–33.00 µg/kg bw per day were reported (Sirot et al., 2009a). For Japanese fishermen's or rice farmers' wives who were known to be high consumers of fish and edible algae and seaweed, mean dietary exposures were 23.57–24.10 µg/kg bw per day, and 95th-percentile dietary exposures were 68.86–78.00 µg/kg bw per day. For 10-year-old children in these communities, mean dietary exposure was 19.71 µg/kg bw per day, and 95th-percentile dietary exposure was 68.86 µg/kg bw per day (Ogawa & Kayama, 2009).

Dietary exposures to total arsenic from total diet studies or other model diets reported since 2003 are presented in Table 18.

A wider range of total dietary exposure was reported in total diet studies or model diet estimates (mean total arsenic dietary exposures from 0.250 to 4.75 µg/kg bw per day for adults), compared with those calculated using individual dietary records, for Europe, Australia and New Zealand, which had estimates using both approaches. Estimates for China, Hong Kong Special Administrative Region, Chile and Bangladesh were within this range. Estimates for children indicate higher total arsenic dietary exposure than for adults from the same country, except for young infants, who rarely consume seafood (FSANZ, 2003; NZFSA, 2006).

7.2.2 Contributions to total arsenic dietary exposure

Most studies reported that fish and seafood commodities were the major contributors to total arsenic dietary exposure, although consumption of these foods usually constitutes only a small part of the diet. For infants, rice and rice cereals also make a major contribution (Tao & Bolger, 1999; Uneyama et al., 2007; FSANZ, 2009a,b).

For the USA, in a summary of total diet studies from 1991 to 1996, Tao & Bolger (1999) reported that for the population 2 years of age and over, the highest proportion of total arsenic dietary exposures was from fish and seafood commodities (76–96%), with infants having a greater contribution from rice and rice cereals (42% fish and seafood commodities, 31% rice cereals). In Uneyama et al. (2007), major contributors to total arsenic dietary exposure were reported to differ by country: for the United Kingdom, fish was the major contributor (93.9%), followed by bread and cereals (3.1%); for Canada, fish was the major contributor (52.2%), followed by bakery goods and cereals (17%), meat and poultry (9.8%) and beverages (5.5%); for Spain, fish was the major contributor (97.7); for Japan, seafood was the major contributor (49.5%), followed by vegetables and seaweed (28.1%) and rice (17.2%).

Table 18. Estimates of dietary exposure to total arsenic using model diets or total diet approach, available since 2003

Country (reference)	Data source	Mean dietary exposure (µg/kg bw per day)	95th-percentile dietary exposure (µg/kg bw per day)	Comments
Australia (FSANZ, 2003)	Total diet study 2000–1001	0.56–0.88 M 25–34 years 0.49–0.78 F 25–34 years 0.50–0.83 boy 12 years 0.28–0.54 girl 12 years 0.55–1.30 child 2 years 0.37–1.40 infant 9 months		Range lower to upper bound (ND = 0 or LOD)
Bangladesh (Rahman et al., 2008)	Mean arsenic from rice grown under experimental conditions, water at maximum limit of 0.05 mg/l	0.20–0.35		Arsenic intake from mean rice consumption of 400–650 g/day plus 4 litres of water
Belgium (Baeyens et al., 2009)	Model diet Arsenic data for seafood collected in 1997–1998, 300 samples, other values from Leblanc et al. (2005)	4.75 whole population	10.82 whole population (90th percentile)	Assumed 60 kg bw for whole population, model diet included consumption of fish, seafood commodities, fruit and soft drinks only
Chile (Muñoz et al., 2005)	Market basket study, food prepared as consumed for analysis	1.13		24 h recall food consumption, mean body weight of 68 kg
China (China, 2010)	Total diet study 2007, 12 provinces for 18–45 males	0.99 overall mean 0.24–3.35 across provinces		63 kg bw for adult males

Table 18 (contd)

Country (reference)	Data source	Mean dietary exposure (µg/kg bw per day)	95th-percentile dietary exposure (µg/kg bw per day)	Comments
China, Hong Kong Special Administrative Region (Cheung, Leung & Wong, 2008)	Fish analysis, assumed 10% inorganic, high consumption amount for seafood only	0.23 freshwater fish 0.66 marine fish		Average body weight 55 kg, 142 g of fish per day
France (Leblanc et al., 2005)	Total diet study 2001–2002	1.04 adult 1.42 child 3–14 years	2.72 adult 3.43 child 3–14 years	Drinking-water included, assumed 60 kg bw adult, 30 kg child 3–14 years
New Zealand (NZFSA, 2006)	Total diet study 2003–2004	1.39–1.44 M 25 years 1.06–1.44 F 25 years 1.27–1.34 boy 11–14 years 0.69–0.74 girl 11–14 years 1.40–1.50 child 5–6 years 1.60–1.77 child 1–3 years 1.45–1.63 infant 6–12 months		Range lower to upper bound (ND = 0 or LOD), presented per week, converted to per day
Slovakia (Pavlovičová & Šalgovičová, 2008)	1) Household budget survey, model diets (diet based on nutrient requirements) 2) Arsenic data collected from 1994 to 2005 68 513 samples	1) 0.25–0.60 adults 2) 0.32–1.16 adults 0.57–1.16 4–6 years 0.42–0.82 7–11 years 0.36–0.70 12–15 years	1) 1.44–3.59 adults 2) 0.92–3.06 adults	2) Dietary exposure ranges are for lowest to highest results reported for individual years from 1994 to 2005, drinking-water not included Average body weight 70 kg adult, 18 kg 4–6 years, 33.5 kg 7–11 years, 47 kg 12–15 years

Table 18 (contd)

Country (reference)	Data source	Mean dietary exposure (μg/kg bw per day)	95th-percentile dietary exposure (μg/kg bw per day)	Comments
Spain (Martí-Cid et al., 2008)	Total diet study	3.19–3.73		Catalonia population, average body weight 70 kg male adult Fish and cereal group main contributors to dietary exposure Arsenic data collected in 2000 survey, ND = ½ LOD; arsenic data collected in 2006 survey, LB (ND = 0) estimate for 50 foods reported

F, female; LB, lower bound; M, male; ND, non-detects

In Australia, fish contributed 13–16% to total arsenic levels when water was excluded and 11–12% when it was included; other seafood commodities contributed 46–55% when water was excluded and 39–43% when it was included (FSANZ, 2009a). Similar results were reported for New Zealand, where fish contributed 26–32% to total arsenic levels when water was excluded and 21–24% when it was included; other seafood commodities contributed 27–38% when water was excluded and 24–29% when water was included (FSANZ, 2009b). Milk and rice were the only other food groups to contribute to total arsenic dietary exposures in Australia (10–13% when water was excluded, 8–11% when water was included) and in New Zealand (13–16% when water was excluded, 9–12% when water was included); rice contributed more than 1% but less than 5% in both countries. Water was reported to contribute 18–21% to total arsenic exposures in Australia and 22–25% in New Zealand (FSANZ, 2009a,b).

7.2.3 Estimates of inorganic arsenic dietary exposure

Estimates of inorganic arsenic dietary exposure either were derived by applying conversion factors to total arsenic levels for different foods or food groups prior to estimating exposure, such as in the 2009 EFSA report (EFSA, 2009), or have used measured inorganic arsenic levels.

Estimates of inorganic arsenic dietary exposure for 19 European countries are presented in Table 19. For Europe, mean inorganic arsenic dietary exposure estimates for different scenarios ranged from 0.21 µg/kg bw per day (lower-bound estimate, 0.05 mg/kg seafood, 50% inorganic arsenic in other foods) to 0.61 µg/kg bw per day (upper-bound estimate, 0.1 mg/kg seafood, 100% inorganic arsenic in other foods) (EFSA, 2009). Other estimates for the United Kingdom were within these ranges (FSA, 2004b, 2009). Estimates for people with high water consumption (mean 0.66 µg/kg bw per day) and high consumption of edible algae (4.03 µg/kg bw per day) were given in the EFSA report (EFSA, 2009).

Reported inorganic arsenic dietary exposures for some non-European countries are given in Table 20. Mean inorganic arsenic dietary exposures for the four studies in the USA were in the same range for the general population, from 0.0 to 0.10 µg/kg bw per day (Meacher et al., 2002; Meliker et al., 2006; Tsuji et al., 2007; Xue et al., 2010), the highest being from the probabilistic estimate by Tsuji et al. (2007), noting that the ranges given for each study relate to the inclusion of different sources of inorganic arsenic. Xue et al. (2010) reported 95th-percentile inorganic arsenic dietary exposures of 0.19 µg/kg bw per day for the general population; Meliker et al. (2006) reported higher 95th-percentile exposures of 0.34 µg/kg bw per day, with a maximum reported exposure of 1.80 µg/kg bw per day, from an area in south-east Michigan where the drinking-water was contaminated.

For France, there was a contrast between a duplicate diet study and estimates for coastal communities, with the latter estimated exposures being much higher than those for the general population (mean duplicate diet 0.18 µg/kg bw per day, assuming 10% total arsenic is inorganic; coastal communities mean 0.43–0.48 µg/kg bw per day, 95th percentile 0.95–0.98 µg/kg bw per day, using measured seafood analysis and other reported values).

Table 19. Predicted dietary exposure to inorganic arsenic, individual records for whole population, median of country means and 95th-percentile estimates for 19 European countries (EFSA, 2009)

Data source	Mean dietary exposure (µg/kg bw per day)	95th-percentile dietary exposure (µg/kg bw per day)	Scenario assumptions
19 European countries (EFSA, 2009), food consumption amounts based on EFSA Concise European Food Consumption Database - General diet Individual dietary records, body weights, whole population Arsenic levels reported in 2008	0.41–0.61 LB–UB	0.72–0.99 LB–UB	Scenario 1: Actual data for fish and seafood commodities, 100% total arsenic in other food is inorganic
	0.29–0.43 LB–UB	0.51–0.69 LB–UB	Scenario 2: Actual data for fish and seafood commodities, 70% total arsenic in other food is inorganic
	0.21–0.31 LB–UB	0.36–0.51 LB–UB	Scenario 3: Actual data for fish and seafood commodities, 50% total arsenic in other food is inorganic
	0.42–0.61 LB–UB	0.73–0.99 LB–UB	Scenario 4: 0.03 mg/kg fish, 0.1 mg/kg seafood commodities, 100% total arsenic in other food is inorganic
	0.30–0.43 LB–UB	0.51–0.69 LB–UB	Scenario 5: 0.03 mg/kg fish, 0.1 mg/kg seafood commodities, 70% total arsenic in other food is inorganic
	0.22–0.31 LB–UB	0.37–0.52 LB–UB	Scenario 6: 0.03 mg/kg fish, 0.1 mg/kg seafood commodities, 50% total arsenic in other food is inorganic
	0.41–0.60 LB–UB	0.72–0.97 LB–UB	Scenario 7: 0.015 mg/kg fish, 0.05 mg/kg seafood commodities, 100% total arsenic in other food is inorganic
	0.29–0.42 LB–UB	0.50–0.68 LB–UB	Scenario 8: 0.015 mg/kg fish, 0.05 mg/kg seafood commodities, 70% total arsenic in other food is inorganic
	0.21–0.30 LB–UB	0.36–0.49 LB–UB	Scenario 9: 0.015 mg/kg fish, 0.05 mg/kg seafood commodities, 50% total arsenic in other food is inorganic

Table 19 (contd)

Data source	Mean dietary exposure (µg/kg bw per day)	95th-percentile dietary exposure (µg/kg bw per day)	Scenario assumptions
- Special diets			
Consumers of algae as food	4.03		Specific diet (10 g algae) added to inorganic exposure from scenario 5
Consumers of bran and germ	0.48		Specific diet (2 g bran and germ) added to UB inorganic exposure from scenario 5
Consumers of fish and seafood commodities	0.47 fish 0.52 seafood		Specific diet (600 g fish or 400 g seafood commodities) added to UB inorganic exposure from scenario 5
Consumers of rice-based diets	1.02 ethnic 0.45 European		Specific diet (300 g raw rice ethnic diet, 9 g European diet plus water) added to UB inorganic exposure from scenario 5
Vegetarians	0.27–0.40		Scenario 5: 0.03 mg/kg fish, 0.1 mg/kg seafood commodities, 70% total arsenic in other food is inorganic; LB and UB values
People with high consumption of water	0.66		Specific diet (2 litres water at 0.002 mg/l [maximum concentration reported in EFSA data set]) added to UB inorganic exposure from scenario 5
France (Leblanc et al., 2000)	0.18		Duplicate diet method, only breakfast and lunch meals provided out of home analysed Total dietary exposure derived by assuming total = breakfast + 2 × lunch values, assumed 10% total arsenic is inorganic, drinking-water not included Assumed 60 kg bw

Table 19 (contd)

