In a number of areas worldwide, oxidation and dissolution of arsenian pyrite, $Fe(As,S)_2$, and arsenopyrite, FeAsS, are additional processes that lead to high concentrations of dissolved arsenic (*12*). The oxidation can be promoted naturally through infiltrating oxygenated ground waters (*13*) or through lowering of the ground-water table (by well-water pumping or climate variations) into a stratigraphic zone containing arsenic-rich sulfides (*14*). The highest natural arsenic concentrations found in the United States (1 to 10 mg/liter) are in the Fairbanks, Alaska, area, where arsenopyrite-rich zones in igneous and metamorphic rocks are being oxidized, and there may also be some iron reduction (*13*).

The key to minimizing risk is to incorporate hydrogeological, geochemical, and microbiological expertise into the decision-making process of water managers, remediation specialists, and policy-makers. The geologic and ground-water conditions that promote high arsenic concentrations are known and can help identify high-risk areas. The western United States has many ground waters where arsenic is found in concentrations >10 μg/liter, and treating them will be expensive but may be trivial compared with potential health-care costs. In the search for adequate water supplies and in the absence of adequate information, it is prudent to test selected wells before opening the tap.

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POLICY FORUM: PUBLIC HEALTH

Arsenic Epidemiology and Drinking Water Standards

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In the United States, setting the maximum contaminant level (MCL) that regulates the concentration of arsenic in public water supplies has been an extraordinarily protracted process (see the table on this page). Recently, the MCL was lowered to 10 μg/liter, from the 50 μg/liter standard established in 1942. However, as early as 1962 the USPHS advised that water concentrations should not exceed 10 μg/liter when "more suitable supplies are or can be made available" (*1*). In 1986, Congress directed the U.S. Environmental Protection Agency (EPA) to revise the standard by 1989, but it failed to do so (*2*). Not until January 2001, in one of the last acts of the Clinton administration, was the announcement of a new U.S. standard of 10 μg/liter made by the EPA (*3*). Two months later, the Bush administration delayed adoption of the standard, citing concerns about the science supporting the rule and its estimated cost (*2*). Nevertheless, in October 2001, under pressure from Congress and following a pivotal report by the National Research Council (NRC) (*4*), the EPA adopted the 10 μg/liter standard (*2*) (see the table, below). We will consider how the regulatory process might interpret and respond more effectively to results from epidemiological studies.

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Arsenic was one of the first chemicals recognized as a cause of cancer. As early as 1879, the high rates of lung cancer in miners in Saxony were attributed in part to inhaled arsenic (*5*). A few years later, skin cancers were reported in patients treated with medicine containing arsenic (*6, 7*). Evidence that arsenic in drinking water could cause skin cancer came much later, in the 1930s, from Argentina (*8*), and subsequently from many other countries (*9*), including a large population in Taiwan (*10*).

In the 1960s, evidence emerged in Argentina that arsenic in drinking water might cause internal cancers, particularly of the lung and urinary tract (*11, 12*). Startling results from Taiwan, appearing in 1985, showed increased mortality from several cancers, especially lung, bladder, and kidney cancers (*13*). Bladder cancer mortality rates for those with more than 600 μg/liter of arsenic in their water were more than 30 to 60 times the rates in the unexposed population (*14*). Such high cancer rates were unprecedented for any water contaminant. By 1992, the combination of evidence from Taiwan and elsewhere was

HISTORY OF U.S. STANDARDS FOR ARSENIC IN DRINKING WATER

1942	USPHS sets an interim drinking water standard of 50 μg As/liter (*50*)
1962	USPHS identifies 10 μg As/liter as the goal (*1*)
1975	EPA adopts the interim standard of 50 μg As/liter set by the USPHS in 1942 (*50*)
1986	Congress directs EPA to revise the standard by 1989 (*2*)
1988	EPA estimates that the ingestion of 50 μg As/liter results in a skin cancer risk of 1 in 400 (*51*)
1992	Internal cancer risk estimated to be 1.3 per 100 persons at 50 μg As/liter (*16*)
1993	World Health Organization recommends lowering arsenic in drinking water to 10 μg As/liter (*52*)
1996	Congress directs the EPA to propose a new drinking water standard by January 2000 (*2*)
1999	NRC estimates cancer mortality risks to be about 1 in 100 at 50 μg As/liter (*28*)
2000	EPA proposes a standard of 5 μg As/liter and requests comment on 3, 10, and 20 μg As/liter (*2*)
2001	(January) Clinton EPA lowers the standard to 10 μg As/liter (*2*)
2001	(March) Bush EPA delays lowering the standard (*2*)
2001	(September) New NRC report concludes that EPA underestimated cancer risks (*4*)
2001	(October) EPA announces it will adopt the standard of 10 μg/liter (*2*)
2002	(February) The effective date for new standard of 10 μg As/liter (*2*)
2006	Compliance date for the new arsenic standard (*2*)

