# Health implications of arsenic in drinking water

*Definitive answers regarding arsenic health risks at low exposures will be elusive without additional research.*

**Frederick W. Pontius, Kenneth G. Brown, and Chien-Jen Chen**

**The adequacy of the current maximum contaminant level (MCL) for arsenic is being evaluated by the US Environmental Protection Agency. If recent theoretical estimates of chronic effects and cancer risks prove accurate, the current MCL may not effectively protect health. Knowledge of arsenic pharmacokinetics and mechanisms in humans, however, is not complete enough to provide a definitive answer, and current epidemiologic evidence is too inconsistent and too fraught with uncertainty regarding arsenic exposure to be helpful in assessing low-level risks.**

Arsenic (As) has been used as a [illegible] nearly 4,000 years.[1] The lethal [illegible] other arsenic-containing compounds (ref[illegible]s arsenicals) are well documented.[2–9] In the United States, the current maximum contaminant level (MCL) for arsenic in drinking water is 0.05 mg/L, which is currently being evaluated for revision by the US Environmental Protection Agency (USEPA). [See Legislation/Regulation, page 6]. The chemical characteristics of arsenic; routes of human exposure; the human health effects of ingested arsenic, with particular attention to drinking water; and the implications of recent studies on the adequacy of the current arsenic MCL are briefly considered in this article.

## Arsenic occurs naturally

Arsenic is a nonmetal in group Va of the periodic chart; this group also contains nitrogen, phosphorus, antimony, and bismuth. The physical appearance of arsenic resembles that of a metal, so it is referred to as a metalloid to distinguish it from a true nonmetal. It commonly exists in several different oxidation states: +V (arsenate), +III (arsenite), 0 (arsenic), and –III (arsine). The oxidation state (or valence state), which indicates the capacity of the atom to combine with other atoms, is used to denote the form of arsenic present.

Tables 1 and 2 summarize common arsenic compounds found in the environment. Arsenic occurs naturally, being the twentieth most abundant ele-

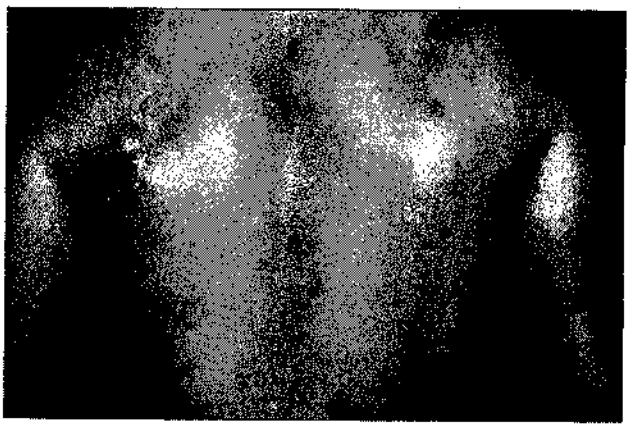
ment in the earth's crust, and is a component of more than 245 minerals. These are mostly ores containing sulfide, along with copper, nickel, lead, cobalt, or other metals. Smelting of these ores produces arsenic trioxide ($As_2O_3$) as a byproduct, which is the raw material for industrial arsenic chemicals. Today, all arsenic trioxide used in the United States is imported.[10] Smelting operations in the United States that previously produced arsenic trioxide caused significant air pollution and land contamination, which is now in remediation. Arsenic is also added to the environment through the burning of arsenic-containing fossil fuels and through volcanic eruptions and other natural processes.

Arsenic and its compounds are mobile in the environment. Weathering of rocks converts arsenic sulfides to arsenic trioxide, which enters the arsenic cycle as dust or by dissolution in rain, rivers, or groundwater.[10] Once liberated from rocks and soils, arsenic cycles among land, air, and water. Volatile forms of arsenic, e.g., arsine ($AsH_3$) and trimethyl arsine [$(CH_3)_3As$], enter the atmosphere from land and water and are returned by rain and atmospheric fallout. The oxidized forms of arsenic are converted back to sulfides by anaerobic processes occurring on land and in water sediments.[11] Water is a primary means of arsenic transport in the environment.

Arsenic trioxide is only slightly soluble in water, forming arsenous acid ($H_3AsO_3$), but arsenic pentoxide ($As_2O_5$), formed by oxidation of $As_2O_3$, is readily soluble in water, forming arsenic acid ($H_3AsO_4$). In neutral or near-neutral pH water, arsenic exists primarily as the anionic species of arsenic-containing acids, with the exception of arsenous acid, which exists primarily as the uncharged species at pH 7.[10]

In water, arsenic is generally found in the arsenate [As(V)] form, but some arsenite [As(+III)] is usually present. In aerated water, arsenite tends to be oxidized to arsenate, especially at alkaline pH. Reduction of arsenate to arsenite can occur at low pH values.

***Extensive epidemiologic studies have documented a link between chronic exposure to arsenic in drinking water and skin cancer in Taiwan.***



Organic compounds containing arsenic, such as monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA), also exist in natural environments, formed by microbial metabolism of inorganic arsenic.[11] When MMA and DMA are present in natural waters, they usually constitute a small percentage of the total arsenic present. However, these compounds are human metabolites of arsenic and will be discussed later.

## Human exposure widespread

Humans are exposed to arsenic primarily from air, food, and water. The concentration of arsenic in air is usually only a few ng As/m$^3$; the average national exposure in the United States has been estimated at 0.006 µg As/m$^3$.[5] Exposures may be higher in polluted areas. For example, the concentration of arsenic in air may reach 1 µg As/m$^3$ near smelters or power plants that burn oil with a high arsenic content.[3] Absorption of inhaled arsenic ranges between 30 to 85 percent, depending on the relative portions of vapor and particulate matter.[5] USEPA[5] has estimated that the general public would be exposed to a range of approximately 0.04–0.09 µg As/d by inhalation.

**The current maximum contaminant level for arsenic in drinking water is being evaluated for revision by USEPA.**

Food is a significant source of arsenic. Regional and individual eating habits greatly affect inorganic arsenic intake because some foods are relatively high in arsenic. For example, marine crabs, lobster, shrimp, and cod typically contain 10–40 mg As/kg based on fresh weight.[7] In comparison, pickerel, catfish, coho salmon, and other freshwater fish, along with pork and beef, typically contain <1 mg As/kg.[7] Based on market-basket surveys of the total arsenic content in US food, the US Food and Drug Administration has estimated that adults ingest an average of about 53 µg As/d from the diet.[3] About half of this amount (27 µg As/d) comes from fish and shellfish, with about 4 µg As/d from meat and poultry, 4–5 µg As/d from grain and grain products, and 3–4 µg As/d from vegetables. Infants (6 months old) and toddlers (2 years old) were estimated to ingest 21.5 and 27.6 µg As/d, respectively. For infants, milk and milk products contributed 63 percent of the total intake. The two largest sources of arsenic in the toddler diet were meat, fish, and poultry (30 percent) and milk and milk products (30 percent).