Data source	Mean dietary exposure (µg/kg bw per day)	95th-percentile dietary exposure (µg/kg bw per day)	Scenario assumptions
France (Sirot et al., 2009b)	0.43 males 0.48 females	0.98 males 0.95 females	996 participants, FFQ for fish and seafood commodities plus mean consumption from French national survey for other foods, fish and seafood commodities analysed Frequent consumers of fish and seafood commodities (>2 meals per week) from coastal area Includes drinking-water
United Kingdom (FSA, 2004b)	0.02–0.08 adults 0.03–0.1 children (4–18 years) 0.02–0.07 vegetarians	*97.5th percentile* 0.05–0.1 adults 0.08–0.2 children 0.05–0.1 vegetarians	Inorganic arsenic analysed when total arsenic high enough for measurement in 1999 total diet study, food consumption from NDNS (range LB–UB values given) Results for elderly "free living" and elderly "institutional" similar to adults
United Kingdom (FSA, 2009)	0.03–0.09 adults 0.06–0.16 children (4–18 years) 0.04–0.10 vegetarians	*97.5th percentile* 0.07–0.17 adults 0.13–0.29 children 0.08–0.16 vegetarians	Inorganic arsenic analysed when total arsenic high enough for measurement in 2006 total diet study, food consumption from NDNS (range LB–UB values given) Results for elderly "free living" and elderly "institutional" similar to adults

FFQ, food frequency questionnaire; LB, lower bound; NDNS, National Diet and Nutrition Survey; UB, upper bound

Table 20. Other estimates of dietary exposure to inorganic arsenic, individual records

Country (references)	Data source	Mean dietary exposure (µg/kg bw per day)	High-percentile dietary exposure (µg/kg bw per day)	Comments
Chile (Díaz et al., 2004)	24 h recall in 1999, 50 participants in area known to have contaminated water, foods prepared as consumed prior to analysis (results in Muñoz et al., 2002)	0.52–0.92 mean food 2.08–21.48 mean food + water		Assumed 60 kg bw to convert to per kg bw Range of values due to different analysed water content at two sampling periods (0.041–0.572 mg/l), water source is river water
Japan (Ogawa & Kayama, 2009)	2007 diet history of middle-aged fishermen's wives (n = 201), rice farmers' wives (n = 125) and 10-year-old children (n = 231)	0.39 fishermen's wives 0.36 rice farmers' wives 0.46 10-year-old children	*95th percentile* 1.29 fishermen's wives 0.83 rice farmers' wives 0.83 10-year-old children *Maximum* 2.87 fishermen's wives 1.63 rice farmers' wives 2.27 10-year-old children	Individual body weight Range LB–UB LB non-detects = 0, UB non-detects = ½ LOQ, conversion factors as in Uneyama et al. (2007), assumed 50% loss of inorganic arsenic from washing nori (algae), 10% from cooking seaweed High dietary exposure for consumers of edible algae, seaweed

Table 20 (contd)

Country (references)	Data source	Mean dietary exposure (µg/kg bw per day)	High-percentile dietary exposure (µg/kg bw per day)	Comments
USA (Schoof et al., 1999; Meacher et al., 2002)	1999 market basket survey, focused on foods likely to contain inorganic arsenic Adults 16–59 years, individual dietary records, CSFII 1989–1991	*Females* 0.04 food 0.046 water 0.08 all sources *Males* 0.05 food 0.04 water 0.09 all sources		Monte Carlo analysis, different source of inorganic arsenic (food, drinking-water, soil, inhalation) Assumed 70 kg bw to convert reported values to per kg bw values
USA (Meliker et al., 2006)	Individual dietary records 2003–2004 Case–control study, 440 elderly adults from south-east Michigan (87% males in study population) Water analysed for each household, other inorganic arsenic levels from literature	0.0–0.06 median	0.16–0.34 95th percentile 0.06–0.23 90th percentile 0.73–1.80 maximum	Monte Carlo analysis of individual dietary records, range for eight metrics taking inorganic arsenic from water from different sources, food and cigarettes into account 8% population with water levels >10 µg/l Estimates given per week, converted to per day

Table 20 (contd)

Country (references)	Data source	Mean dietary exposure (µg/kg bw per day)	High-percentile dietary exposure (µg/kg bw per day)	Comments
USA (Tsuji et al., 2007)	Inorganic arsenic levels from USEPA water data (Schoof et al., 1999) Whole population, children 1–6 years, individual dietary records, CSFII 1994–1996, 1998 Supplemental Children's Survey	0.20–0.21 1–6 years 0.09–0.10 all From food and water	*90th percentile* 0.34–0.36 1–6 years 0.18–0.19 all From food and water	Probabilistic analysis (FARE program) of inorganic arsenic exposure from food, water, soil, treated wood 2-day water consumption calculated from drinking-water plus food processing water Assume 60 kg bw for whole population, 17.3 kg for 1- to 6-year-old children Range LB (water distribution truncated at 0.01 µg/l) to UB (not truncated)
USA (Xue et al., 2010)	TDS analytical values for total arsenic used from 1991–2004, with conversion factors from Schoof et al. (1999) NHANES 2003–2004 1-day data used for food consumption	0.05 food 0.03 water	*95th percentile* 0.19 food 0.11 water	SHEDS – Dietary model, probabilistic model, included food and water consumption (recipes used to convert food to raw agricultural commodities) Assumed all arsenic in water inorganic

CSFII, Continuing Survey of Food Intakes by Individuals; FFQ, food frequency questionnaire; LB, lower bound; UB, upper bound

The European and USA values were much lower than those reported from studies in Chile and Japan. In Chile, where the drinking-water was known to be contaminated, mean inorganic arsenic dietary exposure from food and water ranged from 2.08 to 21.48 µg/kg bw per day. In Japan, in two rural fishing and rice-growing communities known to have high consumption of either fish, algae and seaweed or rice, respectively, mean inorganic arsenic dietary exposures for middle-aged women ranged from 0.36 to 0.39 µg/kg bw per day, with 95th-percentile exposures ranging from 0.83 to 1.29 µg/kg bw per day. For 10-year-old children, mean inorganic arsenic dietary exposure was 0.46 µg/kg bw per day, with a 95th-percentile exposure of 0.83 µg/kg bw per day.

For infants (Table 21), assuming single food consumption, the highest inorganic arsenic dietary exposure would be from 90 g of rice-based cereal (1.63 µg/kg bw per day), followed by 600 ml of water (0.69 µg/kg bw per day), then 800 ml of formula (0.10 µg/kg bw per day) or breast milk (0.03 µg/kg bw per day).

For young children, estimated mean inorganic arsenic dietary exposure from individual dietary records for the United Kingdom, Italy and the USA were in a similar range: Italy, 0.39–0.54 µg/kg bw per day for 0.5- to 7-year-old children (Meharg et al., 2008); United Kingdom, 0.05–0.30 µg/kg bw per day for 1.5- to 4.5-year-old children (FSA, 2004b, 2009); USA, 0.18 µg/kg bw per day for 1- to 6-year-old children (Yost et al., 2004) or from 0.08 µg/kg bw per day for 3- to 5-year-old children to 0.23 µg/kg bw per day for children less than 1 year of age (Xue et al., 2010). For European children aged 1–3 years, predicted median dietary exposures to inorganic arsenic were estimated to be slightly higher, ranging from 0.74 to 1.39 µg/kg bw per day for 1- to 3-year-old children, depending on the scenario used.

For infants and young children with high consumption, 95th-percentile estimates were as follows: Italy, 0.61–1.63 µg/kg bw per day for 0.5- to 7-year-old children (Meharg et al., 2008, as quoted in EFSA, 2009); Europe, 1.47–2.66 µg/kg bw per day for 1- to 3-year-old children (EFSA, 2009); and USA, 0.36 µg/kg bw per day for 1- to 6-year-old children (Yost et al., 2004) or from 0.21 µg/kg bw per day for 3- to 5-year-old children to 0.53 µg/kg bw per day for children less than 1 year of age (Xue et al., 2010).

Inorganic arsenic dietary exposures estimated from total diet studies or model diets are given in Table 22. Uneyama et al. (2007) used set inorganic to total arsenic ratios (see Table 15) to convert reported total arsenic dietary exposures from total diet studies to inorganic arsenic dietary exposures for the United Kingdom, Canada, Spain and Japan, as presented in Table 22. Dietary exposures have been given per kilogram body weight, assuming a 60 kg body weight for adults in all countries. Mean or median inorganic arsenic dietary exposure estimates ranged from 0.02 to 0.909 µg/kg bw per day, with the highest values reported for China (up to 0.76 µg/kg bw per day in one province), Japan (0.56 µg/kg bw per day), Bangladesh (median 0.60 µg/kg bw per day) and China, Province of Taiwan (mean 0.909 µg/kg bw per day, maximum 3.836 µg/kg bw per day), and lower values for Europe, the USA and India.

Inorganic arsenic dietary exposures for infants and young children reported from total diet studies (Table 23) were similar to those from individual dietary records for Europe and the USA.

Table 21. Estimated dietary exposure to inorganic arsenic for infants below 6 months of age and young children

Data source	Food consumption (g/day)	Mean/median dietary exposure (µg/kg bw per day)	95th-percentile exposure (µg/kg bw per day)	Assumptions
Europe				
Infants Arsenic values reported in Sternowsky, Moser & Szadkowsky (2002), Meharg et al. (2008)	*Infants* 800 breast milk 800 formula 90 rice-based food 600 water	 0.03 mean 0.10 mean 1.63 mean 0.69 mean		Mean body weight 6.1 kg for infants below 6 months of age Arsenic in breast milk all inorganic arsenic Maximum level for arsenic in water permitted in legislation (0.01 mg/l) Lower and upper bound values
Children Arsenic levels reported in 2008, food consumption from INRAN or EFSA Concise European Food Consumption Database (EFSA, 2009)	*Children* 0.5–3 years, Italy 4–7 years, Italy 8–12 years, Italy 1–3 years, Europe	 0.39–0.62 mean 0.38–0.54 mean 0.31–0.45 mean 0.74–1.39 median	 0.61–1.24 1.50–1.63 1.32 –1.51 1.47–2.66	 Range of median values across different countries
United Kingdom (FSA, 2004b)	1999 TDS	0.05–0.20 mean (1.5–4.5 years)	0.08–0.25 97.5th percentile (1.5–4.5 years)	Composite samples for 20 TDS food groups, individual diet records from NDNS Range lower bound–upper bound
United Kingdom (FSA, 2009)	2006 TDS	0.10–0.30 mean (1.5–4.5 years)	0.17–0.40 97.5th percentile (1.5–4.5 years)	Composite samples for 20 TDS food groups, individual diet records from NDNS Range lower bound–upper bound

Table 21 (contd)

Data source	Food consumption (g/day)	Mean/median dietary exposure (µg/kg bw per day)	95th-percentile exposure (µg/kg bw per day)	Assumptions
USA (Yost et al., 2004)	Inorganic arsenic levels from Schoof et al. (1999) 2 days of records, 1994–1998 CSFII, 1998 Supplemental Children's Survey	0.18 1–6 years	0.36 1–6 years 97.5th percentile	FARE program probabilistic model, foods consumed converted to raw commodity level, includes water used in cooking (0.8 mg/kg) but not drinking-water Assumes 17.3 kg child
USA (Xue et al., 2010)	TDS analytical values for total arsenic used from 1991–2004, with conversion factors from Schoof et al. (1999) Food consumption NHANES 2003–2004 1-day data	0.23 food <1 year 0.014 water 0.10 food 1–2 years 0.03 water 0.08 food 3–5 years 0.04 water	*95th percentile* 0.53 food <1 year 0.05 water 0.29 food 1–2 years 0.15 water 0.21 food 3–5 years 0.15 water	SHEDS – Dietary model, probabilistic model, included food and water consumption (recipes used to convert food to raw agricultural commodities) Assumed all arsenic in water inorganic

CSFII, Continuing Survey of Food Intakes by Individuals; INRAN, National Research Institute for Food and Nutrition, Italy; NDNS, National Diet and Nutrition Survey; TDS, total diet study

Table 22. Estimated dietary exposure to inorganic arsenic using model diets or total diet approach

Country (reference)	Data source	Mean[a] dietary exposure (µg/kg bw per day)	90th-percentile dietary exposure (µg/kg bw per day)	Comments
Belgium (Baeyens et al., 2009)	Arsenic data for seafood collected in 1997–1998, 300 samples, other values from Leblanc et al. (2005)	0.10 whole population	0.16 whole population	Assumed 60 kg bw for whole population, consumption of fish and seafood commodities, fruit and soft drinks only Measured inorganic arsenic values used for seafood, assumed 50% total arsenic was inorganic for fruit and soft drinks
China (China, 2010)	Total diet study 2007, 12 provinces, diets for males 18–45 years of age	0.43 overall mean 0.24–0.76 across provinces		63 kg bw reported for adult males
China, Province of Taiwan (Schoof et al., 1998)		0.909 mean 0.273 minimum 3.836 maximum		Includes consumption of rice and yams only (225 g wet weight of rice per day, 500 g wet weight of yams per day) Assumed 55 kg body weight to convert to per kg bw
United Kingdom (COT, 2008)	Total diet study	0.02 LB 0.12 UB		Assumed 60 kg bw Tap water not included
USA/Canada (Yost, Schoof & Aucoin, 1998)	Total diet study USA Total diet study Canada	0.2 adults 0.116 F 20–39 years 0.181 M 20–39 years		Conversion factors applied to food groups (Table 15) Assumed 70 kg bw to convert to per kg bw

Table 22 (contd)

Country (reference)	Data source	Mean[a] dietary exposure (μg/kg bw per day)	90th-percentile dietary exposure (μg/kg bw per day)	Comments
Various (Uneyama et al., 2007; Matsuda & Watanabe, 2008)	Total diet study, conversion ratios applied (Table 15)	0.12 United Kingdom 0.29 Canada 0.26 Spain 0.56 Japan		Assumed 60 kg bw for all populations
Various (Meharg et al., 2009)	Per capita rice consumption from FAO production and processing data for 2004 for 10 countries, rice analysis	0.60 median Bangladesh 0.40 median China 0.19 median India 0.02 median Italy 0.035 median USA		Assumed 60 kg bw Inorganic arsenic content derived by regression equation from median total arsenic content, assuming polished rice is 66.7% by weight husked rice (not calculated for all countries)

F, female; FAO, Food and Agriculture Organization of the United Nations; LB, lower bound; M, male; UB, upper bound

[a] Unless otherwise stated.

