February 1989
(edited August 1992)

Arsenic

Guideline

The interim maximum acceptable concentration (IMAC) for arsenic in drinking water is 0.025 mg/L (25 µg/L).

Identity, Use and Sources in the Environment

Arsenic is a metalloid with oxidation states of -3, 0, 3 and 5. It is widely distributed throughout the earth's crust, most often as arsenic sulphide or as metal arsenates and arsenides, and it is present in trace amounts in all living matter.

Arsenicals are used commercially and industrially as alloying agents in the manufacture of transistors, lasers and semi-conductors, as well as in the processing of glass, pigments, textiles, paper, metal adhesives, ceramics, wood preservatives, ammunition and explosives. They are also used in the hide tanning process and, to a limited extent, as pesticides, feed additives and pharmaceuticals, including veterinary drugs.

The principal sources of arsenic in ambient air are the burning of fossil fuels (especially coal), metal production, agricultural use and waste incineration. Arsenic is introduced into water through the dissolution of minerals and ores, from industrial effluents and via atmospheric deposition.[1,2] Natural sources, such as the dissolution of arsenic-containing bedrock, often contribute significantly to the arsenic content of drinking water[3] and groundwater.[4] In well-oxygenated surface waters, pentavalent arsenic is generally the most common species present;[5,6] under reducing conditions, such as those often found in deep lake sediments or groundwaters, the trivalent species is the predominant form.[3,7]

Exposure

The level of arsenic in natural waters generally ranges between 1 and 2 µg/L.[1] In a survey of arsenic levels in the groundwater of the western United States, concentrations exceeded 50 µg/L in several areas; in the alluvial basin region, levels in excess of 1 mg/L were measured in shallow groundwater (<10 m below ground level).[3]

In Saskatchewan, arsenic levels were below 10 µg/L in 88% and below 2 µg/L in 42% of samples taken from water supplies in 121 communities between 1981 and 1985; the maximum level recorded was 34 µg/L.[8] In Massachusetts, the median arsenic concentration in a survey of 204 community water supplies between 1980 and 1983 was below the detection limit (minimum detection limit, 0.8 µg/L; 90th percentile, 1 µg/L); the maximum level detected was 22 µg/L.[9] Elevated concentrations have been reported in areas with natural sources. Levels exceeded 50 µg/L in 33 to 93% of wells in each of seven communities in Nova Scotia; concentrations were greater than 500 µg/L in 10% of the wells sampled (n = 94).[10] In Lane County, Oregon, arsenic concentrations in well water ranged up to 2 mg/L.[4] Elevated levels of arsenic in drinking water from wells in the northern provinces of Argentina have been reported; in Médanos in Buenos Aires Province and La Francia in Córdoba, concentrations as high as 2 mg/L and 12 mg/L, respectively, have been reported. Levels exceeded 1 mg/L at several other locations.[11]

On the basis of results indicating that the concentration of arsenic in drinking water in areas without natural sources is usually less than 5 µg/L and assuming that the average daily intake of drinking water is 1.5 L, the mean daily intake of arsenic from this source (in the predominantly pentavalent inorganic form) will generally be less than 7.5 µg.

Arsenic is concentrated by many species of fish and shellfish and is used as a feed additive for poultry and livestock; fish and meat are therefore the main sources of dietary intake (78.9%, according to a recent U.S. survey).[12] In Canada, arsenic levels ranging from 0.4 to 118 mg/kg have been reported in marine fish sold for human consumption, whereas concentrations in meat and poultry range up to 0.44 mg/kg.[13] Levels in vegetation are generally an order of magnitude lower than those in fish, whereas concentrations in shellfish

are often far higher than those in fish.[14] Exogenous sources of arsenic in the diet include arsenic-containing fungicides used in fruit production.

Recent estimates of the mean daily intake of arsenic in food for adults are as follows: 16.7 µg (range 2.6 to 101 µg) in Canada,[15] 31.9 µg in Poland,[16] 45.9 µg in the United States[12] and 129.0 µg in the United Kingdom.[17] In infants and children aged one to three years, daily intakes of arsenic in food have been reported to be 2.9 µg and 9.4 µg, respectively, in Poland;[16] daily intakes of 1.26 µg and 15.5 µg have been reported for infants and two-year-olds, respectively, in the United States.[18]

It is difficult to compare the intake of arsenic from food directly with that from drinking water, as the form and biological availability of arsenic in these two sources vary. For example, a major portion of the organic arsenic in fish is present as highly complexed forms that are biologically unavailable (e.g., arseno-betaine).[19,20] The remainder is present largely as simple organic complexes, mainly trimethyl arsine, which are rapidly excreted from the body. Seafood contributes much of the daily arsenic intake (52% in the U.K. diet), even where the consumption of fish is low.[17] On the basis of data on the organic and inorganic arsenic contents of various foodstuffs,[17,21] it can be estimated that approximately 25% of the intake of arsenic from food is inorganic and 75% is organic. Assuming that the average daily intake of arsenic from food is 42.1 µg (the geometric mean of the above estimates for adults), the daily intake of inorganic arsenic from food will be approximately 10.5 µg. This contrasts with an intake of <7.5 µg of principally the pentavalent inorganic arsenic species in drinking water.