Studies in Canada indicate that the arsenic content of many foods is mainly inorganic arsenic, typically

**TABLE 1** Properties of selected inorganic arsenic compounds[3]

| Property | Arsenic | Arsenic Trioxide | Sodium Arsenate | Sodium Arsenite |
|---|---|---|---|---|
| Synonyms | Arsenic black, colloidal arsenic, gray arsenic | Arsenic oxide, arsenious acid, arsenious oxide, white arsenic | Disodium arsenate, sodium biarsenate, arsenic acid disodium salt | Arsenious acid sodium salt, sodium metaarsenite |
| Chemical formula | As | $As_2O_3$ ($As_4O_6$) | $Na_2HAsO_4$ | $NaAsO_2$ |
| Molecular weight | 74.9216 | 197.84 | 185.91 | 129.91 |
| Valence state | 0 | +III | +V | +III |
| Water solubility | Insoluble | 37 g/L at 20°C, 101 g/L at 100°C | Soluble | Very soluble |

65–75 percent (Table 3).[12,13] However, fish, fruits, and vegetables primarily contain organic arsenic; less than 10 percent of the arsenic in these foods exists in the inorganic form. USEPA estimates that, overall, about 20 percent of total dietary arsenic intake is in an inorganic form.[3] This estimate is important because inorganic arsenic intake is of primary concern; organic arsenic in foods is less toxic than inorganic forms and most is excreted rapidly.[5] Organic forms of arsenic in seafood, for example, are trimethylated, and most are excreted unchanged.[5]

The arsenic content of soils varies with soil and local conditions. Absorption of arsenic through the skin is not well characterized but is thought to be insignificant.[3] Wester et al[14] reported results of experiments using female Rhesus monkeys and human cadaver skin, finding the rate of arsenic absorption from soil through skin to be about 3–5 percent and 1 percent, respectively. No differences were observed between skin absorption of arsenic from soil and skin absorption from water. Washing with soap and water readily removed most of the arsenic from the skin surface.[15] Ingestion of arsenic-containing soils and house dust are possible routes of exposure. Infants and toddlers can ingest from 100 to 800 mg/d of house dust, and any arsenic associated with the ingested dust contributes to total arsenic exposure.[15]

Ingestion of drinking water is an important source of arsenic exposure, and concentrations are generally highest in groundwater, especially where geochemical conditions favor arsenic dissolution. High arsenic concentrations have been reported in water supply wells in certain areas of Taiwan[16] (up to 1.82 mg/L), Hungary[17] (exceeding 0.1 mg/L), India[18] (exceeding 0.05 mg/L), Mexico[19] (exceeding 0.4 mg/L), and the United States[20] (exceeding 0.1 mg/L). Concentrations of arsenic in surface water, although generally low, also may be high enough for concern under certain geological conditions. High arsenic concentrations have been reported in canals used for water supply in Chile[21] (up to 0.8 mg/L) and Argentina[22] (exceeding 0.25 mg/L). In general, arsenic concentrations in groundwaters and surface waters of most US community water systems are well below the current arsenic MCL. Several studies are in progress to assess arsenic occurrence at low concentrations.[23] [See page 44.]

## Arsenic transformed in the body

Arsenic is a normal component of the human body. Once ingested, soluble forms of arsenic are readily absorbed from the gastrointestinal tract. Absorption rate estimates range from 40 to 100 percent for humans.[3,24] Arsenate, whether inorganic or organic, is better absorbed than arsenite because arsenate is less reactive with membranes of the gastrointestinal tract.[7] Arsenic in drinking water is mostly in the arsenate form, and complete absorption of arsenic from water may occur.

Once absorbed, arsenic is transported by the blood to different organs in the body, mainly in the form of MMA. Typical levels in the blood of people who are not exposed to a significant source of arsenic pollution range from 1 to 5 µg/L As;[3] levels in soft tissues range from 0.01 to 0.1 µg As/g.[3] The highest levels may be found in nails and hair (0.1 to 1 µg As/g) where arsenic accumulates over time.

Metabolism of arsenic (Figure 1) in humans involves two processes. After entering a cell, arsenate [As(V)] is reduced to arsenite [As(III)]. Arsenite is then methylated to form MMA and DMA; this process occurs primarily in the liver.[25,26] Trimethylarsine oxide, although expected to be formed during arsenic metabolism, has not been identified in humans, and its significance in arsenic metabolism is unknown.[24]

**TABLE 2** Properties of selected organic arsenic compounds[3]

| Property | Methylarsonic Acid | Dimethylarsinic Acid |
|---|---|---|
| Synonyms | Methane arsonic acid (MMA), monomethylarsonic acid (MAA) | Cacodylic acid, DMA, DMAA, hydroxydimethylarsinic acid |
| Chemical formula | $CH_3H_2AsO_3$ | $(CH_3)_2HAsO_2$ |
| Molecular weight | 140 | 107 |
| Water solubility—g/L | Soluble | 660 at 25°C |

Inorganic As(V) and As(III) have different mechanisms of action. Arsenate [As(V)] behaves very much like phosphate. Consequently, it can substitute for phosphate in normal cell reactions, interfering with normal cell functions.[7,27] In contrast, arsenite [As(III)] has a high affinity for thiol (-SH) groups in proteins, causing inactivation of a variety of enzymes.[7,15,27] Because arsenate is reduced in the body to arsenite, arsenate in drinking water may have a biological effect identical to arsenite.

In contrast to inorganic arsenic, neither MMA nor DMA binds strongly to biological molecules in humans. Hence, their relative acute toxicity is less than that of inorganic arsenic forms.[27] In general, inorganic As(V) is one tenth as toxic as inorganic As(III), and MMA and DMA are less toxic than inorganic As(V).[15,24] After ingestion, inorganic arsenic that is not immediately excreted or absorbed by tissues is progressively detoxified through the methylation process. However, the chronic effects of MMA and DMA are not known;[27] only a few studies have evaluated DMA.[15]

The form of arsenic significantly affects the rate at which arsenic is excreted from the body. Some of the inorganic arsenic is excreted primarily via urine as the parent form of the ingested arsenic. After methylation, it is also excreted as MMA and DMA. Most blood arsenic is rapidly excreted by humans, with 50–90 percent cleared in two to four days.[3,7] The remainder is cleared 10–100 times more slowly.[7]

The pharmacokinetics of arsenic in the human body are not well understood. Although several pharmacokinetic models have been developed, they only apply to short-term exposure (two to four days) and have several limitations that cause them to yield inaccurate projections.[28] Further development and refinement of pharmacokinetic and pharmacodynamic models are important, however. They may provide insight into arsenic health effects at low levels of exposure and help to interpret epidemiologic studies on As, most of which have used an ecologic study design.

## Is there a threshold effect?

The fact that arsenic can be detoxified in the body suggests that a level of arsenic exposure, or "threshold," exists, below which no adverse health effects result. Arsenic exposures below this threshold would be detoxified, and no adverse effects would be expected; exposures exceeding the threshold would only be partially detoxified, and adverse effects, commensurate with exposure, would be expected. However, the methylation detoxification mechanism and the level at which it is overwhelmed have not been elucidated. Studies of MMA and DMA excretion in humans suggest that doses of inorganic arsenic up to around 200–250 µg/d are detoxified.[6,29,30]

Recently, Hopenhayn-Rich et al[31] have questioned the existence of the methylation threshold in humans. Linear regression applied to data from several published studies failed to show a correlation between percentage of inorganic arsenic and urinary arsenic concentrations. However, Carlson-Lynch et al[32] have noted that the analysis by Hopenhayn-Rich et al[31] cannot be considered conclusive because of the relatively low arsenic exposures in most of the studies evaluated and because the methods used to evaluate methylating capacity were limited. Also, genetic, dietary, and other lifestyle factors may enhance or inhibit methylation and thus influence detoxification. Although some evidence suggests a safe exposure level for arsenic effects, additional research is needed to understand and characterize the potential threshold mechanism in humans.