Table 23. Estimates of dietary exposure to inorganic arsenic for infants up to 1 month of age and young children using model diets or total diet approach

Country (reference)	Data source	Mean dietary exposure (µg/kg bw per day)	95th-percentile dietary exposure (µg/kg bw per day)	Comments
United Kingdom (Meharg et al., 2008)	Analysis of infant rice	0.45 median inorganic arsenic level, 1 serving 0.21 median intake from water	0.74 inorganic arsenic level for 1 serving	Assumed 9.25 kg bw for 1-year-old, 1 serving of infant rice = 20 g Assumed 1 litre of water consumed
USA/Canada (Yost, Schoof & Aucoin, 1998)	Total diet study USA Total diet study Canada	1.19 infant 0.94 toddler 0.32 child 1–4 years		Conversion factors applied to food groups (Table 15) Body weights of 7 kg, 10 kg, 15 kg for infant, toddler, 1- to 4-year-old child, respectively (Egan, Bolger & Carrington, 2007)

7.2.4 Contributions to inorganic arsenic dietary exposure

Uneyama et al. (2007) estimated inorganic arsenic dietary exposure from total arsenic exposures reported from total diet studies for four countries. Major contributors to inorganic dietary exposure were reported, assuming the conversion ratios given in Table 15 and dietary exposures in Table 19. The major food groups contributing to inorganic arsenic dietary exposure differed by country: for the United Kingdom, fish was the major contributor (36.7%), followed by beverages (14.3%), bread (12%) and other cereals (12%); for Canada, bakery goods and cereals were the major contributor (31.3%), followed by meat and poultry (21.6%), beverages (12.2%) and milk and dairy products (9.7%); for Spain, fish was the major contributor (66.1%), followed by milk (6.3%), meat (6.3%), bread (5.3%), potatoes (5.3%), vegetables (5.3%) and fruits (5.3%); for Japan, rice was the major contributor (47.4%), followed by vegetables and seaweed (29.9%), potatoes and cereals (9.3%) and seafood (8.1%).

In a case–control study of bladder cancer of 440 elderly individuals in an area in the USA where 8% of the population was exposed to arsenic in water at levels above 10 µg/l (south-east Michigan), the major contributors to inorganic arsenic dietary exposure were determined by a Monte Carlo analysis of eight metrics that included potential exposure from water, food and cigarettes (Meliker et al., 2006). Results indicated that arsenic in home drinking-water accounted for 55.1% variance and food 37.3% variance, with rice being the largest contributor. In the upper decile

of inorganic arsenic exposure, consumption of plain water and beverages made with water at home and ingestion of arsenic in water at work also contributed to exposure estimates, although water used for cooking and arsenic exposure from cigarettes only minimally altered the inorganic arsenic exposure estimates (95th percentile of inorganic arsenic exposure ranged from 11 to 24 µg/day or from 0.16 to 0.34 µg/kg bw per day, assuming an average body weight of 70 kg). The influence of inorganic arsenic levels in the drinking-water was shown by further analysis of the western area of the USA with arsenic levels in water higher than those in Michigan, where 71% variance was attributed to home drinking-water; and the north-eastern area of the USA, with arsenic levels in water lower than those in Michigan, where 30% variance was attributed to home drinking-water and 57% from food, mainly rice (Meliker et al., 2006).

In a more recent probabilistic analysis for the population of the USA, Xue et al. (2010) reported major food contributors to inorganic arsenic dietary exposure to be vegetables (24%), fruit and fruit juices (18%), rice (17%), beer and wine (12%) and flour, corn and wheat (11%); although water was included, it was not a major contibutor (Xue et al., 2010).

In a duplicate diet study in a rural area of Bangladesh, 90% variance in total arsenic dietary exposures was explained by the inorganic fraction of the diet, with tube well drinking-water concentrations contributing most to the variance; 60% of tube wells contained water with arsenic concentrations below the WHO guideline value of 0.01 mg/l, and 70% were below the Bangladesh water standard of 0.05 mg/l (Kile et al., 2007b).

8. DOSE–RESPONSE ANALYSIS AND ESTIMATION OF CARCINOGENIC RISK

8.1 Identification of key data for risk assessment

8.1.1 Pivotal data from biochemical and toxicological studies

Most studies in experimental animals have not shown increased tumour incidences following chronic oral exposure to inorganic arsenic, and it is considered that experimental animals do not provide a good model for the carcinogenicity of arsenic. Maternal oral exposure to arsenite has resulted in tumours in the offspring. The studies in which increased tumour incidence has been reported were generally designed for mechanistic research. In contrast, studies conducted according to standardized protocols for bioassays used for regulatory purposes were frequently negative. Taking into account the lack of a good animal model for carcinogenicity of arsenic compounds and the large number of data available from epidemiological studies, the Committee did not consider the data from experimental animals appropriate for the dose–response analysis.

Inorganic arsenic compounds have also shown reproductive and neuro-behavioural effects and lesser evidence of immunotoxicity, nephrotoxicity and cardiovascular effects. Although these data provide support for the plausibility of

associations reported in epidemiological studies, they are not pivotal for the dose–response analysis.

8.1.2 Pivotal data from human clinical/epidemiological studies

The main adverse effects reported to be associated with long-term ingestion of inorganic arsenic in humans are cancer, skin lesions, developmental effects, cardiovascular disease, neurotoxicity and diabetes. Of these, the greatest strength of evidence for a causal association is for cancers of the skin, urinary tract and lung and for skin lesions (hyperkeratosis, hyperpigmentation and hypopigmentation) observed in studies in which inorganic arsenic exposure was relatively high due to high levels of inorganic arsenic in drinking-water (e.g. ≥100 µg/l). The nutritional status of exposed populations has been observed to influence cancer risk. Thus, compromised nutrition (e.g. low protein intake) is also likely to be associated with significantly higher risk in these populations (USEPA, 2007; EFSA, 2009). For this report, studies were preferred that included documentation of relatively high concentrations of inorganic arsenic in drinking-water (e.g. >300 µg/l) and also relatively low concentrations (e.g. <100 µg/l) in order to avoid extrapolation below the observed range in the dose–response modelling. Pivotal studies were identified from epidemiological studies reporting a positive association with inorganic arsenic exposure and those adverse effects with the greatest strength of evidence for a causal association, as described in the following section. The relevant populations were located in Bangladesh and north-eastern Taiwan, China (see section 8.2.1).

For bladder cancer, at low levels of exposure to arsenic in drinking-water, smoking appears to be a consistent effect modifier: for those studies in which smoking behaviour was documented, smokers were observed to have a significantly increased risk of bladder cancer compared with non-smokers at a similar level of exposure.

A prospective cohort study in north-eastern Taiwan, China, was selected as a pivotal study for urinary cancer (Chen et al., 2010a). In total, 8086 subjects aged 40 years and older were recruited into the study, with “12 years” of follow-up. Arsenic concentrations in drinking-water were available for 6888 of these subjects. An advantage of the prospective cohort study design is that the cohort is classified in relation to exposure before disease develops, thereby reducing the likelihood of exposure misclassification. Standardized incidence ratios can also be estimated from this study design, unlike for the case–control design, which yields only OR estimates.

Cited bladder cancer case–control studies in which “never smoked” and “ever smoked” subjects were analysed separately are Bates, Smith & Cantor (1995), Kurttio et al. (1999) and Karagas et al. (2004) (Table 4). Karagas et al. (2004) found that among smokers, an elevated OR for bladder cancer was observed for toenail arsenic levels above 0.330 µg/g compared with below 0.06 µg/g. Among never smokers, there was no association between toenail arsenic and bladder cancer risk. A maximum likelihood estimate change point of 0.326 µg/g (95% CI 0.121–0.466) toenail arsenic was observed, which equates to approximately 50 µg/l in drinking-water. Owing to uncertainties regarding the precise relationship between toenail

arsenic and arsenic exposure in food and water, as described below, these studies were not selected for dose–response modelling.

A recent prospective cohort study of lung cancer involving 6888 participants 40 years of age and older with measured arsenic concentrations in drinking-water and "11 years" of follow-up in north-eastern Taiwan, China, was selected as a pivotal study (Chen et al., 2010b). A significant dose–response trend of lung cancer risk was associated with increasing arsenic drinking-water concentration. Advantages of this prospective cohort study design are described above. Smoking 25 pack-years or more and consuming well water with an arsenic level of 100 µg/l or higher yielded an RR of 6.97 (95% CI 3.4–14.3) for lung cancer, with no significant interaction between smoking and arsenic concentration. There was no significant association in non-smokers. The Committee noted that the papers of Chen et al. (2010a,b) related to the same cohort with the same follow-up time, which was an average of 11.5 years.

For the skin cancer end-point, studies with arsenic concentrations of 100 µg/l and below in drinking-water are shown in Table 3. Three studies that reported significant increases in skin cancer related to low-level arsenic exposure in drinking-water used toenail arsenic as a biomarker of exposure (Karagas et al., 2001b; Karagas, Stukel & Tosteson, 2002; Beane Freeman et al., 2004). Although toenail arsenic is deemed qualitatively useful to assess total arsenic exposure over the previous few months, uncertainty in relating this quantitatively to total exposure to inorganic arsenic in food and drinking-water precludes using the results from these studies in the evaluation of dietary exposure to arsenic. A large cohort study in Denmark that examined skin cancer effects found no significant effects with drinking-water arsenic concentrations up to 25 µg/l and thus was not useful for dose–response modelling.

The studies of Rahman et al. (2006) and Ahsan et al. (2006) were selected for dose–response modelling of skin lesions (hyperkeratosis, hyperpigmentation, hypopigmentation) characteristic of arsenic exposure. The foregoing studies established uniform diagnostic criteria to define arsenic-related skin lesions. A recent study conducted in Inner Mongolia, China, reported a significant increase in arsenic-induced skin lesions (Xia et al., 2009); however, concise diagnostic criteria for identification of skin lesions were not described, and therefore this study was not preferred for dose–response modelling.

The concentration of inorganic arsenic in drinking-water was used as the exposure metric in these studies; total dietary exposure to inorganic arsenic was not assessed. This approach does not allow for exposure to inorganic arsenic present in food, which in some populations exceeded that consumed in drinking-water, particularly where the concentration of inorganic arsenic in drinking-water was low. In order to provide an opinion on the risks to health related to the presence of inorganic arsenic in foodstuffs, it was necessary to make assumptions about the total dietary exposure to inorganic arsenic for the populations in which the respective health end-points were studied. Underestimating the total dietary exposure in the study populations will lead to an overestimation of the risk at an estimated exposure in other populations. Similarly, overestimating the total dietary exposure in the study

populations will lead to an underestimation of the risk at an estimated exposure in other populations.

Estimates of the total dietary exposure to inorganic arsenic for the different regions considered varied and are subject to a number of limitations that differ between studies—for example, small numbers of individuals surveyed for consumption habits, analysis of selected foods only and measurement of total arsenic rather than inorganic arsenic. In addition, foods that absorb water during cooking can absorb considerable amounts of arsenic if cooked in water containing relatively high amounts of arsenic (see section 6). This is particularly important for rice and therefore also needs to be taken into account in considering total dietary exposure to inorganic arsenic if foods have been analysed dry rather than as consumed.

The USEPA Science Advisory Board recommended that a range of values from at least 50 µg/day to as high as 200 µg/day should be used in a sensitivity analysis for the Asian study populations (USEPA, 2007). From the available information on occurrence and exposure, the Committee agreed that the lower end of this range was appropriate for the study populations in Bangladesh and north-eastern Taiwan, China, but noted that even higher arsenic exposure from rice should be considered for Bangladesh. To assess an appropriate upper level for modelling for the Bangladeshi population, information on food consumption and known total arsenic levels were used to estimate potential dietary exposures. Reported rice consumption for an adult male in South Asia varies from 400 to 650 g dry weight per day in Bangladesh (Watanabe et al., 2004; Williams et al., 2005; Rahman et al., 2008). Zavala & Duxbury (2008) analysed data sets (total of 887 samples) for total arsenic in rice produced in Bangladesh. The 75th-percentile arsenic concentrations for the two Bangladeshi data sets for a geographically structured national survey and data from five upazilas or subdistricts (~100 samples each from four areas and 40 from a fifth, where four of the five were known to have arsenic-contaminated irrigation water) were 0.3 mg/kg and 0.41 mg/kg, respectively. The highest reported total arsenic level was 1.08 mg/kg. A person consuming 500 g rice daily containing a total arsenic concentration of 1 mg/kg would ingest 500 µg of total arsenic per day. Inorganic arsenic has been found to range from 68% to 85% of total arsenic content, with the lower proportion of inorganic arsenic found at higher total arsenic levels—85% at 0.1 mg/kg and 68% at 1 mg/kg; the remaining arsenic in rice is predominantly DMA^V (Zavala et al., 2008). If inorganic arsenic is assumed to be 70% of the total arsenic concentration, the inorganic arsenic exposure from consuming 500 g rice containing total arsenic at 1 mg/kg would be 350 µg/day. This is an upper estimate compared with that reported by Watanabe et al. (2004) of 52 µg/day and 90 µg/day from rice for females and males, respectively. Inorganic arsenic is found in foods other than rice (Watanabe et al., 2004). Watanabe et al. (2004) also reported total arsenic dietary exposure from other foods for adult females and males in Bangladesh of, respectively, 46 and 63 µg/day from wheat, 22 and 60 µg/day from fish and <1 µg/day from potato. Taking into account that the arsenic in fish is predominantly organic, but there would be a higher proportion of inorganic arsenic in wheat, 400 µg of inorganic arsenic per day was taken as a reasonable estimate for high dietary exposure to inorganic arsenic from

rice and vegetables for adult males in the Bangladeshi study populations before considering the influence of cooking water. Thus, for Bangladesh, a range of 50–400 µg of inorganic arsenic per day from food was selected for modelling purposes.