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CARCINOGENS IN DRINKING WATER

Chemical	MCL (*53*) (μg/liter)	Cancer risk at MCL per 100,000
Arsenic	50	1300 (*16*) 1650* (*4*)
Benzene	5	0.2–0.8 (*54*)
Benz[*a*]pyrene	0.2	4.2 (*54*)
Carbon tetrachloride	5	1.9 (*54*)
Chlordane	2	2 (*54*)
1,2-Dichloroethane	5	1.3 (*54*)
Dichloromethane	5	0.1 (*54*)
Di(2-ethylhexyl)phthalate	6	0.2 (*54*)
Ethylene dibromide	0.05	12.5 (*54*)
Heptachlor	0.4	5.2 (*54*)
Heptachlor epoxide	0.2	5.2 (*54*)
Hexachlorobenzene	1	4.6 (*54*)
Polychlorinated biphenyls (PCBs)	0.5	0.5 (*54*)
Pentachlorophenol	1	0.3 (*54*)
Toxaphene	3	9.6 (*54*)
Vinyl chloride	2	8.4 (*54*)

*Extrapolated upward from results given for 20 μg/liter

sufficient to conclude that ingested inorganic arsenic was likely to cause several internal cancers (*15*). At the same time, a risk assessment estimated the combined cancer mortality risk to be as high as 1 in 100 for people drinking water containing 50 μg/liter of arsenic *(16)*. The epidemiological associations found in Taiwan (*14, 17–21*) have since been confirmed by studies in Japan (*22, 23*), Argentina (*24, 25*), and Chile (*26, 27*). Two reports of the NRC (*4, 28*) affirmed that cancer risks might be of the order of 1 in 100 for 50 μg/liter. This estimated cancer risk is more than 100 times greater than that for any other drinking water contaminant with an MCL (see the table, above).

With such high estimated risks, why did it take so long to reduce the arsenic drinking water standard? One problem was that most drinking water standards have been based on experimental animal studies with little, if any, evidence from studies of people. The absence of a good animal model for arsenic-induced cancer may have impeded its regulation (*29*). Major uncertainties have been tolerated in extrapolating from rodents to humans for other purported carcinogens, whereas the relatively minor uncertainties in epidemiological studies of arsenic exposure were not considered acceptable (*30*).

Uncertainties in epidemiological studies include confounding of the exposure with some other disease cause. For example, smoking is the major cause of lung cancer in most populations. If arsenic-exposed populations smoked heavily, they would have higher rates of lung cancer than other populations. Smoking is not an important confounding factor in this situation, where relative risks are much higher for arsenic in drinking water (*31*). Similarly, diet can have relatively minor effects on the incidence of human cancers, and bladder cancer risks might be increased about 1.5-fold with diets poor in fruits and vegetables (*32*). Yet poor diet was invoked as a reason for uncertainty in the cancer risks estimated from Taiwan, where arsenic exposure was linked to 30- to 60-fold increases in bladder cancer risk (*28, 33, 34*).

Another reason for delay involved extensive discussion concerning whether or not there is a threshold for arsenic exposure, below which it would not cause cancer (*35–38*). Supporters of the threshold hypothesis postulated that, for inorganic arsenic to exert a carcinogenic effect, it would have to exceed the level of exposure at which most of the absorbed inorganic arsenic is methylated and presumably detoxified. However, numerous studies on arsenic methylation in exposed and unexposed populations have provided substantial evidence that a threshold for arsenic methylation does not exist (*35, 39–44*). More recent data suggest that methylation of inorganic arsenic may actually increase its carcinogenic potential (*4*, *45, 46*). Furthermore, studies on human cell cultures have demonstrated genotoxic effects at concentrations of arsenic potentially attainable in human tissue after ingestion of water containing 50 μg/liter or less (*4*). To compound the uncertainties, complex statistical models were used to extrapolate the Taiwanese arsenic data to low exposure levels, producing a wide range of risk estimates (*3*, *47*). Little attention was given to the small margin of safety between 500 μg/liter, causing about 1 in 10 people to die from cancer, and 50 μg/liter, for which risks could be 1 in 100 (*28*). Epidemiology can be used to demonstrate causation of disease in human populations, but it has sensitivity limitations. It would be extremely difficult to prove that consuming water containing 50 μg/liter of arsenic would cause 1 in 100 individuals to die from cancer.

In conclusion, when there is such direct human epidemiological evidence that a substance causes cancer, we should focus on margins of safety, avoiding extensive statistical manipulations of data and excessive debate about potential uncertainties. Prudent public health decisions should not wait until there is proof of serious cancer risks at low exposure.

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