***A high level of arsenic in drinking water is thought to cause Blackfoot disease, endemic to a small area of the southwest coast of Taiwan.***

## Evidence for arsenic essentiality

Studies with minipigs, goats, chicks, hamsters, and rats have indicated that arsenic is an essential nutrient.[33,34] Currently, there are insufficient data for the assessment of arsenic essentiality in humans; therefore, conclusive evidence of human essentiality is lacking.[35] As a result, the Food and Nutrition Board[36] of the National Research Council and USEPA[24] do not consider arsenic to be an essential element for humans.

The potential nutritional requirement for humans has been calculated. The safe and adequate daily dietary intake for humans must be extrapolated from animal studies, and an intake of 12 to 40 µg has been suggested for adults.[35,37] Uthus[37] has noted that no human pathological condition has been attributed to arsenic deprivation, but this may be because arsenic is typically present in the diet.

Recently, Mayer et al[38] reported a positive correlation between lowered arsenic serum levels in hemodialysis patients and central nervous system injury, cancer, and vascular diseases. They conclude that "arsenic should be considered or may be defined to be essential for human life processes." Additional studies are needed, however, to firmly establish the essentiality of arsenic in humans.

## Acute toxicity in humans

Acute arsenic exposure (high concentrations ingested over a short time period) can cause a variety

**TABLE 3** **Inorganic arsenic in food[13]**

| Food | Inorganic Arsenic* *percent* |
|---|---|
| Milk and dairy products | 75 |
| Meat (beef and pork) | 75 |
| Poultry | 65 |
| Fish | |
| Saltwater | 0 |
| Freshwater | 10 |
| Cereals | 65 |
| Rice | 35 |
| Vegetables | 5 |
| Potatoes | 10 |
| Fruits | 10 |

*Speciation of the arsenic content of basic food groups based on preliminary data from the Ontario Research Foundation and other sources; source: Weiler[13] as reported in reference 5

**TABLE 4** **Preliminary USEPA health advisory values estimated to prevent adverse effects (other than cancer) from arsenic ingestion[3]**

| Target Population | Exposure Duration | Health Advisory Value *mg/L** | Basis |
|---|---|---|---|
| Child | One-day | 0.05 | A 1904 published report on the use of Fowlers' solution. |
| Child | Ten-day | 0.05 | A 1956 report on effects observed in adults exposed to arsenic in soy sauce. |
| Child | Longer-term† | 0.05 | A 1975 report on effects observed in adults subchronically exposed to arsenic in medicinals. |
| Adult | Longer-term† | 0.2 | Same as longer-term advisory for a child. |

*HA = (50 µg/kg/d) (Assumed body weight, kg)/(Assumed drinking water consumption, L/d) (Uncertainty factor)
†Generally up to seven years.

of adverse effects. The severity of the effect depends primarily on the level of exposure. The acute toxicity of arsenic in humans has recently been assessed by USEPA[3] and is summarized here. Acute high-dose oral exposure to arsenic typically leads to gastrointestinal irritation accompanied by difficulty in swallowing, thirst, abnormally low blood pressure, and convulsions. Death may occur from cardiovascular collapse. The lethal dose ($LD_{50}$) to humans is estimated at 1–4 mg As/kg for an adult.[3,39,40]

Short-term exposure to doses of >500 µg As/kg/d can cause serious blood, nervous system, gastrointestinal, and other ill effects and also may lead to death.[3] Short-term intake of doses from 30 to 300 µg As/kg/d has not caused serious effects in most people, but some may experience relatively mild effects.[3]

## Chronic noncarcinogenic toxicity in humans

Chronic exposure to low concentrations of arsenic are of primary interest when the health significance of arsenic in drinking water is evaluated. The most common signs of long-term, low-level arsenic exposure from drinking water are dermal changes. These include variations in skin pigments, hyperkeratoses, and ulcerations.[16,41–44]

Vascular effects are also associated with chronic arsenic exposure.[41,45] A small area on the southwest coast of Taiwan where Blackfoot disease, a peripheral vascular disease, is endemic has been studied extensively.[16,41] Blackfoot disease in this area is generally attributed to high arsenic concentrations found in deep wells.[41,42] Although the wells with high arsenic concentrations are no longer used for drinking water, good medical records enable retrospective studies of the population exposed to As. Blackfoot disease symptoms start with spotted discoloration of the skin of extremities, especially the feet. The spots change from white to brown to black. Affected skin gradually thickens, cracks, and ulcerates, and amputation of the affected extremities may be needed. Dietary and lifestyle factors and humic acids are also suspected to contribute to the disease, but its exact etiologic mechanism is unknown.[4,46–50]

Studies in Canada[51] and the United States[52] report neurological effects after chronic exposure from drinking water containing As. Enlargement of the liver was observed in populations in India that were exposed to arsenic in drinking water.[27] An association between ingested arsenic and ischemic heart disease[49,53] and diabetes mellitus[54] have been reported in the area of Taiwan where Blackfoot disease is endemic.

## Ingested arsenic and cancer

Arsenic is classified as a human carcinogen by the International Agency for Research on Cancer[55] and the USEPA.[5] These classifications are based in part on occupational health studies that have firmly established a relationship between inhaled arsenic and lung cancer in humans.[56] Unlike most substances classified as carcinogens, classification of arsenic is based on human data; animal data are inadequate. In fact, arsenic has not been found to cause cancer in animal experiments, making mechanistic studies in animals difficult. At present, the mechanism of action of arsenic in the development of cancer is not known, but evidence suggests that arsenic acts as a promoter rather than an initiator.[57,58]

Several epidemiologic studies have documented an association between chronic exposure to arsenic in drinking water and skin cancer. The most extensive studies have been performed in Taiwan, and existing studies have been the subject of recent reviews.[2,3,5]

Several studies suggest an association between ingested arsenic and internal cancer.[4,59] These include case reports of internal cancer patients who had ingested arsenical medicinals and autopsy studies of German winegrowers who had consumed wine contaminated with As. Recently, several studies have

evaluated internal cancer mortality in relation to arsenic concentrations in drinking water. Studies in Taiwan have found an association between arsenic in drinking water and cancer in the liver, bladder, kidney, lung, nasal cavity, prostate, and other internal sites.[60-64]

Bates and coworkers[4] recently reviewed studies of arsenic ingestion and internal cancers, finding that studies in Taiwan and Japan provide strong evidence. They conclude that "on the basis of current evidence, it appears that ingested inorganic arsenic increases the risk of cancers of the lung, liver, kidney, and bladder, and possibly other internal sites" but noted that confirmatory studies are needed.

Adverse effects have not been observed in every epidemiologic study of arsenic in drinking water. Studies of several US communities served by drinking water supplies or private wells with high arsenic concentrations, including Lane County, Ore.;[65] Millard County, Utah;[52] Lassen County, Calif.;[66] Fairbanks, Alaska;[67] and Fallon, Nev.,[3,47] have failed to show any excessive disorders.[3,4] The difference in findings between studies in the United States and other areas is thought to result from differences in sociodemographic characteristics and dietary intake of the various populations, limitations of design in the US studies, and the relatively small exposed populations studied in the United States, yielding statistical power too low to detect effects. However, these studies suggest that additional research is needed to determine whether arsenic in US drinking waters is associated with adverse effects to the same degree as observed in other areas. Preliminary results of a study in Hungary also found no significant differences in cancer frequency, peripheral neuropathy, or peripheral vascular disorders in adults consuming drinking water contaminated with arsenic compared with an unexposed control population.[17]

## Evaluating the current arsenic MCL

To assess the health protection afforded by the current arsenic MCL, known health effects of arsenic must be quantified. The approach taken usually considers (1) acute toxicity (relatively high exposures for a short time period causing effects other than cancer), (2) chronic toxicity (relatively low exposures for a long period of time causing effects other than cancer), and (3) cancer effects (the risk of contracting cancer at differing lifetime exposure levels).