In the United States, average annual arsenic concentrations in air have been reported to be 0.4 ng/m^3 in rural areas remote from smelting activities, 3 ng/m^3 for all locations and 30 ng/m^3 in areas within 80 km of non-ferrous smelters.[22] In Canada, airborne concentrations of arsenic in a number of major urban centres ranged from <3 to <13 ng/m^3 in 1983 to 1984,[23] whereas more recent (1987 to 1988) levels in Windsor, Ontario, ranged between 1 and 4 ng/m^3.[24] Intake of arsenic through inhalation (principally in the inorganic form), therefore, is likely to be negligible (<1 µg, assuming 20 m^3 of air inhaled per day) compared with the amount ingested (mainly in the organic form).

Analytical Methods and Treatment Technology

Atomic absorption via gaseous hydride formation is considered to be the most suitable method for the determination of arsenic in water, with a detection limit of about 1 µg/L;[10] the practical quantitation limit (PQL) of this method, based on the capability of laboratories to measure arsenic within reasonable limits of precision and accuracy, is 5 µg/L.[25] Graphite furnace atomic absorption spectroscopy in combination with high pressure liquid chromatography is suitable for the determination of various arsenic species for research purposes, with a detection limit of 0.01 ng.[5]

The most effective conventional treatment for the removal of arsenic from water appears to be manganese greensand filters, which may be capable, based on limited data, of reducing arsenic concentrations in water to about 25 µg/L.[26] Other conventional methods, such as alum and ferric sulphate coagulation and lime softening, can reduce arsenic levels in water to about 50 µg/litre, depending on pH and arsenic valence.[27] Special process applications, such as activated alumina and reverse osmosis, appear to be suitable for the reduction of arsenic to low concentrations (i.e., 5 to 10 µg/L), but only with proper pretreatment.[27–30]

Health Effects

Pharmacokinetics and Metabolism

Although the results of available studies indicate that arsenic may be an essential element for several animal species (e.g., goats, minipigs, rats, chicks), there is no evidence that it is essential for humans. A Technical Panel on Arsenic convened by the U.S. Environmental Protection Agency (EPA) was “not aware of case reports describing an arsenic requirement for humans, nor of experimental or epidemiologic-type studies designed to determine whether arsenic is essential.” After reviewing the available data, the Technical Panel concluded that “if arsenic is a required nutrient for humans, current environmental arsenic exposures are not known to produce human arsenic deficiency.”[21]

Ingested elemental arsenic is poorly absorbed and largely eliminated unchanged. Arsenic oxides are readily absorbed (>80%) from the gastrointestinal tract[31] and, to a lesser extent, through the lungs and skin.[32] On the basis of faecal recovery experiments in human volunteers, the absorption of soluble As(III) and As(V) compounds is close to 95%.[1] As(III) tends to accumulate in the tissues, whereas As(V) and organic arsenic are well absorbed but rapidly and almost completely eliminated via the kidneys.[33]

Following ingestion, inorganic arsenic appears rapidly in the circulation, where it binds primarily to haemoglobin;[34] within 24 hours, it is found mainly in the liver, kidneys, lungs, spleen and skin.[32] Skin, bone and muscle represent the major storage organs. The accumulation of arsenic in skin is probably related to the abundance of proteins containing sulfhydryl groups, with which arsenic readily reacts.[31] In humans,

inorganic arsenic does not appear to cross the blood–brain barrier; however, transplacental transfer of arsenic in both humans[35] and mice[36] has been reported.

There appear to be two main processes, with different rates, for the elimination of ingested trivalent arsenic from the body.[37] The first is the rapid urinary excretion of non-methylated arsenic in both the trivalent and pentavalent forms (close to 90% of the total urinary arsenic over the first 12-hour period). The second involves detoxification by sequential methylation of As(III) in the liver to monomethylarsonic acid (MMAA) and dimethylarsinic acid (DMAA).[37,38] Excretion of the methylated compounds commences approximately five hours after ingestion but reaches its maximum level two to three days later. Less important routes of elimination of inorganic arsenic include skin, hair, nails and sweat.[39] The half-life of inorganic arsenic in humans is estimated to be between two and 40 days.[40]

The results of a study in which inorganic arsenic (125, 250, 500 or 1000 µg $NaAsO_2$) was administered orally once a day for five consecutive days to four volunteers indicate that the arsenic methylation capacity is progressively saturated when daily intake exceeds 0.5 mg;[41] it does not, however, appear to be completely saturated even for daily doses as high as 1 mg. Studies with human volunteers indicate that most ingested organic arsenic is rapidly excreted unchanged (>80% of the dose within four days).[42–44]

Effects in Humans

The acute toxicity of the various arsenic compounds in humans is predominantly a function of their rate of removal from the body. Arsine (AsH_3) is considered to be the most toxic form, followed by the arsenites As(III), arsenates As(V) and organic arsenic compounds. Lethal doses for the most common arsenic compounds (AsH_3, As_2O_3, As_2O_5, MMAA and DMAA) in humans range from 1.5 mg/kg bw (As_2O_3) to 500 mg/kg bw (DMAA).[45]

Symptoms of acute arsenic intoxication associated with the ingestion of well water containing arsenic at 1.2 and 21.0 mg/L have been reported.[46,47] Early clinical symptoms include abdominal pain and vomiting, diarrhoea, pain to the extremities and muscles and weakness with flushing of the skin. These symptoms are often followed by numbness and tingling of the extremities, muscular cramping and the appearance of a papular erythematous rash two weeks later.[48] A month later, symptoms may include burning paraesthesias of the extremities, palmoplantar hyperkeratosis, Mee's lines on fingernails and progressive deterioration in motor and sensory responses.[48–50]