For north-eastern Taiwan, China, the Committee considered that the range of 50–200 µg of inorganic arsenic per day from food for modelling purposes was consistent with the data available.

For modelling purposes, it is important to estimate the range of water consumed as drinking-water and via food due to use in food preparation. As discussed in EFSA (2009), estimated values for daily water intake were 1.7–3.5 litres direct consumption and 1 or 1.6 litres indirect consumption through use in cooking (e.g. preparation of food such as rice, sweet potato, yam, bread) (NRC, 1999, 2001; Watanabe et al., 2004; Kile et al., 2007b; Signes-Pastor et al., 2008; Pal et al., 2009). This provides a combined range of about 3–5 litres of water per day and was considered appropriate for the Bangladeshi study populations. For north-eastern Taiwan, China, rice forms a lesser proportion of the diet, and hence less water is likely to be used in cooking rice. It was noted that some would be used in the preparation of yams. Therefore, the Committtee identified a lower range of 2–4 litres of water consumption per day for this population.

From within the above ranges, the Committee identified average exposures of 140 and 75 µg of inorganic arsenic per day from food, respectively, for Bangladesh and north-eastern Taiwan, China, together with 4 and 3 litres direct plus indirect water consumption, respectively. These values were used in extrapolating from concentration in water to total dietary exposure to inorganic arsenic in the dose–response modelling. From the available data, an average body weight of 55 kg was identified for the epidemiological study populations.

8.2 General modelling considerations

8.2.1 Dose–response modelling and BMD calculations

In the dose–response analysis using the USEPA benchmark dose (BMD) software (BMDS version 2.1.1), the nine different dichotomous models were fitted to the adjusted data. Those resulting in acceptable fits based on statistical considerations were selected to derive BMD and lower limit on the BMD (BMDL) values for a benchmark response (BMR) at the low end of the observed range of the data. Doses in units of milligrams per person per day were initially used for deriving BMDs. These were then converted to milligrams per kilogram body weight per day by dividing by a body weight of 55 kg per person.

8.2.2 Selection of data

For modelling of urinary and lung cancer dose–response, the studies of Chen et al. (2010a,b) were preferred, respectively, as these are prospective studies with a reasonable follow-up time of an average of 11.5 years that have documented exposure categories below 100 µg/l and assessed smoking behaviour and water use history.

In order to utilize the adjustment made for other variables (e.g. smoking) in the original analyses in the studies of lung cancer (Chen et al., 2010b) and urinary tract cancer (Chen et al., 2010a) in north-eastern Taiwan, China, and the Ahsan et al. (2006) study of skin lesions in Bangladesh, adjusted cases were calculated for each exposure group (i.e. other than the referent group) from RRs. This two-step process involved calculating case frequency by multiplying the rate in the referent group by the relative risk and then estimating the number of adjusted cases by multiplying the number of subjects by the case frequency. For the two Chen et al. (2010a,b) studies, the resulting adjustment was small relative to the reported cases (see Tables 24 and 25).

The study of urinary tract cancer (Chen et al., 2010a) showed a significantly increased RR trend with increasing arsenic concentration in water when adjusted for sex, age and smoking; for exposures above 100 µg/l, RRs were more than 5, whereas the risk was elevated but not significant for exposures below 100 µg/l. Table 24 shows the data used in dose–response modelling.

Table 24. Association of urinary cancer in relation to person-years of observation with arsenic exposure in an arseniasis-endemic area in north-eastern Taiwan, China

Inorganic arsenic in water		Inorganic arsenic total dietary exposure[b]		Cohort incidence[c]	RR	*N*	Adjusted cases[d]
Category range (µg/l)	Central estimate[a] (µg/l)	µg/person per day	µg/kg bw per day				
<10	5	90	1.6	0.002 2	1	2288	5
10–49.9	30	165	3.0	0.003 6	1.66	2093	8
50–99.9	75	300	5.5	0.005 3	2.42	907	5
100–299.9	200	675	12.3	0.009 05	4.13	909	8
≥300	450	1425	25.9	0.017 0	7.8	691	12

[a] Point estimate of the range of inorganic arsenic in drinking-water.
[b] Central estimate, assuming consumption of 3 litres of water per day, including that used in cooking, and 75 µg of inorganic arsenic in food per day and body weight of 55 kg.
[c] Referent group (<10 µg/l) is actual case rate per person; other rates are calculated from RRs.
[d] Referent group is actual cases. Other case estimates are obtained by multiplying group size by incidence.
Source: Chen et al. (2010a).

The study of lung cancer (Chen et al., 2010b) found a significant dose–response trend ($P = 0.001$) of lung cancer risk associated with increasing arsenic concentration. Increase in RR was nonsignificant below 100 µg/l, but a significant increase in RR was shown for exposures above 100 µg/l. Table 25 shows the data used in dose–response modelling.

Table 25. Association of lung cancer cases in relation to total population studied with arsenic exposure in an arseniasis-endemic area in north-eastern Taiwan, China

Inorganic arsenic in water		Inorganic arsenic total dietary exposure[b]		Cohort incidence[c]	RR	*N*	Adjusted cases[d]
Category range (µg/l)	Central estimate[a] (µg/l)	µg/person per day	µg/kg bw per day				
<10	5	90	1.6	0.021	1	2288	48
10–49.9	30	165	3.0	0.023	1.1	2093	48
50–99.9	75	300	5.5	0.021	0.99	907	19
100–299.9	200	675	12.3	0.032	1.54	909	29
≥300	450	1425	25.9	0.047	2.25	691	33

[a] Point estimate of the range of inorganic arsenic in drinking-water.
[b] Central estimate, assuming consumption of 3 litres of water per day, including that used in cooking, and 75 µg of inorganic arsenic in food per day and body weight of 55 kg.
[c] Referent group (<10 µg/l) is actual case rate per person; other rates are calculated from RRs.
[d] Referent group is actual cases. Other case estimates are obtained by multiplying group size by incidence.
Source: Chen et al. (2010b).

For skin lesions, data from two pivotal studies in Bangladesh were modelled. In a cross-sectional study reported by Ahsan et al. (2006), dose-dependent effects were observed with increased inorganic arsenic exposure. Adjusted cases were calculated from adjusted relative risks in the same manner as for the two Chen et al. (2010a,b) studies. However, as the total number of cases in the Ahsan et al. (2006) study was increased by about 15% by this adjustment, the case estimates were further adjusted by normalizing relative to the total number of reported cases so that the overall case frequency in the cohort was the same (i.e. the number of cases in the referent group was adjusted as well). The data set from this study is listed in Table 26.

Rahman et al. (2006) reported a case–control study also conducted in Bangladesh. In this study, the referents were randomly selected in the study areas. The OR for skin lesions, in both males and females, increased along with arsenic exposure. The results from a case–control study cannot be used for dose–response modelling because the ratios are not based on population rates. However, information was provided in the paper that allowed estimation of relative prevalence rates for the area from which the study cohort was drawn. Two assumptions played a role in this estimation. First, it was assumed that the distribution of arsenic exposures in the rest of the population was proportional (n = 164 000) to those in the study cohort (n = 2334). Second, it was assumed that there were additional cases in the rest of the population, with a prevalence determined by the number of cases detected in the individuals who were originally selected for the control group (6 of 1830).

Table 26. Association of skin lesion cases and controls with arsenic exposure in Bangladesh

Inorganic arsenic in water		Inorganic arsenic total dietary exposure[b]		Prevalence[c]	RR	*N*	Actual cases	Adjusted cases[d]
Category range (µg/l)	Category average estimate [a] (µg/l)	µg/person per day	µg/kg bw per day					
0.1–8	1.8	147	2.7	0.025	1	2259	57	48
8.1–40	23	232	4.2	0.048	1.91	2122	90	86
40.1–91	62	388	7.1	0.076	3.03	2202	144	141
91.1–175	125	640	11.6	0.094	3.71	2185	162	171
175.1–864	255	1160	21.1	0.136	5.39	2183	242	249

[a] Median of the concentration range of inorganic arsenic in drinking-water.
[b] Central estimate, assuming consumption of 4 litres of water per day, including that used in cooking, and 140 µg of inorganic arsenic in food per day and body weight of 55 kg.
[c] Referent group (<0.1–8 µg/l) is actual case rate per person; other rates are calculated from RRs.
[d] Adjusted cases for groups other than the referent group were estimated by first multiplying group size by prevalence and then normalizing all groups (including the referent group) to the total unadjusted cohort prevalence.
Source: Ahsan et al. (2006).

The data and estimated cases from this study are listed in Table 27.

8.3 Benchmark dose estimates

8.3.1 Chen et al. (2010b), lung cancer

The data (see Table 25) were fit with all nine dichotomous models provided by the BMDS modelling software. The log-probit model was fit in both constrained (*c* parameter > 1) and unconstrained forms. In the former case, the log-probit model provided a relatively poor fit and relatively high BMD and BMDL values (see Table 28 and Figure 2). Although the fit was improved by removing the constraint, the BMDL values were over 100-fold lower than for any of the other models and were outside the dose range from the study (see Table 28 and Figure 3). The Committee therefore found it preferable to exclude both forms of the log-probit model. The BMR selected at the low end of the observed data range was 0.5% increased incidence. The lowest $BMDL_{0.5}$ of 3 µg/kg bw per day was generated by the quantal-linear model (along with several other equivalent models).

Plots for the probit model, which provided the best fit, and the quantal-linear model, which provided the lowest BMDL (along with several other equivalent models), are shown in Figures 4 and 5, respectively.

Table 27. Association of skin lesion cases and controls with arsenic exposure in Bangladesh

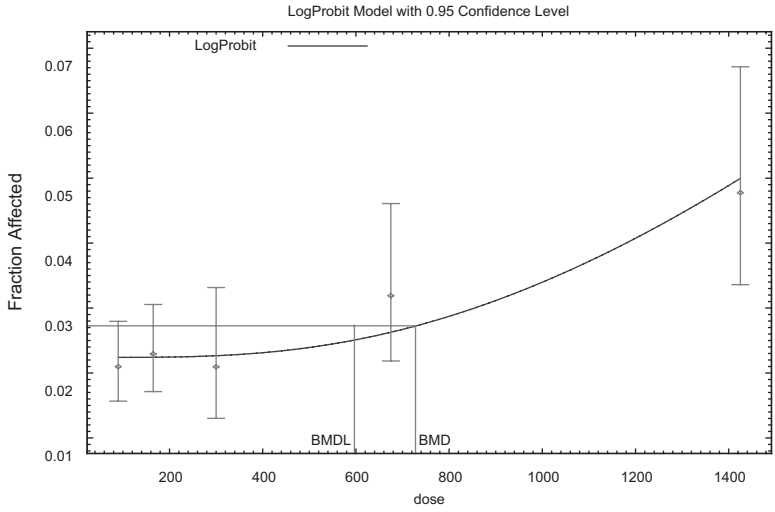
Inorganic arsenic in water		Inorganic arsenic total dietary exposure scenario[b]		Original cohort		Estimates for total population	
Category range (µg/l)	Average estimate[a] (µg/l)	µg/person per day	µg/kg bw per day	Cases	Controls	Cases[c]	Estimated group size[c]
<10	5	160	2.9	25	230	52	20 902
10–49	30	260	4.7	53	261	110	23 770
50–149	100	540	9.8	124	551	256	50 205
150–299	225	1040	18.9	194	551	401	50 350
≥300	450	1940	35.3	108	237	223	21 708

[a] Midpoint except for the highest category.
[b] Central estimate, assuming consumption of 4 litres of water per day, including that used in cooking, and 140 µg of inorganic arsenic in food per day and body weight of 55 kg.
[c] Number of additional cases and subjects estimated for the population from which the cohort was drawn; see text for additional explanation.
Source: Rahman et al. (2006).