**Acute toxicity.** USEPA[3] recently presented preliminary calculations of the concentration of arsenic that can be ingested in drinking water over a one-day, 10-day, and longer-term period without adverse health effects (other than cancer). These values are known as health advisories (HAs), summarized in Table 4. They conclude that short-term (1–90 days) or longer-term (2–3 years) intake of 50 µg As/kg/d can lead to gastrointestinal, liver, nervous system, and/or dermal effects. The values in Table 4 were calculated assuming 10 kg body weight for a child, 70 kg body weight for an adult, 1-L/d water consumption for a child, 2-L/d water consumption for an adult, and an uncertainty factor of 10.

In general, arsenic concentrations in US drinking waters are far below the concentrations that constitute a lethal or short-term toxic dose. For example, a 70-kg adult consuming an assumed 2 L/d of drinking water containing 0.05 mg/L of total arsenic (the current MCL) would ingest 0.1 mg/d of arsenic from drinking water, compared with a 70-mg lethal dose (assuming 1 mg/kg) and a 3.5-mg/d dose (assuming 50 µg/kg/d) associated with short-term toxicity.

Arsenic poisoning from drinking water can occur, however, if concentrations are high. For example, in 1972, arsenic poisoning was reported in Perham, Minn.[68] Eleven of 13 employees exposed to arsenic concentrations of 2.1–11.8 mg/L from their employer's well experienced ill effects over a 10-week period. The three who received the highest exposure experienced signs of subacute and chronic poisoning.

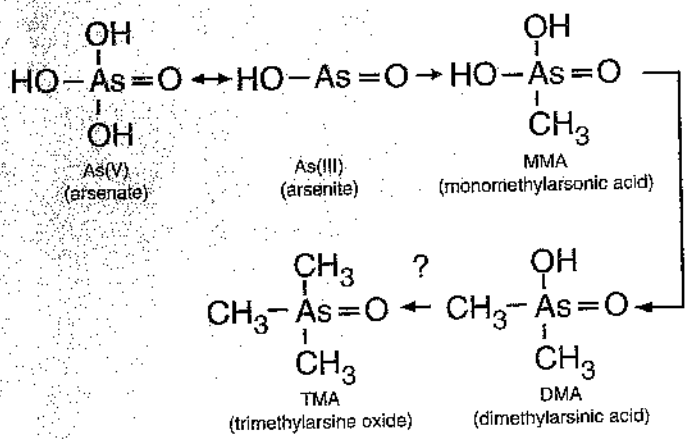
**Chronic noncarcinogenic toxicity.** USEPA[3] recently assessed the arsenic concentration that can be present in drinking water and still avoid the adverse effects (not considering cancer) of chronic exposure. For noncarcinogenic effects, the agency determines a "no effect level" for chronic or lifetime periods of exposure, known as the reference dose (RfD). The RfD represents the exposure level thought to be without significant risk to humans (including sensitive subgroups) when the contaminant is ingested over a lifetime.[69] Calculation of the RfD is based on the assumption that detoxification occurs up to a certain threshold dose. As the threshold is exceeded, the biologic response is a function of the dose applied and the duration of exposure. Available human and animal toxicology data for the contaminant are reviewed to identify the highest no-observed-adverse-effect-level (NOAEL) or the lowest-observed-adverse-effect-level (LOAEL). The RfD, measured in mg/kg body weight/d is calculated as follows:

$$\text{RfD} = \text{NOAEL or LOAEL}/\text{Uncertainty factors}$$

**TABLE 5** Uncertainty factors used by USEPA in reference dose calculations[69]

| Factor | Criterion |
|---|---|
| 10 | Valid data on acute or chronic human exposure are available and supported by data on acute or chronic toxicity in other species. |
| 100 | Data on acute or chronic toxicity are available for one or more species but not for humans. |
| 1,000 | Data on acute or chronic toxicity in all species are limited or incomplete, or data on acute or chronic toxicity identify a LOAEL (not a NOAEL) for one or more species, but data on humans are not available. |
| 1 to 10 | Other considerations (such as significance of the adverse health effect, pharmacokinetic factors, or quality of available data) may necessitate use of an additional uncertainty factor. |

**FIGURE 1** Compounds involved in arsenic




Uncertainty factors are used to account for differences in response to toxicology within the human population and between humans and animals (Table 5). Determination of the RfD is shown in Figure 2.

Using the RfD, a drinking water equivalent level (DWEL) is calculated. The DWEL represents a lifetime exposure at which adverse health effects are not anticipated to occur, assuming 100 percent of the exposure is from drinking water:

$$\text{DWEL (mg/L)} = \text{RfD} \times \text{Body weight (kg)} \div \text{Drinking water volume (L/d)}$$

Existing studies of arsenic toxicity in humans following chronic oral exposure were compared by USEPA.[3] The studies by Tseng et al[16] and Tseng[41] were primarily used to estimate a dose of 0.8 µg/kg/d, at which no adverse effects (dermal or vascular) were observed. An RfD of 0.3 µg/kg/d was calculated by dividing this figure by an uncertainty factor of 3 to account for a lack of data regarding reproductive toxicity and effects on sensitive subpopulations. Using the RfD and assuming a 70-kg adult body weight and a 2-L/d drinking water consumption, a DWEL of 10 µg/L was derived. This value represents the concentration of arsenic in drinking water below which no chronic effects (other than cancer) would be expected, assuming 100 percent of the exposure is from drinking water.

USEPA scientists disagreed on an uncertainty factor for the arsenic RfD.[24,56] The USEPA Risk Assessment Council decided on an uncertainty factor of 3 but stated that in applying the agency's methodology, arguments can be made to support an RfD value ranging from 0.1 to 0.8 µg/kg/d. This translates into a range for the DWEL of 4–28 µg/L. The USEPA Science Advisory Board (SAB) has reviewed the derivation of the DWEL, concluding that inclusion of the uncertainty factor of 3 was unnecessary.[15]

As discussed previously, drinking water is only one source of arsenic exposure. To calculate an allowable drinking water concentration, arsenic contributed from other sources must be subtracted from the total allowable intake. The total allowable intake is calculated using the RfD. The fraction of the total allowable arsenic intake that would be contributed by drinking water is known as the relative source contribution (RSC). USEPA uses an RSC default value of 20 percent if good data are not available or if the actual value is less than 20 percent. If the drinking water contribution is 80 percent or more, a default value of 80 percent is used to protect individuals whose total exposure may be higher than available data.

If an RfD of 0.3 µg/kg/d is assumed, then the allowable intake for a 70-kg adult would be 21 µg As/d. Assuming that inhalation and dermal exposure are insignificant and that the intake from food is 50 µg As/d (20 percent of which is inorganic), then the allowable intake from drinking water for an adult would be 11 µg As/d. This translates to a drinking water concentration of about 5 µg/L, assuming a 2-L/d intake. The allowable drinking water concentration for the RfD range of 0.1 to 0.8 µg/kg/d under these assumptions is 0 to 23 µg/L.