Signs of chronic arsenicalism, including dermal lesions, peripheral neuropathy, skin cancer, peripheral vascular disease and possibly cancers of other organs, have been observed in populations ingesting arsenic-contaminated drinking water in Taiwan,[51,52] Chile,[53–55] the United States,[56] Mexico[57] and Canada.[58] Dermal lesions, such as hyperpigmentation, warts and hyperkeratosis of the palms and soles, were the most commonly observed symptoms, occurring after minimum exposure periods of approximately five years. Skin cancer (squamous cell carcinoma, basal cell carcinoma and Bowen's disease) was observed only following ingestion for a period of approximately 25 years.[51,52] Adverse effects have not been associated with the ingestion of arsenic in five additional studies conducted in the United States;[59–61] this may be attributable to shorter exposure periods,[59,60] lower waterborne concentrations,[61] the insensitivity of the study design[61] or the small numbers of people surveyed.

Numerous adverse effects, particularly among children, have been associated with the consumption of arsenic-contaminated water in Antofagasta, Chile (mean arsenic concentration, 0.6 mg/L). Effects on the skin (leukomelanoderma, hyperkeratosis), respiratory system (chronic coryza, cough, bronchopulmonary diseases), cardiovascular system (myocardial infarction, peripheral vascular disorders such as ischaemia of the tongue, Raynaud's phenomenon, acrocyanosis) and digestive system (abdominal pain, chronic diarrhoea) were observed in children under 16 years of age.[54,55] The prevalence of these symptoms decreased after the installation of a water treatment plant in 1972 (mean arsenic concentration, 0.08 mg/L); however, prevalence rates were still higher than those of the control population.[55] Although dermal lesions in young people ingesting drinking water containing high arsenic concentrations have been reported elsewhere,[52,57] cardiovascular toxicity in children has not been observed in studies other than those conducted in Chile. The appearance of these severe effects is surprising in view of the short period of exposure (average of seven years).

The largest epidemiological study on arsenic to date was conducted in Taiwan, where a population of 40 421 was divided into three groups based on the arsenic content of their well water (high ≥0.60 mg/L, medium 0.30 to 0.59 mg/L and low 0.01 to 0.29 mg/L).[51] There was a clear dose–response relationship between exposure to arsenic and the frequency of dermal lesions, "blackfoot disease" (a peripheral vascular disorder)[62] and skin cancer. However, there were several methodological weaknesses and potential confounding factors that complicate the interpretation of the results of this investigation. For example, the investigators were not "blinded" as to whether persons being examined were from the arsenic-endemic area. The socioeconomic conditions in the study area are poor, and the population subsists on food somewhat low in protein and fat.[51]

Exposure to arsenic from sources other than drinking water was also not examined, and there is some, albeit not well-documented, indication that these sources may have contributed significantly to the total exposure of the Taiwanese population.[63,64] In addition, several unknown fluorescent compounds and ergot alkaloids have been detected in samples of the water supply,[65] and it is possible that one of these compounds may be the aetiological agent responsible for "blackfoot disease," rather than arsenic.[62,65] It has been suggested, for example, that humic acid in artesian well water is the cause of blackfoot disease, not arsenic.[66]

More recent epidemiological evidence for an association between the incidence of various cancers of the internal organs and the ingestion of arsenic-contaminated water comes from a study conducted in a limited area of southwest Taiwan. In this study, standardized mortality ratios (SMRs) for cancers of the bladder, kidney, skin, lung, liver and colon were significantly elevated in the area of arsenic contamination. The SMRs for bladder, kidney, skin, lung and liver cancer also correlated well with the prevalence rate for blackfoot disease.[67] In an additional case–control study of 69 bladder, 76 lung and 59 liver cancer mortality cases as well as 368 community controls matched for age and sex, the odds ratios of developing bladder, lung and liver cancers for those who had used artesian well water for 40 or more years were 3.90, 3.39 and 2.67, respectively, compared with those who had never used artesian well water. Dose–response relationships were observed for all three cancer types by duration of exposure, and the odds ratios were not changed significantly when several other risk factors were taken into consideration in logistic regression analysis.[68] The Technical Panel on Arsenic established by the U.S. EPA concluded that although these studies demonstrated a qualitative relationship between the ingestion of arsenic-contaminated water and internal cancers, the data were not sufficient to assess the dose–response relationship.[21]

In an ecological analysis in which cancer mortality was examined in relation to arsenic concentrations in drinking water in the villages of the contaminated area of Taiwan (0.1 to 0.29 mg/L, 0.30 to 0.59 mg/L and ³ 0.60 mg/L), there were significant dose–response relationships for age-adjusted rates of cancers of the bladder, kidney, skin and lung in both sexes and cancers of the prostate and liver in men (the total number of cancers at each site ranged from nine cancers of the prostate in men to 268 lung cancers in both sexes).[69] A study examining the ecological correlations between arsenic levels in well water and mortality from various malignant neoplasms in Taiwan demonstrated a significant association between the arsenic level in well water and cancers of the liver, nasal cavity, lung, skin, bladder and kidney in both sexes and prostate cancer in men.[70]