Table 28. $BMD_{0.5}$ for lung cancer based on Chen et al. (2010b)

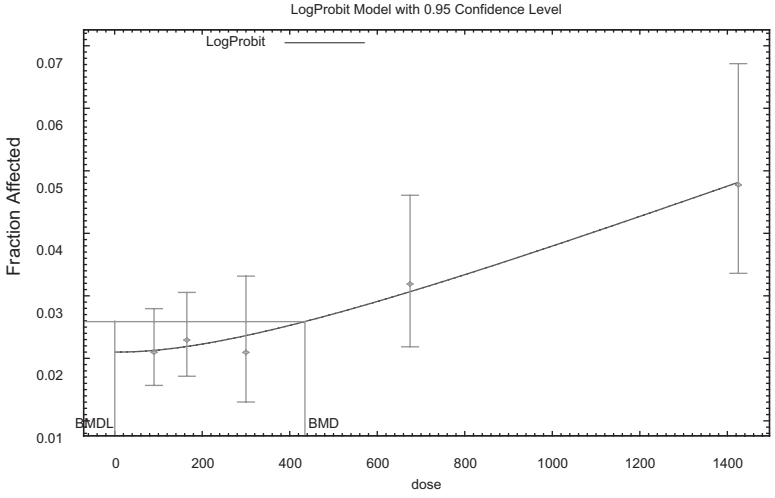
Model name	*P*-value	$BMD_{0.5}$ (µg/person per day)	$BMDL_{0.5}$ (µg/person per day)	$BMD_{0.5}$ (µg/kg bw per day)	$BMDL_{0.5}$ (µg/kg bw per day)
Gamma	0.79	402	167	7.3	3.0
Logistic	0.92	351	273	6.4	5.0
Log-logistic	0.79	400	165	7.3	3.0
Log-probit (constrained)	0.67	728	597	13.2	10.8
Log-probit (unconstrained)	0.80	435	0.4	7.9	0.006
Multistage	0.78	357	167	6.5	3.0
Multistage cancer	0.89	250	165	4.5	3.0
Probit	0.92	336	257	6.1	4.7
Weibull	0.79	399	167	7.2	3.0
Quantal-linear	0.89	250	165	4.5	3.0

Figure 2. Log-probit model with constraint



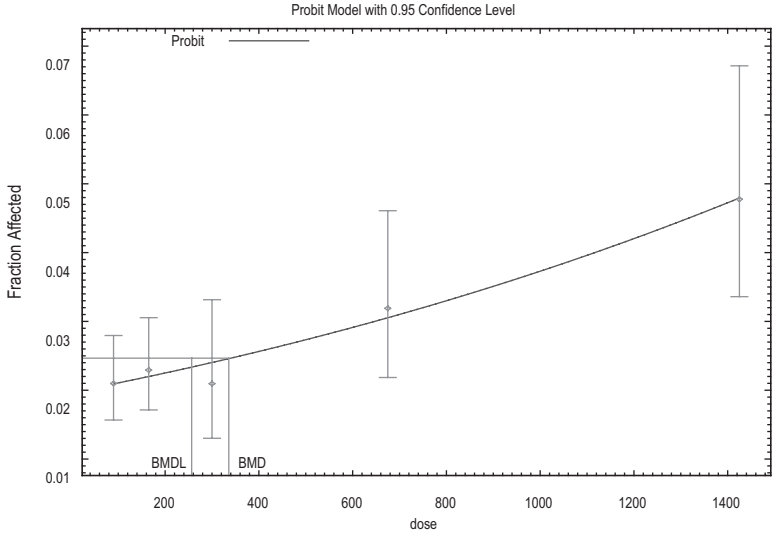
Notes: x-axis: exposure in µg/person per day; y-axis: cohort incidence. The line is the central estimate resulting from the fit of the model to the data. The vertical bars are the confidence intervals around the data.

Figure 3. Log-probit model without constraint



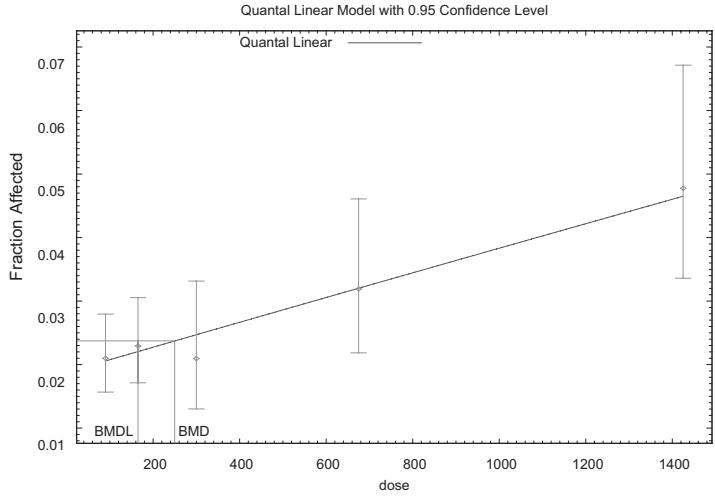
Notes: x-axis: exposure in µg/person per day; y-axis: cohort incidence. The line is the central estimate resulting from the fit of the model to the data. The vertical bars are the confidence intervals around the data.

Figure 4. Probit model for lung cancer based on Chen et al. (2010b)



Notes: x-axis: exposure in µg/person per day; y-axis: cohort incidence. The line is the central estimate resulting from the fit of the model to the data. The vertical bars are the confidence intervals around the data.

Figure 5. Quantal-linear model for lung cancer based on Chen et al. (2010b)



Notes: x-axis: exposure in µg/person per day; y-axis: cohort incidence. The line is the central estimate resulting from the fit of the model to the data. The vertical bars are the confidence intervals around the data.

8.3.2 Chen et al. (2010b), lung cancer, sensitivity analyses

Two sensitivity analyses using four different models (probit, logistic, log-logistic and quantal-linear) were performed to evaluate the impact of some of the dosimetry assumptions on the $BMD_{0.5}$ calculation. For this analysis, four different models were examined. The first analysis examined the impact of the estimates of dietary arsenic concentrations and water intakes. The second examined the impact of assuming that the risk is driven entirely by water intake. The latter analysis would be more accurate if the dietary exposure is nearly proportional to arsenic well water concentrations and allows calculation of a benchmark concentration (BMC). $BMD_{0.5}$ estimates are presented in Table 29 and Table 30.

Table 29. $BMD_{0.5}$ for lung cancer based on Chen et al. (2010b) with varying dietary arsenic exposures and water consumptions

Model name	Arsenic exposure in diet (µg/day)	Water consumption (litres/day)	*P*-value	$BMD_{0.5}$ (µg/person per day)	$BMDL_{0.5}$ (µg/person per day)	$BMD_{0.5}$ (µg/kg bw per day)	$BMDL_{0.5}$ (µg/kg bw per day)
Quantal-linear	200	4	0.89	333	220	6.1	4.0
Logistic	200	4	0.92	489	385	8.9	7.0
Probit	200	4	0.92	466	361	8.5	6.6
Log-logistic	200	4	0.79	580	219	10.5	4.0
Quantal-linear	50	4	0.89	333	220	6.1	4.0
Logistic	50	4	0.92	459	354	8.3	6.4
Probit	50	4	0.92	439	333	8.0	6.1
Log-logistic	50	4	0.79	510	220	9.3	4.0
Quantal-linear	200	2	0.89	167	110	3.0	2.0
Logistic	200	2	0.92	266	215	4.8	3.9
Probit	200	2	0.92	252	201	4.6	3.6
Log-logistic	200	2	0.78	337	109	6.1	2.0
Quantal-linear	50	2	0.89	167	110	3.0	2.0
Logistic	50	2	0.92	234	182	4.3	3.3
Probit	50	2	0.92	224	171	4.1	3.1
Log-logistic	50	2	0.79	267	110	4.9	2.0

The scenarios with respect to exposure to inorganic arsenic from food and volume of drinking-water consumed resulted in a range of 2.0–7.0 µg/kg bw per day for the $BMDL_{0.5}$, with the volume of drinking-water having the larger impact.

Table 30. $BMD_{0.5}$ and $BMC_{0.5}$ for lung cancer based on Chen et al. (2010b) and drinking-water alone

Model name	Arsenic exposure in diet (µg/day)	Water consumption (litres/day)	*P*-value	$BMD_{0.5}$ (µg/person per day)	$BMDL_{0.5}$ (µg/person per day)	$BMC_{0.5}$ (µg/l)	$BMCL_{0.5}$ (µg/l)
Quantal-linear	0	3	0.89	250	165	83	55
Logistic	0	3	0.92	337	258	112	86
Probit	0	3	0.92	323	243	108	81
Log-logistic	0	3	0.79	363	165	121	55

While changes in drinking-water assumptions produced proportional changes in the $BMD_{0.5}$ estimates, the impacts of assumed dietary exposure were more variable and model dependent. For the quantal-linear model (and the other related models), the dietary exposure estimate had virtually no effect. For the other models, changing dietary exposure altered the $BMD_{0.5}$ and $BMDL_{0.5}$ estimates somewhat (20–25%), but the difference was considerably less than the proportional change in the assumed dietary exposures (a factor of 4). Focusing on drinking-water only, as reported in the epidemiological studies, resulted in a $BMCL_{0.5}$ of 55 µg/l.

8.3.3 Chen et al. (2010a), urinary tract cancer

The data (see Table 24) were fit with all nine dichotomous models provided by the BMDS modelling software. The log-probit model provided a relatively poor fit and relatively high BMD and BMDL values (see Table 31). The log-probit model was therefore also excluded from the analysis of the Chen et al. (2010a) urinary tract data set. The BMR selected at the low end of the observed data range was 0.5% increased incidence. The lowest $BMDL_{0.5}$ of 5.2 µg/kg bw per day was again generated by the quantal-linear model (and other equivalent models).

A plot for the log-logistic model, which provided the best fit together with the lowest BMDL, is shown in Figure 6.

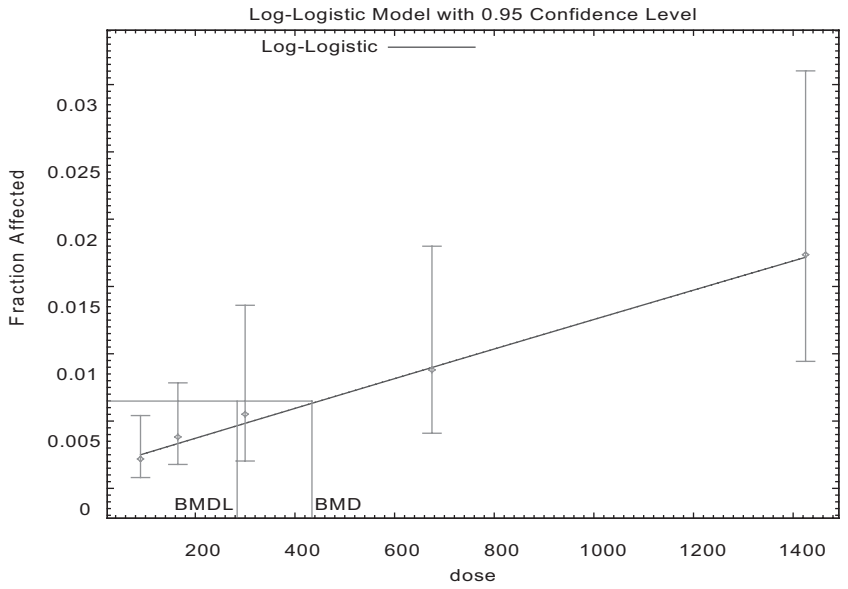
8.3.4 Ahsan et al. (2006), skin lesions

The data (see Table 26) were fit with all nine dichotomous models provided by the BMDS modelling software. None of the models provided a good fit, as judged by the *P*-value. Because it provided a much better fit than any of the other models, the unconstrained log-probit model was included (see Table 32). The BMR selected at the low end of the observed data range was 5% increased prevalence. The log-probit model, which also provided the lowest $BMDL_5$ (5.4 µg/kg bw per day), is illustrated in Figure 7. Most of the other models, with the possible exception of the log-logistic, are excluded on the basis of fit.

Table 31. $BMD_{0.5}$ for urinary cancer based on Chen et al. (2010a)

Model name	*P*-value	$BMD_{0.5}$ (µg/person per day)	$BMDL_{0.5}$ (µg/person per day)	$BMD_{0.5}$ (µg/kg bw per day)	$BMDL_{0.5}$ (µg/kg bw per day)
Gamma	0.96	436	286	7.9	5.2
Logistic	0.65	763	625	13.9	11.4
Log-logistic	0.96	434	284	7.9	5.2
Log-probit	0.26	923	753	16.8	13.7
Multistage	0.96	436	286	7.9	5.2
Multistage cancer	0.96	436	286	7.9	5.2
Probit	0.70	727	587	13.2	10.7
Weibull	0.96	436	286	7.9	5.2
Quantal-linear	0.96	436	286	7.9	5.2

Figure 6. Log-logistic model for urinary tract cancer based on Chen et al. (2010a)

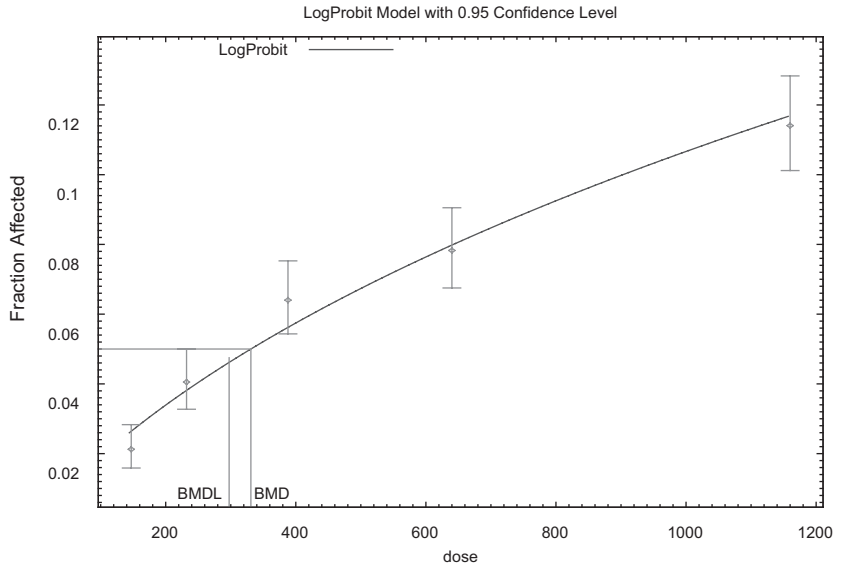


Notes: x-axis: exposure in µg/person per day; y-axis: cohort incidence. The line is the central estimate resulting from the fit of the model to the data. The vertical bars are the confidence intervals around the data.