**Cancer risk.** The risk of contracting cancer from ingesting arsenic in drinking water must be extrapolated from epidemiologic data. To do this, several assumptions must be made, the most important of which is the mathematical function (dose–response relationship) used to model the risk posed by arsenic concentrations below the levels at which excess cancers have actually been observed. USEPA arsenic risk estimates are based on the linearized multistage model (LMM), which assumes disease-occurrence data are linear at low doses. The model is used to calculate an upper-bound excess cancer risk (Figure 3). However, because cancer mechanisms are not well understood, the LMM does not necessarily predict cancer risk more accurately than other extrapolation models. The LMM was chosen for consistency and conservativeness to ensure that decisions made on the basis of risk projections protect health.

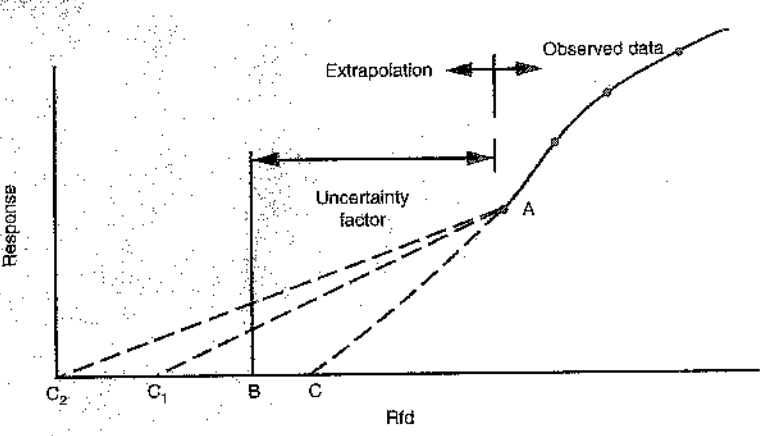
The LMM uses dose–response data from a selected carcinogenicity study to calculate a human carcinogenic potency factor ($q_1^*$), expressed as $(\mu g/kg/d)^{-1}$, that can be used to calculate a unit risk. The unit risk is the theoretical lifetime cancer risk associated with consuming 1 µg/L As:

$$\text{Unit risk (per µg/L)} = q_1^* \times \text{Drinking water volume (L/d)} \div \text{Body weight (kg)}$$

Epidemiologic studies have observed excess cancer risk at arsenic concentrations several times greater

than the current MCL. These studies provide knowledge of the likely shape of the dose–response relationship for some cancer sites down to concentrations of about 150 to 200 µg/L. Little is known definitively about the excess cancer risk posed by concentrations below about 100 µg/L, which also encompasses the concentrations at which essentiality and a threshold effect are postulated. The analysis is further complicated by the fact that each cancer site (e.g., bladder, skin, lung) will likely have a unique dose–response relationship, and current knowledge is inadequate to state conclusively which cancer site presents the greatest risk.

**FIGURE 2** **Example of reference dose determination for noncarcinogenic effects**




*A—NOAEL or LOAEL (experimentally derived), B—Rfd or "no effect" level, C—presumed threshold for adverse effect, $C_1$—another possible presumed threshold for adverse effect, $C_2$—nonthreshold end point of toxicity*

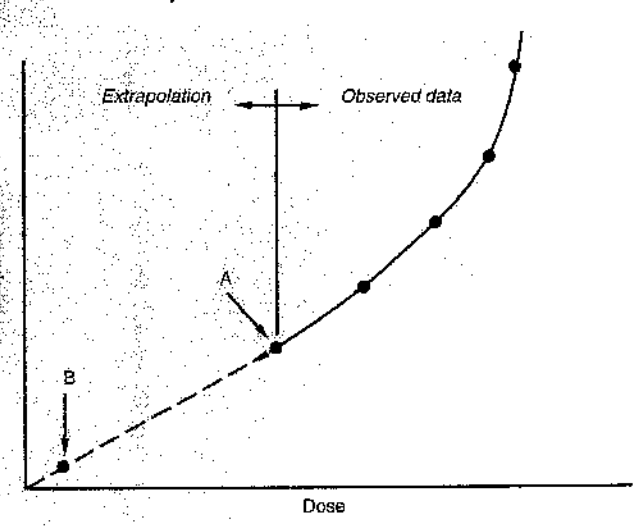
The strongest evidence is for a relationship between arsenic and skin cancer. USEPA initially published an assessment of skin cancer risk for arsenic in drinking water in 1984 based on extrapolation of data reported by Tseng et al[16] and Tseng.[41] Disagreement within USEPA over aspects of the 1984 assessment led USEPA's Risk Assessment Forum to convene a technical panel to further address the issues of concern.[5] The panel results, published in 1988, included a reanalysis of the Tseng data and estimates of As-induced skin cancer that were substantially lower than the 1984 value.[5,70] In 1993, USEPA[3] reaffirmed its 1988 analysis and unit cancer risk of $5 \times 10^{-5}$/µg/L, estimating a 1:10,000 (or $10^{-4}$) individual risk of skin cancer at 2 µg/L As. This concentration is 25 times lower than the current MCL. The $10^{-4}$ risk level is the highest USEPA generally allows when setting standards for carcinogens. However, the data on skin cancer incidence reported by Tseng et al[16] and Tseng[41] have several limitations, especially with respect to prediction of skin cancer rates in the United States. USEPA[5] noted that the uncertainties are such that skin cancer risk estimates could be lower by as much as an order of magnitude, relative to risk estimates associated with most other carcinogens. As-induced skin cancer is treatable and usually not fatal in the United States.

**Drinking water is only one source of arsenic. Other sources include food and air.**

At the time of the 1988 USEPA report,[5] evidence was mounting of an association between ingested arsenic and cancer of internal organs. The studies by Chen et al in 1985[64] and 1986[60] demonstrated a qualitative relationship between arsenic exposure and increased risk of cancer at several internal sites. The 1988 USEPA report noted, however, that additional details of the Taiwan data published by Chen et al[60,64] were needed to assess the dose–response relationships. Those additional data of interest to USEPA were first published in a letter to *Lancet*,[63] which grouped exposures into three categories (<0.30, 0.30–0.59, and >0.6 mg/L As), consistent with the groupings used in the previous Tseng study.[16] The authors noted that various cancer mortality rates were significantly higher in the study population than for the general population of Taiwan. In addition, a significant dose–response relationship was observed between arsenic concentrations in drinking water from artesian wells and the mortality rates for cancers of the bladder, kidney, skin, prostate, lung, and liver.

Smith et al[71] extrapolated the preliminary results of Chen et al[63] from the published letter to calculate lung, liver, kidney, and bladder cancer risks for the United States population. Three exposure groups were used, consistent with the groupings already mentioned. Linear extrapolation resulted in an estimate of 1:1,000 for the lifetime risk of contracting liver, lung, bladder, or kidney cancer from consuming 1.6 L/d of drinking water containing 2.5 µg/L As. Smith et al's estimates of the risk of death from one of these cancers as a result of a lifetime consumption of water containing 0.05 mg/L As at a rate of 1 L/d are alarming—9.4/1,000 for males and 17.3/1,000 for females. The investigators note, however, that "further studies are needed to confirm these findings."[71] The analysis by Smith et al[71] has drawn attention to the potential for internal cancer risks in the United States,

**FIGURE 3** Example extrapolation using the linearized multistage dose–response model




*A—lowest observed dose tumor incidence, B—tumor incidence extrapolated to lower dose corresponding to level of concern*

but its estimates have been noted to have great uncertainty and to contain some omissions.[32,72]

Brown and Chen[73,74] have reanalyzed the Taiwan data used for the Smith et al[71] study, finding nonlinear dose–response relationships. Exposure data were aggregated into 11 categories rather than three, allowing a more precise definition of the dose–response relationship. Below the current MCL, the dose–response relationship appeared erratic, and further analysis of the Taiwan data at the village level found potential problems resulting from a wide range of arsenic concentrations in water from artesian and shallow wells in some villages. This limits the study's utility for low-level extrapolations.