In a study conducted in Mexico, the health status of the populations of two rural towns with average arsenic concentrations of 0.41 ± 0.114 mg/L ("exposed") and 0.005 ± 0.007 mg/L ("control") in their water supplies was examined.[57] The prevalence of non-specific symptoms, such as nausea, epigastric pain, colic abdominal pain, diarrhoea, headache and oedema, was significantly higher in the "exposed" population; the relative risks for these various symptoms ranged from 1.9 to 4.8. The relative risk of developing cutaneous lesions ranged from 3.6 to 36. In this study, only 9.6% of the individuals with skin lesions were under 20 years of age; for the studies conducted in Chile, this value was reported to be 78.7%.[71] The prevalence of skin cancer (including the precancerous lesion papular keratosis and ulcerative lesions) in the "exposed" population in Mexico was 6.4% compared with 1.06% in the population with similar exposure in Taiwan (0.30 to 0.59 mg/L group).[51] This variation could be due, in part, to the differences in the proportion of the various forms of arsenic salts ingested: 70% As(V) in the Mexican study compared with 89% As(V) in the Taiwanese study. The Mexican study suffered from methodological weaknesses; for example, the investigators were not blinded, and drinking water was assumed to be the only source of arsenic.

In a case–control study of 270 children with congenital heart disease and 665 healthy children, maternal consumption during pregnancy of drinking water containing detectable arsenic concentrations was associated with a threefold increase in the occurrence of coarction of the aorta (the prevalence odds ratio adjusted for all measured contaminants and source of drinking water was 3.4 with 95% confidence limits of 1.3 to 8.9).[9] However, there was no adjustment for maternal age, socioeconomic status or previous reproductive history. Exposure was determined by matching the results of available water analyses for the water supplies serving the mothers to their dates of conception. However, for 101 of the mothers residing in communities served by multiple water supplies, it was necessary to average contaminant concentrations from more than one source in the community; the mean interval from the date of analysis to date of conception for the entire study population was 227 days.

In a case–control study in Massachusetts of 286 women with spontaneous abortions and 1391 women with live births, elevated odds ratios for miscarriages were associated with exposure to arsenic in drinking water.[72] The odds ratios for spontaneous abortion adjusted for maternal age, educational level and history of prior spontaneous abortion for women

exposed to arsenic in their drinking water at undetectable concentrations, 0.0008 to 0.0013 mg/L and 0.0014 to 0.0019 mg/L were 1.0, 1.1 and 1.5, respectively. Exposure was determined by matching each woman to the results of a tap water sample taken in her city or town during pregnancy. However, the median interval from the date of matched metal analysis sample to the date of conception was 2.1 years, and it was reported that the variability of concentrations of metals in 20 Massachusetts towns and cities over the seven-year period between 1978 and 1985 was 10- to 100-fold. It would be desirable, however, to follow up these preliminary results in studies designed to more accurately assess exposure.

Effects in Experimental Animals and *In Vitro*

There were significant reductions in cardiac output and stroke volume in male Wistar rats and female New Zealand rabbits ingesting drinking water containing 50 µmg As(III)/mL drinking water for 18 and 10 months, respectively. In contrast, there was no effect on cardiac function in rats following ingestion of the same concentration of As(V) for 18 months.[73]

With the exception of the partially positive results of a recent study described below, the carcinogenicity of arsenic has not been confirmed in bioassays in animal species. In the recent investigation, the potential of arsenic compounds [DMAA, MMAA, As(III) and As(V)] to act as promoters or initiators was investigated. Male Wistar rats were partially hepatectomized, injected intraperitoneally with a single dose of diethylnitrosamine (30 mg/kg bw) and, on day 7, administered the maximum tolerated doses (MTDs) of each of the arsenic compounds in drinking water for 7, 25 or 43 weeks (promotion protocol). The protocol for determination of initiation was similar but did not include diethylnitrosamine treatment. The initiation potential of arsenate and arsenite was also investigated in a study in which partially hepatectomized rats were exposed 18 to 24 hours later to 160 mg/L [As(III)] or 320 mg/L [As(V)] in drinking water for three days and then fed food pellets containing 0.05% phenobarbital four days later for seven weeks. There were no significant increases in the incidence of tumours of the liver in any of the arsenic-exposed rats for any time periods of treatment in either the initiation or promotion protocols. In the promotion protocol, however, there was a significant increase in the incidence of tumours of the kidney in the group exposed to the MTD of As(III) (160 mg/L) for 25 weeks.[74] Based on the results of their studies, the authors also concluded that the chronic toxicity of arsenic compounds in drinking water cannot be predicted from acute toxicity studies, because DMAA was as "toxic" as arsenate and arsenite.