Table 32. BMD_5 for skin lesions based on Ahsan et al. (2006)

Model name	*P*-value	BMD_5 (µg/person per day)	$BMDL_5$ (µg/person per day)	BMD_5 (µg/kg bw per day)	$BMDL_5$ (µg/kg bw per day)
Gamma	0.004	507	447	9.2	8.1
Logistic	0.000	779	729	14.2	13.3
Log-logistic	0.007	485	424	8.8	7.7
Log-probit	0.148	331	297	6.0	5.4
Multistage	0.004	507	447	9.2	8.1
Multistage cancer	0.004	507	447	9.2	8.1
Probit	0.000	746	695	13.6	12.6
Weibull	0.004	507	447	9.2	8.1
Quantal-linear	0.004	507	447	9.2	8.1

Figure 7. Log-probit model for Ahsan et al. (2006) skin lesion study



Notes: x-axis: exposure in µg/person per day; y-axis: prevalence. The line is the central estimate resulting from the fit of the model to the data. The vertical bars are the confidence intervals around the data.

8.3.5 *Ahsan et al. (2006), skin lesions, sensitivity analyses*

Two sensitivity analyses using three different models (log-probit, log-logistic and multistage cancer) were performed to evaluate the impact of some of the dosimetry assumptions on the BMD calculation. The first analysis examined the impact of the estimates of dietary arsenic exposures and water intakes. The second examined the impact of assuming that the risk is driven entirely by water intake. The latter analysis would be more accurate if the dietary exposure is nearly proportional to arsenic well water concentrations and allows calculation of a BMC. BMD_5 estimates are presented in Table 33 and Table 34.

The scenarios with respect to exposure to inorganic arsenic from food and volume of drinking-water consumed resulted in a range of 2.8–11.5 µg/kg bw per day for the $BMDL_5$, with the assumption for food having the larger impact. However, most of the models did not provide a good fit.

Focusing on drinking-water only, as reported in the epidemiological studies, the log-probit model gave the best fit and also the lowest $BMCL_5$, which was 47 µg/l.

Table 33. BMD_5 for skin lesions based on Ahsan et al. (2006) with varying dietary arsenic exposures and water consumptions

Model name	Arsenic exposure in diet (µg/day)	Water consumption (litres/day)	*P*-value	BMD_5 (µg/person per day)	$BMDL_5$ (µg/person per day)	BMD_5 (µg/kg bw per day)	$BMDL_5$ (µg/kg bw per day)
Log-probit	400	5	0.012	665	616	12.1	11.2
Log-logistic	400	5	0.004	671	622	12.2	11.3
Multistage cancer	400	5	0.009	671	631	12.2	11.5
Log-probit	50	5	0.773	248	213	4.5	3.9
Log-logistic	50	5	0.007	612	536	11.1	9.8
Multistage cancer	50	5	0.004	633	558	11.5	10.1
Log-probit	400	3	0.002	567	535	10.3	9.7
Log-logistic	400	3	0.001	571	536	10.4	9.7
Multistage cancer	400	3	0.000	528	496	9.6	9.0
Log-probit	50	3	0.568	178	156	3.2	2.8
Log-logistic	50	3	0.007	366	321	6.7	5.8
Multistage cancer	50	3	0.004	380	335	6.9	6.1

Table 34. BMD_5 and BMC_5 for skin lesions based on Ahsan et al. (2006) and drinking-water alone

Model name	Arsenic exposure in diet (µg/day)	Water consumption (litres/day)	*P*-value	BMD_5 (µg/person per day)	$BMDL_5$ (µg/person per day)	BMC_5 (µg/l)	$BMCL_5$ (µg/l)
Log-probit	0	4	0.6189	310	189	78	47
Log-logistic	0	4	0.0066	492	431	123	108
Multistage cancer	0	4	0.0038	507	447	127	112

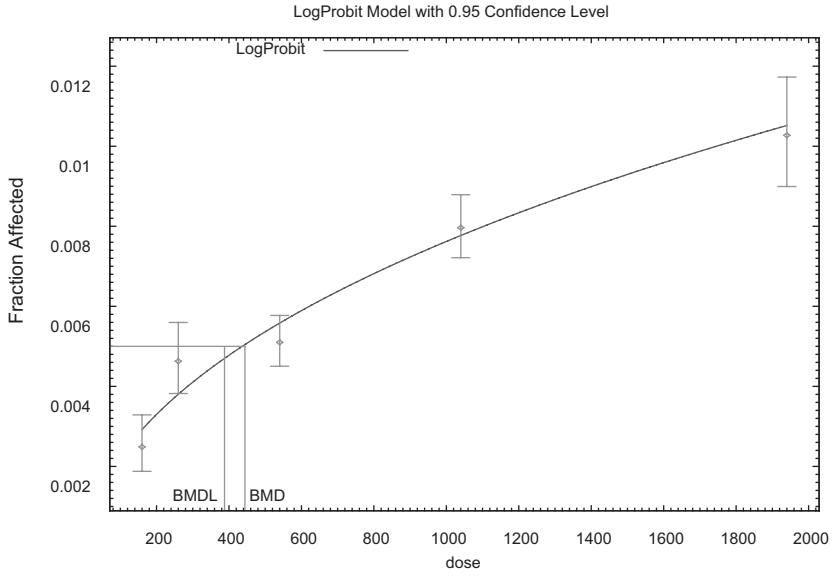
8.3.6 Rahman et al. (2006), skin lesions

The data (see Table 27) were fit with all nine dichotomous models provided by the BMDS modelling software. None of the models provided a good fit, as judged by the *P*-value. Because it provided a much better fit than any of the other models, the unconstrained log-probit model was included (see Table 35). The BMR selected at the low end of the observed data range was 0.5% increased prevalence. As it provided both the best fit and the lowest $BMDL_{0.5}$ (5.4 µg/kg bw per day), the log-probit model is illustrated in Figure 8. Most of the other models, with the possible exception of the log-logistic model, are excluded on the basis of fit.

Table 35. $BMD_{0.5}$ for skin lesions based on Rahman et al. (2006)

Model name	*P*-value	$BMD_{0.5}$ (µg/person per day)	$BMDL_{0.5}$ (µg/person per day)	$BMD_{0.5}$ (µg/kg bw per day)	$BMDL_{0.5}$ (µg/kg bw per day)
Gamma	0.0034	507	447	9.2	8.1
Logistic	0	779	729	14.2	13.3
Log-logistic	0.0035	485	424	8.8	7.7
Log-probit (unconstrained)	0.0442	331	297	6.0	5.4
Multistage	0.0034	507	447	9.2	8.1
Multistage cancer	0.0034	507	447	9.2	8.1
Probit	0	746	695	13.6	12.6
Weibull	0.0034	507	447	9.2	8.1
Quantal-linear	0.0034	507	447	9.2	8.1

Figure 8. Log-probit model for Rahman et al. (2006) skin lesion study



Notes: x-axis: exposure in µg/person per day; y-axis: prevalence. The line is the central estimate resulting from the fit of the model to the data. The vertical bars are the confidence intervals around the data.

9. COMMENTS

9.1 Absorption, distribution, metabolism and excretion

Absorption of arsenic depends on the chemical species and its solubility as well as the matrix in which it is present. Soluble arsenicals in water are highly bioavailable. Inorganic arsenic is rapidly cleared from blood both in humans and in most experimental animal species that have been tested; an exception is rats, in which arsenic binds to erythrocytes, delaying clearance. Inorganic arsenic is metabolized primarily by stepwise reduction of pentavalent arsenic (arsenate) to trivalent arsenic (arsenite) followed by oxidative addition of methyl groups, although alternative pathways have also been proposed that include methylated arsenical glutathione metabolites. Most ingested arsenic species are excreted via the kidney within a few days. Ingested inorganic arsenic is excreted as inorganic arsenate and arsenite and as the pentavalent methylated metabolites MMA^{V} and DMA^{V}, with lesser amounts of the trivalent methylated metabolites, MMA^{III}, DMA^{III} and thioarsenical metabolites. Whereas it has previously been assumed that methylation of inorganic arsenic was a detoxification route, it is not entirely clear whether or not this is correct, because, based on limited in vitro and in vivo data, MMA^{III} and DMA^{III} appear to be more toxic than inorganic arsenic and have high affinity for thiols and cellular proteins.

Major organic arsenicals present in fish when ingested undergo very little biotransformation and are excreted almost entirely unchanged. However, some organoarsenicals, such as arsenolipids present in cod liver and arsenosugars in mussels and algae, can be metabolized to DMA^{V} when ingested.

9.2 Toxicological data

Arsenic toxicity depends on the chemical form and its solubility and varies among animal species and with route of administration. Generally, trivalent arsenic is more toxic than the pentavalent forms. Oral administration of inorganic arsenicals to laboratory animals has a number of effects, including effects on the cardiovascular, respiratory, gastrointestinal, haematological, immune, reproductive and nervous systems. MMA^{V} administration to experimental animals has been shown to have effects on the gastrointestinal tract, kidney, thyroid and reproductive system, with the effect seen at the lowest doses being diarrhoea. DMA^{V} has effects on the urinary bladder, kidneys, thyroid and fetal development.

Studies in experimental animals conducted according to standard protocols have generally not shown increased tumour incidences following chronic oral exposure to inorganic arsenic. However, evidence of tumour promotion and co-carcinogenicity has been reported. In addition, studies involving administration of arsenite to pregnant mice in their drinking-water have shown evidence of transplacental carcinogenesis.

MMA^{V} has not shown evidence of carcinogenicity in 2-year cancer bioassays with doses equivalent to up to 100 mg/kg bw per day. DMA^{V} (administered in drinking-water at 50 mg/l) was carcinogenic in the urinary bladder of rats, but not mice. DMA^{V} is not genotoxic, and its carcinogenic mode of action is considered to involve cytotoxicity to the bladder epithelium and sustained increased cell proliferation; the rat is considered to be particularly sensitive to DMA^{V} because of slower elimination and possibly a greater potential for metabolism to DMA^{III} compared with other species. The NOAEL was equivalent to 0.73 mg/kg bw per day.

In its most recent evaluation, IARC concluded that there is sufficient evidence for carcinogenicity of inorganic arsenic compounds in experimental animals and sufficient evidence for carcinogenicity of DMA^{V} in experimental animals. Evidence from a wide range of studies has led to the conclusion that arsenic compounds do not react directly with DNA. There are a number of proposed mechanisms of carcinogenicity of inorganic arsenic, including oxidative damage, epigenetic effects and interference with DNA damage repair.

Because of a general lack of data on both exposure to and toxicity of organic arsenicals, the Committee further considered only inorganic arsenic for this report.

Taking into account the lack of a good animal model for carcinogenicity of inorganic arsenic compounds and the large number of data available from epidemiological studies, the Committee did not consider the data from experimental animals appropriate for the dose–response analysis.

9.3 Observations in humans

The main adverse effects reported to be associated with long-term ingestion of inorganic arsenic by humans are cancer, skin lesions, developmental effects, cardiovascular disease, neurotoxicity and diabetes.

The classification of arsenic as a carcinogen was originally based on evidence of skin cancers. Studies in Taiwan, China, and other regions where high exposures to arsenic in drinking-water occurred have confirmed the relationship. Significant associations between exposure to high levels of ingested arsenic in drinking-water and bladder cancer have been observed in ecological studies from Chile, Argentina and Taiwan, China, and cohort studies in Taiwan, China. Some of the studies showed an association only in smokers. In studies from Chile, Argentina and Taiwan, China, exposure to arsenic at high concentrations in drinking-water has been shown to be associated with lung cancer. Again, when smokers and non-smokers were compared, the associations were stronger in the smokers. Nutritional status of exposed populations has been observed to influence cancer risk. Thus, compromised nutrition (e.g. low protein intake) is likely to be associated with significantly higher risk. The evidence for an association with cancers at other sites, including prostate, liver and kidney, is less conclusive.

Epidemiological studies in different regions of the world have consistently demonstrated a strong association between long-term inorganic arsenic ingestion and skin lesions, typically in the form of hyperkeratosis, hyperpigmentation or hypopigmentation. Observations of skin lesions following low chronic exposure have suggested that these characteristic dermal changes are sensitive indications of the toxic effects of inorganic arsenic.