More recently, Guo et al[75] reported results of a multiple variable approach to evaluating epidemiologic data, which was applied to arsenic in drinking water and skin cancer in Taiwan. Application of multiple linear regression models to analyze multiple exposure variables was compared with analysis of data using the mean well-water arsenic concentration as the only arsenic exposure variable. Findings support the hypothesis of a nonlinear dose–response relationship between arsenic and skin cancers in Taiwan and the existence of a threshold above 0.32 mg/L. Additional data collection in Taiwan at the individual level has been proposed in an attempt to confirm the hypothesis generated in this study.[76]

## Does the current arsenic MCL protect health?

At high concentrations, arsenic in drinking water can cause detrimental if not fatal effects. In light of current knowledge regarding chronic arsenic health risks, a key question remains: does ingesting arsenic in drinking water at concentrations below the current MCL and at the low concentrations typical of US drinking water supplies cause detrimental effects?

Cancer risk estimates are the primary factor driving the concern over whether the current MCL is adequate. As discussed, USEPA's cancer risk estimate of 1:10,000 at 2 µg/L As is based on skin cancer. The agency has decided not to include internal cancer in its risk estimate because of concerns over the suitability of existing data for making extrapolations about low-dose risks.[77]

The World Health Organization (WHO) recently set a provisional guideline for arsenic in drinking water at 0.01 mg/L based on skin cancer risk.[78] WHO estimates an excess skin cancer risk at this concentration at $6 \times 10^{-4}$. The WHO notes that "guideline values for carcinogenic substances have been computed from mathematical models that cannot be verified experimentally," and "At best, these estimates must be regarded as rough estimates of cancer risk."

The California Environmental Protection Agency recently proposed a recommended public health level of 0.000002 mg/L based on linear extrapolation of Tseng et al[16] skin cancer data and assuming a 20 percent relative source contribution for drinking water.[79] This estimate, however, is highly uncertain and imprecise because of dependence on the Tseng et al[16] data, extrapolation of risk from Taiwan to the US population, and sensitive assumptions on the shape of the dose–response relationship.

The current MCL may not protect health if recent theoretical estimates of chronic effects and cancer risk prove accurate. However, current knowledge of arsenic pharmacokinetics and mechanisms in humans is inadequate to provide a definitive answer, and current epidemiologic evidence has been too inconsistent and too fraught with uncertainty regarding arsenic exposure to be helpful in assessing low-level risks.

## Additional research needed

Definitive answers to questions regarding arsenic health risks at low exposures will be elusive without additional research. In recent years, various research studies have been proposed for improving arsenic risk assessment,[80] including short-term research[8] and an epidemiological study in the United States to examine bladder cancer, which is under consideration by the National Cancer Institute.[82] Several studies are in progress, although much of the previously recommended research has not been funded.

Key research studies needed for improving arsenic risk assessment are currently being formulated. The USEPA Health Effects Research Laboratory convened a panel in early 1994 to recommend an epidemiologic strategy for arsenic in drinking water. The panel's report is due this month.[83]

The Society of Environmental Geochemistry and Health convened an international arsenic task force in 1993 to evaluate the current knowledge regarding arsenic and health. The task force recently urged USEPA to improve its risk assessment and arsenic research program before proceeding with a substantial downward revision of the current arsenic MCL.[84] An interim task force report is expected this fall, and a final report is planned for 1995.

North et al[85] argues, based on decision analysis, that additional research funding to answer key questions related to arsenic risk assessment is economically justified, considering the substantial cost that a significant lowering of the current MCL would impose.

Until the results of new research are forthcoming, risk estimates will be driven primarily by the policy and default assumptions that regulatory agencies use regarding essentiality, threshold, dose–response function, cancer potency factor, and other key factors needed to calculate arsenic risks estimates. Although regulatory-driven risk estimates for arsenic are thought to be conservative and are necessary to meet statutory requirements and regulatory deadlines, they may not reflect actual health risks of arsenic in US drinking waters at low concentrations.


## Acknowledgment

The authors thank Charles Abernathy, Rebecca Calderon, and Linda Elinoff for their reviews and helpful comments on the draft manuscript.


## References


1. *Casarett and Doull's Toxicology: The Basic Science of Poisons* (C.D. Klassen; M.O. Amdur; & J. Doull, editors). MacMillan Publ. Co., New York (3rd ed., 1986).
2. Special Arsenic Issue. *Envir. Geochem. & Health* (John R. Fowle III, ed.), 14:2 (June 1992).
3. Life Systems Inc. Draft Drinking Water Criteria Document on Arsenic. USEPA Human Risk Assessment Branch, Washington, D.C. (1993).
4. Bates, M.N.; Smith, A.H.; & Hopenhayn-Rich, C. Arsenic Ingestion and Internal Cancers: A Review. *Amer. Jour. Epidemiol.*, 135:5:462 (Mar. 1, 1992).
5. USEPA. Special Report on Ingested Inorganic Arsenic. Skin Cancer; Nutritional Essentiality. EPA/625/3-87/013, Washington, D.C. (1988).
6. Petito, C.T. & Beck, B.D. Evaluation of Evidence of Nonlinearities in the Dose–Response Curve for Arsenic Carcinogenesis. *Trace Substances in Envir. Health*, XXIV:143 (1990).
7. National Academy of Sciences Safe Drinking Water Committee. Drinking Water and Health. National Academy Press, Washington, D.C. (1977).
8. National Academy of Sciences Safe Drinking Water Committee. Drinking Water and Health, Volume 3. National Academy Press, Washington, D.C. (1980).
9. Society of Environmental Geochemistry and Health. Proc. International Conference on Arsenic Exposure and Health Effects. July 28–30, 1993, New Orleans, La.; Science Reviews, Northwood, England (1994).
10. Clifford, D.A. & Zhang, Z. Arsenic Chemistry and Speciation. Proc. AWWA WQTC. Miami, Fla., Nov. 7–11, 1993,
11. Tamaki, S. & Frankenberger, W.T. Environmental Biochemistry of Arsenic. *Rev. Environ. Contam. Toxicol.*, 124:79 (1992).
12. Weiler, R.R. Unpubl. data. Ministry of the Environment Rep. 87-48-45000-057, Toronto, Ont. (1987). Data presented in reference 5.
13. Dabeka, R.W. et al. Survey of Arsenic in Total Diet Food Composites and Estimation of the Dietary Intake of Arsenic By Canadian Adults and Children. *Jour. AOAC*, 76:1:14 (Jan.–Feb. 1993).
14. Wester, R.C. et al. In Vivo and in Vitro Percutaneous Absorption and Skin Decontamination of Arsenic From Water and Soil. *Fundamental & Appl. Toxicol.*, 20:336 (1993).
15. USEPA Science Advisory Board Drinking Water Committee. An SAB Report: Review of the Draft Drinking Water Criteria Document on Inorganic Arsenic. EPA-SAB-DWC-94-005 (Nov. 1993).
16. Tseng, W.P. et al. Prevalence of Skin Cancer in an Endemic Area of Chronic Arsenism in Taiwan. *Jour. Natl. Cancer Inst.*, 40:453 (1968).
17. Borzsonyi, M. et al. Epidemiological Studies on Human Subjects Exposed to Arsenic in Drinking Water in Southeast Hungary. *Arch. Toxicol.*, 66:77 (1992).
18. Chakraborti, D. Arsenic in Ground Water in Six Districts of West Bengal, India. Society of Environmental Geochemistry and Health Workshop on Arsenic: Epidemiology and PBPK Modeling, Annapolis, Md., June 27–28, 1994.
19. Cebrian, M.E. et al. Alterations in the Profile of Urinary Arsenic Metabolites in Humans Chronically Exposed to Arsenic in Mexico. Society of Environmental Geochemistry and Health Workshop on Arsenic: Epidemiology and PBPK Modeling, Annapolis, Md., June 27–28, 1994.
20. Valentine, J.L.; Kang, H.K.; & Spivey, G. Arsenic Levels in Human Blood, Urine, and Hair in Response to Exposure Via Drinking Water. *Environ. Res.*, 20:24 (1979).
21. Sancha, A.M. et al. Human Exposure to Arsenic in Water: A Study of Atacamenan Settlements in Northern Chile. Book of Posters. SEGH Intl. Conf. on Arsenic Exposure and Health Effects, New Orleans, La., July 28–30, 1993.
22. Smith, A.H. et al. Epidemiological and Biomarker Findings Concerning Arsenic and Bladder Cancer in Chile and Argentina. Society of Environmental Geochemistry and Health Workshop on Arsenic: Epidemiology and PBPK Modeling, Annapolis, Md., June 27–28, 1994.