Arsenic does not appear to be mutagenic in bacterial and mammalian assays, although it can induce chromosome breakage, chromosomal aberrations and sister chromatid exchange in a linear, dose-dependent fashion in a variety of cultured cell types, including human cells.[21,75] Most of the chromosomal aberrations are lethal events, so that the cells do not survive more than one or two generations; consequently, the damage caused by arsenic has no genetic consequences.[21] Trivalent arsenic is approximately an order of magnitude more potent than As(V) in this respect. The clastogenic effect of arsenic appears to be due to interference with DNA synthesis, as arsenic induces sister chromatid exchange and chromosomal aberrations only when present during DNA replication.[76] Arsenic has also been shown to block dividing cells in the S and G_2 phases.[77]

In early studies, teratogenic effects of arsenic in chicks, golden hamsters and mice were reported.[9,78] In a more recent investigation,[79] arsenate was teratogenic in the offspring of pregnant hamsters following exposure on days 4 to 7 of gestation by minipump implantation. The threshold blood level for teratogenesis was 4.3 µmol/kg.[80] The specific form of arsenic that is responsible for teratogenesis is not known, although there is evidence to suggest that it is arsenite rather than arsenate.[81] In studies with mice and hamsters, MMAA and DMAA have been considerably less teratogenic than As(III) or As(V).[37]

Classification and Assessment

Arsenic is a documented human carcinogen; it has, therefore, been classified in Group I (carcinogenic to humans). Toxic effects other than cancer have also been observed in populations ingesting arsenic-contaminated water supplies; however, carcinogenicity is considered to be the critical effect for derivation of the guideline.

Data available on the association between internal cancers and ingestion of arsenic in drinking water are limited and insufficient for quantitative risk estimation. Based on the increased incidence of skin cancer observed in the Taiwanese population,[52] however, the U.S. EPA has estimated lifetime skin cancer risks associated with the ingestion of arsenic in drinking water using a multistage model modified to take into account incidence stratified by age group. The model was quadratic as well as linear in dose, and there was an adjustment for the larger water consumption of Taiwanese compared with North American men. Based on this model, lifetime risks of skin cancer in the general population in Canada for ingestion of 1 µg/L of arsenic in drinking water were estimated to range from

1.3×10^{-5}* (based on Taiwanese women) to 3.6×10^{-5}* (based on Taiwanese men).

On the basis of a review of available data, it has been concluded that the EPA model is the most appropriate for estimation of the skin cancer risks associated with the ingestion of arsenic in drinking water. The estimated concentrations in drinking water corresponding to lifetime skin cancer risks of 10^{-5}, 10^{-6} and 10^{-7} (based on Taiwanese men) are as follows:*

Lifetime risk	Concentration in drinking water (µg/L)
10^{-5}	0.28
10^{-6}	0.028
10^{-7}	0.0028

It should be borne in mind that these estimates probably represent a worst-case situation because of concomitant exposure to other compounds in the water in Taiwan and possible dietary deficiencies of the Taiwanese population compared with North American populations. Moreover, methylation (i.e., detoxification) of inorganic arsenic is progressively but not completely saturated when daily intake of humans exceeds approximately 500 µg, and this has not been taken into consideration in derivation of the quantitative estimates of risk.

Rationale

Because arsenic is classified in Group I (carcinogenic to humans), the maximum acceptable concentration (MAC) is derived based on consideration of available practicable treatment technology and estimated lifetime cancer risk. Because the MAC must also be measurable by available analytical methods, the PQL is also taken into consideration in its derivation.

An interim maximum acceptable concentration (IMAC) of 0.025 mg/L (25 µg/L) for arsenic was established, therefore, on the basis of the following considerations:

(1) The IMAC must be measurable and achievable at reasonable cost. Although several conventional treatment processes remove arsenic from water, only activated alumina and reverse osmosis, with proper pretreatment, appear to be suitable for the reduction of arsenic to low concentrations (i.e., 5 to 10 µg/L) in small to mid-size communities. Owing to their complexity and cost, however, these processes are not considered to be practicable for such application at this time.

Manganese greensand filters, which are commonly used by smaller communities for iron and/or manganese removal, appear capable, based on limited data, of reducing arsenic concentrations to about 25 µg/L. Because arsenic in groundwater is generally associated with iron and/or manganese, such filters are considered to be a practicable treatment method.

(2) The PQL (based on the ability of laboratories to measure arsenic within reasonable limits of precision and accuracy) is 5 µg/L, well below the IMAC.

(3) The MAC is designated as interim because the lifetime skin cancer risk associated with the ingestion of drinking water containing arsenic at the IMAC is greater than the range that is considered generally to be essentially negligible. Based on the incidence of skin cancer in men in Taiwan, the estimated lifetime cancer risk associated with ingestion of water containing arsenic at the IMAC is 9.0×10^{-4}. However, this value may overestimate the actual risk in North American populations owing to concomitant exposure to other compounds in the water in Taiwan and possible dietary deficiencies of the Taiwanese population. Moreover, there are dose-dependent variations in the metabolism of arsenic that could not be taken into consideration in the quantitative risk assessment. Also, only a small proportion of arsenic-induced skin cancers (1 to 14%) are fatal. However, there is also recent evidence that cancers of internal organs have been associated with the ingestion of arsenic-contaminated water. Until more definitive data are available, these cancers will not be taken into consideration in the quantitative estimate of risk.

The IMAC will be reviewed periodically in light of developments in treatment technology and additional data on health risks associated with exposure to arsenic in drinking water.

References

1. Hindmarsh, J.T. and McCurdy, R.F. Clinical and environmental aspects of arsenic toxicity. CRC Crit. Rev. Clin. Lab. Sci., 23: 315 (1986).

2. Hutton, M. and Symon, C. The quantities of cadmium, lead, mercury and arsenic entering the U.K. environment from human activities. Sci. Total Environ., 57: 129 (1986).

3. Welch, A.H., Lico, M.S. and Hughes, J.L. Arsenic in ground water of the western United States. Ground Water, 26: 333 (1988).