Available epidemiological studies indicate a positive relationship between high concentrations of inorganic arsenic in drinking-water and sensitive end-points for peripheral and central neurotoxicity. There is some evidence that exposure of children to inorganic arsenic in areas with elevated arsenic concentrations (>50 µg/l) in drinking-water produces effects on cognitive performance, but so far this is not conclusive.

The cardiovascular outcomes that have been associated with chronic exposure to arsenic through drinking-water include blackfoot disease, increased mortality or prevalence of coronary heart disease, peripheral arterial disease, myocardial infarction and stroke, and other cardiovascular end-points, such as increased blood pressure and prolonged QT interval of the electrocardiogram. The association between blackfoot disease and inorganic arsenic exposure has been confirmed by many studies, but blackfoot disease has been reported primarily in an area along the south-western coast of Taiwan, China, where arsenic contamination in well water is very high (170–880 µg/l). Except for blackfoot disease, the reported associations between inorganic arsenic exposure and cardiovascular disease prevalence/mortality and other cardiovascular end-points currently do not provide sufficient evidence of causality and are not considered pivotal for the assessment.

Studies conducted in Bangladesh and Taiwan, China, indicated an extra risk of diabetes among high-exposure populations. In addition, recent findings suggest

that in utero arsenic exposure impaired child thymic development and that enhanced morbidity and immunosuppression might occur. However, as a result of limitations in the studies, the relationship between arsenic exposure and these outcomes remains uncertain.

The Committee concluded that the greatest strength of evidence for a causal association between inorganic arsenic and adverse effects in humans is for cancers of the skin, urinary bladder and lung and skin lesions (hyperkeratosis, hyperpigmentation and hypopigmentation) observed in studies in which levels of arsenic in drinking-water were relatively high (e.g. ≥100 µg/l). For this evaluation, studies were preferred that included documentation of exposure from drinking-water both at higher concentrations (e.g. ≥300 µg/l) and also at relatively lower concentrations (e.g. <100 µg/l). This was in order to assess effects across a broad gradient of exposure and to avoid extrapolation below the observed range in the dose–response modelling. For skin cancer, three of the four most recent studies of low-level exposure utilized toenail arsenic as a biomarker of exposure; however, the relationship between toenail arsenic and total dietary exposure to inorganic arsenic remains uncertain. Further, as arsenic-related skin lesions may be a possible precursor to skin cancer and have been reported at lower concentrations of arsenic in drinking-water compared with skin cancer, the Committee considered the data for skin lesions to be a more sensitive adverse effect than skin cancer. Thus, pivotal data were identified from epidemiological studies reporting a positive association with arsenic exposure and these effects (i.e. cancers of the lung and urinary tract and skin lesions).

9.4 Analytical methods

The most common detection techniques for arsenic are ICP-MS, ICP-AES, HG-AAS and HG-AFS. ICP-AES is generally adequate for determination of total arsenic in foods, and its sensitivity can be improved by coupling to HG. ICP-MS has the highest sensitivity without derivatization. HG-AAS and HG-AFS have LODs in the microgram per kilogram range, which is adequate for all foods. For speciation with HG-based detection systems, some organoarsenic species require oxidation to species that form volatile arsines prior to their detection.

Samples prepared for total arsenic determination are mineralized by either wet or dry methods. Microwave is the most common closed system used in wet mineralization, although temperatures higher than those that can be achieved by microwave are needed for the complete degradation of some organoarsenic species. This leads to an underestimation of total arsenic in some foods when HG-based detection systems are used. Recent developments, such as microwave-induced combustion methods, are solving this problem. In dry mineralization, addition of ashing aids is necessary to avoid arsenic losses by volatilization.

Methodological research in the last decade has been targeted to arsenic speciation. Quantitative extraction of arsenic species from food matrices is one of the main methodological problems, and efficiencies vary widely, depending on the nature of the matrix and the method used. Polar solvents assisted by ultrasound, accelerated solvent extraction or microwave are commonly used. Extraction of

arsenite is especially difficult to achieve, because of binding to thiol groups in proteins. Separation of arsenic species is most commonly achieved by HPLC. Multidimensional chromatography (different columns and conditions) may be needed for samples with a large number of arsenic species; up to 23 species have been found in seaweed and seafood, for example. Further difficulties are that the elution may not be quantitative under certain conditions, and the eluent may change the arsenic oxidation state.

Most of the current work on arsenic speciation has been targeted to characterization of arsenic species profiles in food products, without special attention to inorganic arsenic. There is a current need for validated and horizontal methods for selective extraction and determination of inorganic arsenic and for certified reference materials for inorganic arsenic in foods. Further, it would be more appropriate to report total inorganic arsenic than arsenite and arsenate, because various extraction/analytical procedures may change the oxidation state.

9.5 Effects of processing

Peeling of vegetables and polishing of rice reduce the content of total arsenic. Washing or soaking rice and seaweed and discarding the water before cooking reduce arsenic levels, especially inorganic forms. Decreases in arsenic levels with boiling have been described for rice, pasta, seaweed and seafood products, except where the water used is contaminated with arsenic, when levels may increase. The main arsenic species solubilized are AB, DMA and arsenosugars for seafood products and inorganic arsenic for cereals and seaweed. Limited studies in which seafood was heated at temperatures above 150 °C have reported that up to 11% of AB is transformed to TMAO and TMA^+.

9.6 Prevention and control

Commercial-scale water treatment processes to remove arsenic in water are available. Simple arsenic removal systems for household wells have also been developed. Low-cost systems in arsenic-endemic areas generally utilize elemental iron, iron or aluminium oxides and carbon as adsorbents for arsenic. Many household treatment systems fail prematurely because of high levels of phosphate in water, and maintenance and disposal of arsenic-contaminated wastes are difficult. Studies in Bangladesh have shown that most rural households prefer sharing uncontaminated wells or filtering low-arsenic surface water through sand to treating groundwater. Sand filtration gives mixed results with respect to removal of biological pathogens. Spatial variability in groundwater arsenic contamination in Argentina, Chile and the river deltas of South and South-east Asia is very high, so villages usually have a mixture of contaminated and uncontaminated wells. Deeper groundwater aquifers often have low arsenic levels that can be used to develop community water supplies.

Apart from processing possibilities, practical prevention and control approaches for arsenic in foods are limited. Attempts to reduce arsenic uptake into food crops by additions of phosphate fertilizer and iron oxides have given equivocal and unconvincing results with several vegetable and cereal crops. Silicate additions

to soil have been shown to reduce arsenic levels in rice grain where soils are low in silicate. Growing rice under less reducing soil conditions can dramatically reduce grain arsenic levels. However, the challenge is to do this without substantial loss of yields in uncontaminated soils. Very limited identification of "low" and "high" arsenic rice varieties has been reported, and more data are needed before recommendations can be made to farmers and consumers.

9.7 Levels and patterns of contamination in food commodities

Data on total arsenic contents of foods for evaluation at the present meeting were obtained from the literature and from data submitted to the Committee by Australia, Brazil, France, Japan, New Zealand and Singapore. The total number of analytical results (single or composite) evaluated at the present meeting was 17 498. Table 8 in section 6.1 summarizes the ranges of total arsenic concentrations by food category, based on results with quantified values (minimum to maximum). The highest total arsenic concentrations have been found in seaweed, fish and shellfish, mushrooms and fungi, rice and rice products and some meat products. The levels in the remaining food products usually do not exceed 1 mg/kg. In some food groups, the number of non-detectable/non-quantifiable results was important (n = 9081) and influences the derivation of mean concentrations; this was the case with milk products (66%), meat and meat products (74%), eggs and egg products (65%), bakery wares (70%), cereals other than rice (80%) and vegetables other than mushrooms (86%).

Table 9 in section 6.1 summarizes the ranges of levels of inorganic arsenic obtained from the literature and from data submitted by Japan, France and Singapore (minimum to maximum). The total number of analytical (single or composites) results evaluated at the present meeting was 1737.

Levels of inorganic arsenic in foods and beverages usually do not exceed 0.1 mg/kg, with mean values generally less than 0.03 mg/kg. However, seaweed, rice and some fish and seafood commodities have higher inorganic arsenic levels, as do food crops grown in arsenic-contaminated soils.

In the seaweed *Hizikia fusiforme*, inorganic arsenic is more than 50% of total arsenic, with levels usually ranging from 30 to 130 mg/kg. In other seaweed species, inorganic arsenic is less than 15% of total arsenic, with levels normally below 2 mg/kg. The proportion of inorganic arsenic in rice varies from 17% to 100% of total arsenic and in vegetables from 33% to 74%, with maximum concentrations of 0.5 and 0.6 mg/kg, respectively. The proportion of inorganic arsenic usually does not exceed 10% of the total arsenic in fish and fish products, but it was found to reach 15% in shellfish from areas with some degree of arsenic contamination.

There are a variety of organoarsenic species in foods. For MMA and DMA, no information was available on their oxidation state in food products. In meat, DMA is the major species found in most studies, together with AB and minor amounts of MMA. In poultry meat, the presence of nitarsone, a phenylarsonic acid used as a coccidiostat, has also been reported. The greatest variety of arsenic species in vegetables has been detected in seaweeds, where arsenosugars are the major species, with smaller amounts of DMA, arsenolipids and thioarsenic compounds.

Mushrooms also contain many arsenic species, including AB, MMA, TMAO, DMA, AC and TMA^+. For other vegetables, MMA has been found in carrot, radish and potatoes, and MMA and DMA in chard and aubergines. Arsenic species found in fish and fish products include AB, arsenosugars, MMA, DMA, AC, TMA^+, TMAO, DMAE, TMAP, arsenolipids and thioarsenic compounds. AB is the major species (80–90%), except in some kinds of shellfish, where arsenosugars are the major species found.

9.8 Food consumption and dietary exposure assessment

Dietary exposure estimates for arsenic were reported by the Committee at the twenty-seventh meeting and were not revised at the thirty-third meeting. Only values for total arsenic were given for several European countries, the USA, Canada and the Republic of Korea; these ranged from 10 to 200 µg/day from food (0.17–3.33 µg/kg bw per day, assuming a 60 kg bw). Estimated dietary exposures to total arsenic from water ranged from 15 to 750 µg/day (0.25–12.5 µg/kg bw per day), reflecting arsenic concentrations in water of 10 µg/l and 500 µg/l and assuming a consumption of 1.5 litres of water a day. The Committee at the twenty-seventh meeting noted that water and seafood were the major sources of total arsenic, with other foods making minor contributions.

The focus of the Committee at the present meeting was on dietary exposure to inorganic arsenic; however, the majority of dietary exposure estimates submitted for evaluation were for total arsenic. The main factors influencing dietary exposure to inorganic arsenic are the water supply, type of food consumed and food preparation methods.

Where water is contaminated with arsenic, it is one of the most significant sources of inorganic arsenic exposure. It is also a major source of inorganic arsenic in food produced by irrigation with arsenic-contaminated water and from food preparation and cooking. Rice takes up high amounts of arsenic, but speciation of arsenic in rice varies between different regions, with a higher inorganic content in rice grown in Asia compared with the USA. Rice tends to be a major source of inorganic arsenic from food, particularly in Asia and other countries where it is a staple food. The level of inorganic arsenic in the rice consumed also varies, depending on food processing and preparation methods.

Arsenic contamination of groundwater is widespread, and there are a number of regions where arsenic contamination of drinking-water is important. Areas affected include southern Asia (e.g. Bangladesh, India), South-east and East Asia (e.g. China, including Taiwan, Mongolia, Viet Nam), the Americas (e.g. Argentina, Canada, Chile, Mexico, USA) and Europe (e.g. Finland, Hungary, Romania). Exposure to inorganic arsenic from water can be very variable, with high and low arsenic sources present in close proximity. Contaminated water that is used for drinking and food preparation would normally contain arsenic at concentrations between 10 and 200 µg/l. However, concentrations above 200 µg/l have been reported in some areas. The amount of water consumed also varies according to the region, temperature, physical activity and type of food, with soups and rice being examples of foods that will either contain high quantities of water or take up large

quantities of water. This can result in a total water consumption of between 1.5 and 5 litres per day.

The fact that water consumption and water used in cooking are not always included in dietary exposure estimates also makes direct comparison of reported total and inorganic arsenic dietary exposures found in different studies difficult, as exposure will be underestimated where water has not been included. In estimating dietary exposure to inorganic arsenic, variations in the different species of arsenic within a food category and between food categories need to be considered.

A summary of reported national inorganic arsenic estimates is given in Table 36, with ranges taken from various studies for some countries. It is particularly difficult to predict dietary exposures to arsenic at a regional level due to the complex factors discussed above that influence exposure at a local level. International estimates using the 13 Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme (GEMS/Food) consumption cluster diets were not generated, as the Committee considered that this level of generalization was not appropriate for estimating dietary exposures to inorganic arsenic.