23. Reid, J. Arsenic Occurrence: USEPA Seeks Clearer Picture. *Jour. AWWA*, 86:9:44 (Sept. 1994).
24. Abernathy, C.O. Presentation before the AWWA Technical Advisory Group, Washington, D.C. (Oct. 25, 1993).
25. McKinney, J.D. Metabolism and Disposition of Inorganic Arsenic in Laboratory Animals and Humans. *Envir. Geochem. & Health*, 14:43 (1992).
26. Thompson, D.J. A Chemical Hypothesis for Arsenic Methylation in Mammals. *Chem. Biol. Interactions*, 88:89 (1993).
27. Abernathy, C.O. & Ohanian, E.V. Health Effects of Inorganic Arsenic in Drinking Water. Proc. AWWA WQTC, Miami, Fla., Nov. 7–11, 1993.
28. Brown, J.P. et al. Pharmacokinetic Modeling of Inorganic Arsenic in Rodents and Humans: Short-Term Exposure. Society of Environmental Geochemistry and Health Workshop on Arsenic: Epidemiology and PBPK Modeling, Annapolis, Md., June 27–28, 1994.
29. Marcus, W.L. & Rispin, A.S. Threshold Carcinogenicity Using Arsenic as an Example. *Adv. Modern Environ. Toxicol., Vol. XV* (C.R. Cothern, M.A. Mehlman, & W.L. Marcus, editors). Risk Assessment and Risk Management of Industrial and Environmental Chemicals. Princeton Publ. Co., Princeton, N.J. (1988).
30. USEPA Science Advisory Board. Science Advisory Board's Review of the Arsenic Issues Relating to the Phase II Proposed Regulations From the Office of Drinking Water. EPA-SAB-EHC-89-038. Memorandum to William K. Reilly (1989).
31. Hopenhayn-Rich, C.; Smith, A.H.; & Goeden, H.M. Human Studies Do Not Support The Methylation Threshold Hypothesis For The Toxicity of Inorganic Arsenic. *Environ. Res.*, 60:2:161 (Feb. 1993).
32. Carlson-Lynch, H.; Beck, B.D.; & Boardman, P.D. Arsenic Risk Assessment. *Envir. Health Perspectives*, 102:4:354 (April 1994).
33. Anke, M. Arsenic. *Trace Elements in Human and Animal Nutrition, Volume 2*. Academic Press, Orlando, Fla. (1986).
34. Nielsen, F.H. Nutritional Requirements for Boron, Silicon, Vanadium, Nickel, and Arsenic: Current Knowledge and Speculation. *FASEB Jour.*, 5:12:2661 (Sept. 1991).
35. Uthus, E.O. Evidence for Arsenic Essentiality. *Envir. Geochem. & Health*, 14:55 (1992).
36. National Research Council. *Recommended Dietary Allowances*. National Academy Press, Washington, D.C. (10th ed., 1989).
37. Uthus, E.O. Estimation of Safe and Adequate Daily Intake for Arsenic. *Risk Assessment of Essential Elements*. Intl. Life Sciences Inst. Press, Washington, D.C. (1994)..
38. Mayer, D.R. et al. Essential Trace Elements in Humans. Serum Arsenic Concentrations in Hemodialysis Patients in Comparison to Healthy Controls. *Biol. Trace Elem. Res.*, 37:1:27 (Apr. 1993).
39. Vallee, B.L.; Ulmer, D.D.; & Wacker, W.E.C. Arsenic Toxicology and Biochemistry. *AMA Arch. Indus. Health*, 21:56 (1960).
40. Winship, K.A. Toxicology of Inorganic Arsenic Salts. *Adv. Drug React. Act. Poison Rev.*, 3:129 (1984).
41. Tseng, W.P. Effects and Dose–Response Relationships of Skin Cancer and Blackfoot Disease With Arsenic. *Envir. Health Perspectives*, 19:109 (1977).
42. Chen, C.-J. et al. Atherogenicity and Carcinogenicity of High-Arsenic Artesian Well Water. Multiple Risk Factors and Related Malignant Neoplasms of Blackfoot Disease. *Arteriosclerosis*, 8:452 (1988).
43. Abernathy, C.O. & Ohanian, E.V. Noncarcinogenic Effects of Inorganic Arsenic. *Envir. Geochem. & Health*, 14:2:35 (1992).
44. Cebrian, M.E. et al. Chronic Arsenic Poisoning in the North of Mexico. *Human Toxicol.*, 2:121 (1983).
45. Borgono, J.M. et al. Arsenic in the Drinking Water of the City of Antofagasta: Epidemiological and Clinical Study Before and After the Installation of a Treatment Plant. *Envir. Health Perspectives*, 19:103 (1977).
46. Lu, F.J. Blackfoot Disease: Arsenic or Humic Acid? *Lancet*, 336:115 (1990).
47. Chen, S.-L. et al. Arsenic Species in Groundwaters of the Blackfoot Disease Area, Taiwan. *Envir. Sci. & Technol.*, 28:5:877 (May 1994).
48. Guo, H.-R. & Lu, F.-J. Letter to the Editor Re: Arsenic Ingestion and Internal Cancers: A Review. *Amer. Jour. Epidemiol.*, 139:12:1233 (June 15, 1994).
49. Chen, C.-J. Blackfoot Disease. (Letter). *Lancet*, 336:442 (1990).
50. Engel, R.R. & Receveur, O. Letter to the Editor Re: Arsenic Ingestion and Internal Cancers: A Review. *Amer. Jour. Epidemiol.*, 138:10:896 (1993).
51. Hindmarch, J.T. et al. Electromyographic Abnormalities in Chronic Environmental Arsenicalism. *Jour. Anal. Toxicol.*, 1:270 (1977).
52. Southwick, J.W.; Western, A.E.; & Beck M.M. An Epidemiological Study of Arsenic in Drinking Water in Millard County, Utah. *Arsenic: Industrial, Biomedical, Environmental Perspectives* (W.H Lederer & R.J. Fensterheim, editors). Van Nostrand Reinhold Co., New York, N.Y. (1983).
53. Wu, M.M. et al. Dose–Response Relationship Between Arsenic Concentrations in Well Water and Mortality From Cancers and Vascular Diseases. *Amer. Jour. Epidemiol.*, 130:6:1123 (1989).
54. Lai, M.-S. et al. Ingested Inorganic Arsenic and Prevalence of Diabetes Mellitus. *Amer. Jour. Epidemiol.*, 139:5:484 (1994).
55. International Agency for Research on Cancer (IARC). *IARC Monographs on the Evaluation of the*