4. Nadakavukaren, J.J., Ingermann, R.L., Jeddeloh, G. and Falkowski, S.J. Seasonal variation of arsenic concentration in well water in Lane County, Oregon. Bull. Environ. Contam. Toxicol., 33: 264 (1984).

5. Irgolic, K.J. Speciation of arsenic compounds in water supplies. Report No. EPA-600/S1-82-010, U.S. Environmental Protection Agency, Research Triangle Park, NC (1982).

6. Cui, C.G. and Liu, Z.H. Chemical speciation and distribution of arsenic in water, suspended solids and sediment of Xiangjiang River, China. Sci. Total Environ., 77: 69 (1988).

* Average adult body weight = 70 kg; average daily intake of drinking water = 1.5 L.

7. Lemmo, N.V., Faust, S.O., Belton, T. and Tucker, R. Assessment of the chemical and biological significance of arsenical compounds in a heavily contaminated watershed. Part 1. The fate and speciation of arsenical compounds in aquatic environments—A literature review. J. Environ. Sci. Health, A18: 335 (1983).

8. Nargant, D. Personal communication. Saskatchewan Department of Environment (1986).

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

10. Méranger, J.C., Subramanian, K.S. and McCurdy, R.F. Arsenic in Nova Scotian groundwater. Sci. Total Environ., 39: 49 (1984).

11. Grinspan, D. and Biagini, R. [Chronic endemic regional hydroarsenicism. The manifestations of arsenic poisoning caused by drinking water.] Med. Cutan. Ibero-Latino-Am., 13: 85 (1985) (in Spanish).

12. Gartrell, M.J., Craun, J.C., Podrebarac, D.S. and Gunderson, E.L. Pesticides, selected elements, and other chemicals in adult total diet samples, October 1980–March 1982. J. Assoc. Anal. Chem., 69: 146 (1986).

13. Department of National Health and Welfare. Food/field monitoring project FM-35. Bureau of Chemical Safety, Ottawa (1983).

14. Subramanian, K.S. Arsenic. In: Quantitative trace analysis of biological materials: principles and methods for determination of trace elements and trace amounts of some macro elements. H.A. McKenzie and L.E. Smythe (eds.). Elsevier Science Publishers B.V., Amsterdam (1988).

15. Dabeka, R.W., McKenzie, A.D. and Lacroix, G.M.A. Dietary intakes of lead, cadmium, arsenic and fluoride by Canadian adults: a 24-hour duplicate diet study. Food Addit. Contam., 4: 89 (1987).

16. Nabrzyski, M., Gajewska, R. and Lebiedzinska, A. [Arsenic content of daily diets of children and adults.] Rocz. Panstw. Zakl. Hig., 36: 113 (1985) (in Polish).

17. Hazell, T. Minerals in foods: dietary sources, chemical forms, interactions, bioavailability. World Rev. Nutr. Diet., 46: 1 (1985).

18. Gartrell, M.J., Craun, J.C., Podrebarac, D.S. and Gunderson, E.L. Pesticides, selected elements, and other chemicals in infant and toddler total diet samples, October 1980–March 1982. J. Assoc. Off. Anal. Chem., 69: 123 (1986).

19. World Health Organization. Toxicological evaluation of certain food additives and contaminants—Arsenic. Report prepared by the 33rd meeting of the Joint FAO/WHO Expert Committee on Food Additives (Food Additives Series 24), Geneva. p. 155 (1988).

20. Vahter, M., Marafante, E. and Dencker, L. Metabolism of arseno-betaine in mice, rats and rabbits. Sci. Total Environ., 30: 197 (1983).

21. U.S. Environmental Protection Agency. Special report on ingested inorganic arsenic. Skin cancer; nutritional essentiality. Report No. EPA-625/3-87/013, Risk Assessment Forum, Washington, DC (1988).

22. Ball, A.L., Rom, W.N. and Glenne, B. Arsenic distribution in soils surrounding the Utah copper smelter. Am. Ind. Hyg. Assoc. J., 44: 341 (1983).

23. The Environmental Applications Groups Ltd. Identification of sources of inhalable particulates in Canadian urban areas. Final report. Prepared for Environment Canada (1984).

24. Environment Canada. Tables of inhalable particulate and inorganic compound concentrations in two monitoring stations (Windsor and Walpole Island) in the Windsor/Walpole Air Monitoring Network in Ontario. Unpublished report (1988).

25. U.S. Environmental Protection Agency. Health advisory—Arsenic. Office of Drinking Water, Washington, DC (1985).

26. Saskatchewan Department of Environment and Public Safety. The removal of arsenic from the Village of Love water supply using oxidation/filtration. Departmental report, Regina, June (1990).

27. Sorg, T.J. and Logsdon, G.S. Treatment technology to meet the interim primary drinking water regulations for inorganics: Part 2. J. Am. Water Works Assoc., 70(7): 379 (1978).

28. Sorg, T.J., Forbes, R.W. and Chambers, D.S. Removal of radium-226 from Sarasota County, Fla., drinking water by reverse osmosis. J. Am. Water Works Assoc., 72(4): 230 (1980).

29. Schneiter, R.W. and Middlebrooks, E.J. Arsenic and fluoride removal from groundwater by reverse osmosis. Environ. Int., 9: 289 (1983).