Table 36. Summary of inorganic arsenic dietary exposure estimates

Country/region	Mean exposure (µg/kg bw per day)	Upper-percentile exposure (µg/kg bw per day)
Europe		
Europe[a] (EFSA)	0.21–0.61 adult 0.31–1.39 child 1–8 years 0.03–1.63 infant <12 months	0.36–0.99 adult (95th) 0.61–2.66 child 1–8 years (95th) —
Belgium[b]	0.10 all	0.16 all (90th)
France TDS[c]	0.10 adult 0.14 child 3–14 years	0.27 adult (95th) 0.34 child 3–14 years (95th)
United Kingdom TDS[c]	0.02–0.12 adult 0.03–0.20 child 1–18 years 0.45 infant <12 months	0.05–0.16 adult (97.5th) 0.08–0.40 child 1–18 years (97.5th) 0.74 infant (95th)
North America		
Canada TDS[c]	0.29 all	
USA TDS, other studies[d]	0.08–0.20 adult 0.12–0.32 child 1–6 years 0.24–1.19 infant <12 months	0.16–0.34 adult (95th) — —
South America		
Chile[e]	2.08–21.48 adult	

Table 36 (contd)

Country/region	Mean exposure (µg/kg bw per day)	Upper-percentile exposure (µg/kg bw per day)
Asia		
Bangladesh[f]	1.68–3.00 adult	
China TDS[c]	0.24–0.76 adult	
China, Province of Taiwan[g]	0.91 adult	
Japan TDS, other study[h]	0.36–0.46 adult	0.83–1.29 adult (95th)

TDS, total diet study

[a] Individual dietary records for 19 European countries, different scenarios using conversion factors, drinking-water included.

[b] Individual dietary records for Belgium, analysed inorganic values for fish and seafood commodities only, drinking-water not included.

[c] Total diet studies; France 2001–2002 TDS, 10% total arsenic assumed to be inorganic, drinking-water included; Canada 1985–1988 TDS, conversion factors from Uneyama et al. (2007) applied to total arsenic, drinking-water not included; China 2007 TDS analysed inorganic arsenic, drinking-water included; United Kingdom 2006 TDS analysed inorganic arsenic, drinking-water included, previous TDSs did not.

[d] Various studies based on individual dietary records for USA from 1986–1987 Nationwide Food Consumption Survey or 1994–1996, 1998 supplement Continuing Survey on Food Intakes by Individuals, inorganic arsenic levels from Schoof et al. (1998), drinking-water included in some studies.

[e] Small community in Chile, drinking-water included, seasonal contamination of river water used as drinking-water source.

[f] Small community in Bangladesh, total arsenic reported, assumed 70% total arsenic is inorganic, drinking-water not included.

[g] Small community in Taiwan, China, only rice and yams with analysed inorganic arsenic values included, drinking-water not included.

[h] Two studies; Japan 2000 TDS, drinking-water included, conversion factors from Uneyama et al. (2007) applied to total arsenic; other study of women in fishing and rice-farming communities, analysed inorganic arsenic for fish, shellfish, seaweed and edible algae, Japan TDS values for other foods, drinking-water not included.

In most circumstances, it would be expected that estimates of dietary exposure to inorganic arsenic using individual dietary records would be more accurate than those obtained using population food consumption figures, such as normally used in total diet studies or model diets. However, it is not possible to assume this is the case; for example, the EFSA estimates for European countries used individual records but assigned inorganic arsenic values derived from conversion factors applied to total arsenic levels for broad food groups, introducing uncertainties in the estimates and tending to overestimate dietary exposure compared with individual country studies in the region.

In general, the ranges of dietary exposure to inorganic arsenic for North America and Europe were similar but were lower than those reported for countries

in Asia. An exception was Bangladesh, for which mean dietary exposure to inorganic arsenic was estimated to be up to 3 times that in other Asian countries. Mean dietary exposure to inorganic arsenic for adults in a community in Chile was 7 times higher at the upper end of the reported range than that reported for adults elsewhere.

For infants and children, a limited amount of information was available for Europe and the USA; in general, estimates of dietary exposure to inorganic arsenic for children were higher than those for adults from the same population when expressed per kilogram of body weight.

With the exception of dietary exposure estimates for inorganic arsenic for Bangladesh and Chile, mean reported dietary exposures for adults or whole populations were less than 1 µg/kg bw per day, and upper-percentile dietary exposures were less than 1.5 µg/kg bw per day. For infants and children, mean dietary exposure estimates for inorganic arsenic were less than 2 µg/kg bw per day, and upper-percentile estimates were less than 3 µg/kg bw per day. The mean dietary exposures of up to 3 µg/kg bw per day for Bangladesh were for a small community known to have contaminated water; the results from the study in Chile would need to be confirmed.

For countries where rice is the staple food, rice and water were the major contributors to total inorganic arsenic dietary exposures, with wheat and vegetables being minor contributors. In Europe and North America, where wheat-based products and potatoes are staple foods, these were major contributors to inorganic arsenic dietary exposure, as well as other vegetables, milk and meat and their products. Water can contribute up to 50% of total dietary exposure in areas in these regions where the water is not contaminated. Although total arsenic levels are higher in fish and shellfish than in other foods, consumption of fish and shellfish does not have a major influence on dietary exposure to inorganic arsenic, as the majority of arsenic in fish and in the edible portion of shellfish is organic. The exception to this is for populations (e.g. Japan) or individuals in other populations who consume high levels of seaweed and other edible algae, some species of which are very high in inorganic arsenic and consumption of which can make a significant contribution to inorganic arsenic dietary exposure. No studies included dietary supplements, although some of these may contain appreciable amounts of inorganic arsenic, which may also mean that dietary exposures to inorganic arsenic are underestimated for individuals taking these supplements on a regular basis.

9.9 Dose–response analysis

The following studies were selected for dose–response modelling of the respective end-points. For lung cancer, data were from a recent prospective study in north-eastern Taiwan, China, of 6888 residents for whom arsenic concentrations in drinking-water had been ascertained, with an average 11.5 years of follow-up. Residents 40 years of age and older at study initiation with 178 incident lung cancer cases identified (Chen et al., 2010b) were used for modelling. An earlier case–control study of lung cancer (Ferreccio et al., 2000) was not preferred for modelling due to potential selection bias in hospital-based controls. For urinary cancer (Chen et al., 2010a), data from the same prospective study in north-eastern Taiwan, China, with 45 incident cases of urinary cancer were used for dose–response modelling. Three arsenic-related skin lesion case–control studies were considered: two

conducted in Bangladesh (Ahsan et al., 2006; Rahman et al., 2006) and one conducted in Inner Mongolia, China (Xia et al., 2009). Substantial differences exist among the studies in factors such as case definition, exposure assessment methods and assessment of possible confounders, including smoking and sun exposure. Considering these differences, these studies were not used for the evaluation.

The exposure metric in these studies was concentration of arsenic in drinking-water; total dietary exposure to inorganic arsenic from food and water was not assessed. In order to provide an opinion on the risks to health related to the presence of inorganic arsenic in foodstuffs, it was necessary to convert from the arsenic concentrations in drinking-water to total dietary exposure to inorganic arsenic. This conversion required assumptions about the arsenic exposure from food before cooking and the volumes of drinking-water consumed directly and in cooking for the populations in which the respective health end-points were studied. Because of the uncertainty about actual exposure, the Committee used average estimates of exposure from food and volumes of water consumed to extrapolate from concentrations in drinking-water to total dietary exposure to inorganic arsenic from food and water. A range of low to high values for exposure from food and volume of water consumed was identified to be used in a sensitivity analysis, taking into account the dietary habits and levels of arsenic in food in the relevant region (north-eastern Taiwan, China). The identified ranges were 50–200 µg/day from food excluding water and volumes of 2–4 litres of water consumed directly and used in cooking per day. The average estimates were 75 µg/day from food and 3 litres of water per day. From the available data, an average body weight of 55 kg was assumed for this population.

In order to utilize the adjustment made for other variables (e.g. smoking) in the original analyses in the studies in north-eastern Taiwan, China, of cancers of the lung (Chen et al., 2010b) and urinary tract (Chen et al., 2010a), adjusted cases were calculated based on the RRs. This two-step process involved calculating case frequency by multiplying the rate in the referent group by the RR and then estimating the number of adjusted cases by multiplying the number of subjects by the case frequency. The resulting adjustment was small relative to the reported number of cases.

In the dose–response analysis using the USEPA BMD software (BMDS version 2.1.1), the nine different dichotomous models were fitted to the adjusted data. Those resulting in acceptable fits based on statistical considerations were selected to derive BMD and BMDL values for a BMR at the low end of the observed range of the data (Table 37). All nine models resulted in an acceptable fit for the lung and urinary tract data. In modelling the epidemiological data, the BMD and BMDL estimated by the log-probit model differed from those of other models, with higher values when the model was constrained within the BMDS and very much lower values when unconstrained. In consequence, the Committee decided that the outputs of the log-probit model should be excluded from the assessment.

The lowest calculated BMDL was 3.0 µg/kg bw per day for a 0.5% increased incidence of lung cancer above background over the average 11.5 years of follow-up, based on average estimates of the exposure. A sensitivity analysis to investigate the impact of uncertainty in the exposure estimate in this study indicated that this $BMDL_{0.5}$ could be in the range of 2.0–7.0 µg/kg bw per day, with the assumption

made with respect to volume of drinking-water consumed and used in cooking having a greater impact than the assumption regarding inorganic arsenic in food.

Table 37. Ranges of $BMD_{0.5}$ and $BMDL_{0.5}$ values for lung and urinary cancer associated with dietary exposure to inorganic arsenic, based on average estimates of exposure

	$BMD_{0.5}$ (μg/kg bw per day)	$BMDL_{0.5}$ (μg/kg bw per day)
Lung cancer (Chen et al., 2010b)	4.5–7.3	3.0–5.0
Urinary cancer (Chen et al., 2010a)	7.9–13.9	5.2–11.4

$BMD_{0.5}$, benchmark dose for 0.5% increased incidence of cancer over background in north-eastern Taiwan, China, with average 11.5 years of follow-up; $BMDL_{0.5}$, lower 95% confidence limit for the benchmark dose for 0.5% increased incidence of cancer over background.

10. EVALUATION

From epidemiological studies measuring arsenic levels in drinking-water, inorganic arsenic has been identified as a human carcinogen. It is present naturally in food and water because of geochemical conditions, and consequently exposure varies significantly in different regions and even within regions, primarily through the presence or absence of arsenic in groundwater sources for drinking-water.

The approach to quantitative assessment of cancer risk from inorganic arsenic is limited, inter alia, by the lack of information on total exposure in the available epidemiological studies. The inorganic arsenic BMDL for a 0.5% increased incidence of lung cancer was determined by using a range of assumptions to estimate exposure from drinking-water and food with differing concentrations of inorganic arsenic. The $BMDL_{0.5}$ was computed to be 3.0 μg/kg bw per day (2.0–7.0 μg/kg bw per day based on the range of estimated total dietary exposure). The uncertainties in this $BMDL_{0.5}$ relate to the assumptions regarding total exposure and to extrapolation of the $BMDL_{0.5}$ to other populations due to the influence of nutritional status, such as low protein intake, and other lifestyle factors on the effects observed in the studied population. The Committee noted that the PTWI of 15 μg/kg bw (2.1 μg/kg bw per day) is in the region of the $BMDL_{0.5}$ and therefore was no longer appropriate, and the Committee withdrew the previous PTWI.

The Committee noted that more accurate information on the inorganic arsenic content of foods as they are consumed is needed to improve assessments of dietary exposures to inorganic arsenic species. Analytical constraints to achieving this goal include the lack of validated methods for selective determination of inorganic arsenic species in food matrices and the lack of certified reference materials for inorganic arsenic in foods. The proportion of inorganic arsenic in some foods was found to vary widely, indicating that dietary exposures to inorganic arsenic should be based on actual data rather than using generalized conversion factors from total arsenic measurements.

Reported mean dietary exposure to inorganic arsenic in the USA and various European and Asian countries ranged from 0.1 to 3.0 µg/kg bw per day. Drinking-water was a major contributor to total inorganic arsenic dietary exposures and, depending on the concentration, can also be an important source of arsenic in food through food preparation and possibly irrigation of crops, particularly rice. The proportion of total exposure to inorganic arsenic arising from food relative to the proportion from water increases as the concentration of inorganic arsenic in the water decreases. At the lower end of the exposure range, food can also be a major contributor to total inorganic arsenic exposure.

For certain regions of the world where concentrations of inorganic arsenic in drinking-water exceed 50–100 µg/l, some epidemiological studies provide evidence of adverse effects. There are other areas where arsenic concentrations in water are elevated (e.g. above the WHO guideline value of 10 µg/l) but are less than 50 µg/l. In these circumstances, there is a possibility that adverse effects could occur as a result of exposure to inorganic arsenic from water and food, but these would be at a low incidence that would be difficult to detect in epidemiological studies.

10.1 Recommendations

There is a need for validated methods for selective extraction and determination of inorganic arsenic in food matrices and for certified reference materials for inorganic arsenic.

There is a need for improved data on occurrence of different species of arsenic in, and their bioavailability from, different foods as consumed in order to improve the estimates of dietary and systemic exposure. Further information on the toxicity of arsenic species found in food is also required.

The Committee recommended that future epidemiological studies of the health impacts of arsenic should incorporate appropriate measures of total exposure to inorganic arsenic, including from food and from water used in cooking and processing of food.

Further, it is recommended that epidemiological studies not only focus on relative risks, but also analyse and report the data such that they are suitable for estimating exposure levels associated with additional (lifetime) risks, so as to make their results usable for quantitative risk assessment.

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