*Carcinogenic Risk of Chemicals to Humans, Volume 20* (1980).
56. USEPA, Integrated Risk Information System. Arsenic, Inorganic (Oct. 1, 1991).
57. MASS, M.J. Human Carcinogenesis by Arsenic. *Envir. Geochem. & Health*, 14:49 (1992).
58. YEAGER, J.W. & WIENCKE, J.K. Enhancement of Chromosomal Damage by Arsenic: Implications for Mechanism. *Envir. Health Perspectives*, 101(Suppl. 3):79 (1993).
59. CUZICK, J.; SASIENI, P.; & EVANS, S. Ingested Arsenic, Keratoses, and Bladder Cancer. *Amer. Jour. Epidemiol.*, 136:4:417 (1992).
60. CHEN, C.-J. ET AL. A Retrospective Study on Malignant Neoplasms of Bladder, Lung, and Liver in Blackfoot Disease-Endemic Area in Taiwan. *Brit. Jour. Cancer*, 53:399 (1986).
61. CHEN, C.-J. ET AL. Cancer Potential in Liver, Lung, Bladder, and Kidney Due to Ingested Inorganic Arsenic in Drinking Water. *Brit. Jour. Cancer*, 66:888 (1992).
62. CHEN, C.-J. & WANG, C.J. Ecological Correlation Between Arsenic Level in Well Water and Age-Adjusted Mortality From Malignant Neoplasms. *Cancer Res.*, 50:5470 (1990).
63. CHEN, C.-J.; KUO, T.L.; & WU, M.M. Arsenic and Cancers (Letter). *Lancet*, I(8575/6):414 (1988).
64. CHEN, C.-J. ET AL. Malignant Neoplasms Among Residents of a Blackfoot Disease-Endemic Area in Taiwan: High-Arsenic Artesian Well Water and Cancers. *Cancer Res.*, 45:5895 (1985).
65. MORTON, W. ET AL. Skin Cancer and Water Arsenic in Lane County, Ore. *Cancer*, 37:2523 (1976).
66. GOLDSMITH, J.R. Evaluation of Health Implications of Elevated Arsenic in Well Water. *Water Res.*, 6:1133 (1972).
67. HARRINGTON, J.M. ET AL. A Survey of a Population Exposed to High Concentrations of Arsenic in Well Water in Fairbanks, Alaska. *Amer. Jour. Epidemiol.*, 108:377 (1978).
68. FEINGLASS, E.J. Arsenic Intoxication From Well Water in the US. *New England Jour. Med.*, 228:828 (1973).
69. BARNES, D.G. & DOURSON, M. Reference Dose: Description and Use in Health Risk Assessment. *Regulatory Toxicol. & Pharmacol.*, 8:4:471 (Dec. 1988).
70. BROWN, K.G. ET AL. A Dose–Response Analysis of Skin Cancer From Inorganic Arsenic in Drinking Water. *Risk Analysis*, 9:4:519 (1989).
71. SMITH, A.H. ET AL. Cancer Risks From Arsenic in Drinking Water. *Envir. Health Perspectives*, 97:259 (1992).
72. BROWN, K.G. Review of Cancer Risks From Arsenic in Drinking Water by A.H. Smith et al. Prepared for USEPA, Office of Science and Technology, Washington, D.C. (Feb. 15, 1993).
73. BROWN, K.G. & CHEN, C.-J. On the Observed Dose–Response for Internal Cancers and Arsenic in Drinking Water in the Blackfoot Disease-Endemic Region of Taiwan. Proc. SEGH Intl. Conf. on Arsenic Exposure and Health Effects, New Orleans, La., July 28–30, 1993, Science Reviews, Northwood, England (in press).
74. BROWN, K.G. & CHEN, C.-J. Significance of Exposure Assessment to Analysis of Cancer Risk From Inorganic Arsenic in Drinking Water in Taiwan. *Risk Analysis* (unpubl.).
75. GUO, H.-R. ET AL. Using Ecological Data to Estimate a Dummy Variable Regression Model for Individual Data: The Association Between Arsenic in Drinking Water and Incidence of Skin Cancer. Society for Risk Analysis Ann. Mtg., Savannah, Ga., Dec. 1993.
76. GUO, H.-R. Personal communication (1994).
77. SHANK-GIVENS, H.L. The Arsenic Drinking Water Regulation Background Information. USEPA, Office of Ground Water and Drinking Water, Washington, D.C. (May 16, 1994).
78. *Guidelines for Drinking-Water Quality*. WHO, Geneva, Switzerland (2nd ed., 1993).
79. BROWN, J.P. & FAN, A.M. Draft Arsenic Recommended Public Health Level for Drinking Water. California Environmental Protection Agency (Mar. 4, 1992).
80. FOWLE, J.R. Health Effects of Arsenic in Drinking Water: Research Needs. *Envir. Geochem. & Health*, 14:63 (1992).
81. FOWLE, J.R. ET AL. Arsenic Health Research Needs. *Trace Substances in Environmental Health-XXV* (Barbara D. Beck, editor) (1992).
82. SMITH, A.H. Personal communication (1994).
83. CALDERON, R. Personal communication (1994).
84. Letter from W.R. Chappell, chair, SEGH Arsenic Task Force, to R. Perciasepe, USEPA Assistant Administrator for Water (Dec. 13, 1993).
85. NORTH, D.W.; SELKER, F.K.; & GUARDINO, T. Estimating the Value of Research: An Illustrative Calculation for Ingested Inorganic Arsenic. Decision Focus Inc., Mountain View, Calif. (Oct. 1992).

**About the author:** *Frederick W. Pontius is associate director for regulatory affairs at AWWA, 6666 W. Quincy Ave., Denver, CO 80235. A graduate of the University of Colorado (Boulder) with BS (civil engineering) and MS (sanitary engineering) degrees, Pontius has been with AWWA since 1982. Pontius monitors and evaluates legislation and regulations that affect the water industry. He prepares official AWWA statements regarding drinking water issues and represents AWWA at meetings, workshops, and study groups. His work has been published previously by* JOURNAL AWWA *and* JOURNAL WPCF. *Kenneth G. Brown is president of Kenneth G. Brown Inc., 3207 Winged Elm Lane, Chapel Hill, NC 27514. Chien-Jen Chen is professor and director at the Institute of Public Health, College of Public Health, National Taiwan Univ., Taipei, Taiwan.*