30. Bellack, E. Arsenic removal from potable water. J. Am. Water Works Assoc., 63(7): 454 (1971).

31. Fowler, B.A., Ishinishi, N., Tsuchiya, K. and Vahter, M. Arsenic. In: Handbook on the toxicology of metals. L. Friberg, G.F. Nordberg and V.B. Vouk (eds.). Elsevier/North-Holland Biomedical Press, Amsterdam. p. 293 (1979).

32. Wickstroem, G. Arsenic in the ecosystem of man. Work Environ. Health, 9: 2 (1972).

33. Bertolero, F., Pozzi, G., Sabbioni, E. and Saffiotti, U. Cellular uptake and metabolic reduction of pentavalent to trivalent arsenic as determinants of cytotoxicity and morphological transformation. Carcinogenesis, 8: 803 (1987).

34. Axelson, O. Arsenic compounds and cancer. J. Toxicol. Environ. Health, 6: 1229 (1980).

35. Gibson, R.S. and Gage, L.A. Changes in hair arsenic levels in breast and bottle fed infants during the first year of infancy. Sci. Total Environ., 26: 33 (1982).

36. Hood, R.D., Vedel-Macrander, G.C., Zaworotko, M.J., Tatum, F.M. and Meeks, R.G. Distribution, metabolism, and fetal uptake of pentavalent arsenic in pregnant mice following oral or intraperitoneal administration. Teratology, 35: 19 (1987).

37. Lovell, M.A. and Farmer, J.G. Arsenic speciation in urine from humans intoxicated by inorganic arsenic compounds. Hum. Toxicol., 4: 203 (1985).

38. Buchet, J.P. and Lauwerys, R. Study of inorganic arsenic methylation by rat liver *in vitro*: relevance for the interpretation of observations in man. Arch. Toxicol., 57: 125 (1985).

39. International Commission on Radiological Protection. Report of the Task Group on Reference Man. ICRP Publication 23. Pergamon Press, Oxford (1975).

40. Pomroy, C., Charbonneau, S.M., McCullough, S. and Tam, G.K.H. Human retention studies with ^{74}As. Toxicol. Appl. Pharmacol., 53: 550 (1980).

41. Buchet, J.P., Lauwerys, R. and Roels, H. Urinary excretion of inorganic arsenic and its metabolites after repeated ingestion of sodium metaarsenite by volunteers. Int. Arch. Occup. Environ. Health, 48: 111 (1981).

42. Buchet, J.P., Lauwerys, R. and Roels, H. Comparison of the urinary excretion of arsenic metabolites after a single oral dose of sodium arsenite, monomethylarsonate, or dimethylarsinate in man. Int. Arch. Occup. Environ. Health, 48: 71 (1981).

43. Luten, J.B., Riekwel-Booy, G. and Rauchbaar, A. Occurrence of arsenic in plaice (*Pleuronectes platessa*), nature of organo-arsenic compound present and its excretion by man. Environ. Health Perspect., 45: 165 (1982).

44. Tam, G.K.H., Charbonneau, S.M., Bryce, F. and Sandi, E. Excretion of a single oral dose of fish-arsenic in man. Bull. Environ. Contam. Toxicol., 28: 669 (1982).

45. Buchet, J.P. and Lauwerys, R.R. Evaluation of exposure to inorganic arsenic. Cah. Med. Trav., 19: 15 (1982).

46. Wagner, S.L., Maliner, J.S., Morton, W.E. and Braman, R.S. Skin cancer and arsenical intoxication from well water. Arch. Dermatol., 115: 1205 (1979).

47. Feinglass, E.J. Arsenic intoxication from well water in the United States. N. Engl. J. Med., 288: 828 (1973).

48. Murphy, M.J., Lyon, L.W. and Taylor, J.W. Subacute arsenic neuropathy: clinical and electrophysiological observations. J. Neurol. Neurosurg. Psychiatry, 44: 89 (1981).

49. Wesbey, G. and Kunis, A. Arsenical neuropathy. Ill. Med. J., 150: 396 (1981).

50. Fennell, J.S. and Stacy, W.K. Electrocardiographic changes in acute arsenic poisoning. Ir. J. Med. Sci., 150: 338 (1981).

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

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

53. Borgono, J.M. and Greiber, R. Epidemiological study of arsenicism in the city of Antofagasta. In: Trace substances in environmental health. V. D.D. Hemphill (ed.). University of Missouri, Columbia, MO. p. 13 (1971).

54. Zaldívar, R. A morbid condition involving cardio-vascular, broncho-pulmonary, digestive and neural lesions in children and young adults after dietary arsenic exposure. Zentralbl. Bakteriol., I. Abt. Orig. B, 170: 44 (1980).

55. Zaldívar, R. and Ghai, G.L. Clinical epidemiological studies on endemic chronic arsenic poisoning in children and adults, including observations on children with high- and low-intake of dietary arsenic. Zentralbl. Bakteriol. Hyg., I. Abt. Orig. B, 170: 409 (1980).

56. Valentine, J.L., Campion, D.S., Schluchter, M.D. and Massey, F.J. Arsenic effects on human nerve conduction. In: Proceedings of the 4th International Symposium on Trace Element Metabolism in Man and Animals, held in Perth, Western Australia, 11–15 May 1981. J.M. Gawthorne, J.M. Howell and C.L. White (eds.). Springer-Verlag, Berlin. p. 409 (1982).

57. Cebrian, M.E., Albores, A., Aguilar, M. and Blakely, E. Chronic arsenic poisoning in the north of Mexico. Hum. Toxicol., 2: 121 (1983).

58. Hindmarsh, J.T., McLetchie, O.R., Hefferman, L.P.M., Hayne, O.A., Ellenberger, H.A., McCurdy, R.F. and Thiebaux, H.J. Electromyographic abnormalities in chronic environmental arsenicalism. J. Anal. Toxicol., 1: 270 (1977).

59. Southwick, J.W., Western, A.E., Beck, M.M., Whitely, T., Isaacs, R., Petajan, J. and Hansen, C.D. An epidemiological study of arsenic in drinking water in Millard County, Utah. In: Arsenic: industrial, biomedical, and environmental perspectives. W.H. Lederer and R.J. Fensterheim (eds.). Van Nostrand Reinhold Company, New York, NY. p. 210 (1983).

60. Kreiss, K., Zack, M.M., Feldman, R.G., Niles, C.A., Chirico-Post, J., Sax, D.S., Landrigan, P.J., Boyd, M.H. and Cox, D.H. Neurologic evaluation of a population exposed to arsenic in Alaskan well water. Arch. Environ. Health, 38: 116 (1983).

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

62. Yu, H.S., Sheu, H.M., Ko, S.S., Chiang, L.C., Chien, C.H., Lin, S.M., Tserng, B.R. and Chen, C.S. Studies on blackfoot disease and chronic arsenism in southern Taiwan: with special reference to skin lesions and fluorescent substances. J. Dermatol. (Tokyo), 11: 361 (1984).

63. Li, G., Fei, W. and Yen, Y. Survey of arsenic levels in the rice grain from various locations in Taiwan. Natl. Sci. Counc. Mon., 7: 700 (1979).

64. Heydorn, K. Environmental variation of arsenic levels in human blood determined by neutron activation analysis. Clin. Chim. Acta, 28: 349 (1970).

65. Chen, C.J., Wu, M.M., Lee, S.S., Wang, J.D., Cheng, S.H. and Wu, H.Y. Atherogenicity and carcinogenicity of high-arsenic artesian well water. Multiple risk factors and related malignant neoplasms of blackfoot disease. Arteriosclerosis, 8: 452 (1988).

66. Lu, F.J. Blackfoot disease: arsenic or humic acid? Lancet, 336(8707): 115 (1990).

67. Chen, C.J., Chuang, Y.C., Lin, T.M. and Wu, H.Y. Malignant neoplasms among residents of a blackfoot disease-endemic area in Taiwan: high-arsenic artesian well water and cancers. Cancer Res., 45: 5895 (1985).

68. Chen, C.J., Chuang, Y.C., You, S.L., Lin, T.M. and Wu, H.Y. A retrospective study on malignant neoplasms of bladder, lung and liver in a blackfoot disease endemic area of Taiwan. Br. J. Cancer, 53: 399 (1986).

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

70. Chen, C.-J. and Wang, C.J. Ecological correlation between arsenic level in well water and age-adjusted mortality from malignant neoplasms. Cancer Res., 50: 5470 (1990).

71. Zaldivar, R. Arsenic contamination of drinking water and foodstuffs causing endemic chronic poisoning. Beitr. Pathol., 151: 384 (1974).

72. Aschengrau, A., Zierler, S. and Cohen, A. Quality of community drinking water and the occurrence of spontaneous abortion. Arch. Environ. Health, 44: 283 (1989).

73. Carmignani, M., Boscolo, P. and Castellino, N. Metabolic fate and cardiovascular effects of arsenic in rats and rabbits chronically exposed to trivalent and pentavalent arsenic. Arch. Toxicol., Suppl. 8: 452 (1985).

74. Shirachi, D.Y., Tu, S.H. and McGowan, J.P. Carcinogenic potential of arsenic compounds in drinking water. Report No. EPA-600/S1-86/003, U.S. Environmental Protection Agency, Research Triangle Park, NC (1986).

75. Jacobson-Kram, D. and Montalbano, D. The Reproductive Effects Assessment Group's report on the mutagenicity of inorganic arsenic. Environ. Mutagen., 7: 787 (1985).

76. Crossen, P.E. Arsenic and SCE in human lymphocytes. Mutat. Res., 119: 415 (1983).

77. Petres, J., Baron, D. and Hagedorn, M. Effects of arsenic cell metabolism and cell proliferation: cytogenetic and biochemical studies. Environ. Health Perspect., 19: 223 (1977).

78. Hood, R.D. and Bishop, S.L. Teratogenic effects of sodium arsenate in mice. Arch. Environ. Health, 24: 62 (1972).

79. Ferm, V.H. and Hanlon, D.P. Constant rate exposure of pregnant hamsters to arsenate during early gestation. Environ. Res., 37: 425 (1985).

80. Hanlon, D.P. and Ferm, V.H. Concentration and chemical status of arsenic in the blood of pregnant hamsters during critical embryogenesis. 1. Subchronic exposure to arsenate utilizing constant rate administration. Environ. Res., 40: 372 (1986).

81. Hanlon, D.P. and Ferm, V.H. Concentration and chemical status of arsenic in the blood of pregnant hamsters during critical embryogenesis. 2. Acute exposure. Environ. Res., 40: 380 (1986).