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Arsenic: risk assessment for California drinking water standards

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Abstract

Six California counties contain 15 water systems with arsenic concentrations above the 50 ppb Maximum Contaminant Level (MCL). Arsenic compounds are carcinogenic in humans by oral and inhalation routes. They are also fetotoxic and teratogenic in mice, rats and hamsters and cause a variety of toxic effects in the gastro-intestinal tract, circulatory system, skin, liver, kidney, nervous system and heart. The US EPA has identified an oral human chronic No-Observable-Adverse-Effect Level (NOAEL) of 0.0008 mg/kg-d based on skin and vascular effects. In 1988 EPA estimated the human carcinogenic potency of arsenic in drinking water to be about 2×10^{-3}/μg/kg-d with a 10^{-6} lifetime skin cancer risk equivalent to consumption of 2 l/day at 20 ppt. Recently Smith et al. (1990) estimated the potency of arsenic to be 5.3×10^{-3}/μg/kg-d based on the same human data. Also Chen et al. (1988) and Chen and Wang (1990) identified the additional tumor sites of liver, lung, bladder, kidney, nasal cavity and prostate. The lifetime risk of developing skin cancer at the 50 ppb MCL level (2 l/day) is about 8 in 1000. Preliminary analysis of the recent data on other tumor sites indicate comparable risks of: females – lung, 11.0; bladder, 6.7; kidney, 3.4; liver, 0.3; males – lung, 6.1, bladder, 2.2; kidney, 1.4; liver, 0.2. On the basis of a skin cancer potency of 5.3×10^{-3}/μg/kg-d, a Recommended Public Health Level (RPHL) of 2 ppt (0.002 μg/l) is being proposed in accordance with the provisions of the Safe Drinking Water Act of 1989. This value assumes a body weight of 70 kg, a water consumption of 2 l/day, a relative source contribution of 20%, and a lifetime extra cancer risk of 10^{-6}.

1. Introduction

Arsenic is a natural element that occurs widely in the environment in both organic and inorganic forms. Occasionally arsenic is found in drinking water. A causal association between human arsenic exposure, usually in the form of inorganic compounds containing trivalent arsenite (As(III)) or pentavalent arsenate (As(V)), and

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various forms of human cancer has been known for many years [1]. The International Agency for Research on Cancer (IARC) evaluated arsenic in 1980 and classified "arsenic and arsenic compounds" in Group 1, which includes "chemicals and groups of chemicals which are causally associated with cancer in humans" [2]. The US Environmental Protection Agency has classified arsenic in Group A, human carcinogen, on the basis of increased lung cancer mortality in populations exposed primarily through inhalation, and an increased skin cancer incidence in several populations consuming drinking water with high arsenic concentrations [3].

In 1976 the EPA established a primary drinking water standard (Maximum Contaminant Level) of 50 μg/l (50 ppb) for inorganic arsenic based on skin cancer incidence in humans. This is the same mandatory limit established previously by the US Public Health Service (1962) [4]. The State of California adopted the same standard following EPA's action in the 1970s. Since about 1985 the California Department of Health Services, currently Cal/EPA OEHHA, has been directed to develop new MCLs for over 36 water contaminants and to evaluate existing MCLs. Since passage of the California Safe Drinking Water Act of 1989, OEHHA is required to propose Recommended Public Health Levels (RPHLs) for water contaminants without consideration of technical and economic factors. For carcinogen contaminants the RPHL and anticipated exposure should correspond to a negligible risk of one extra lifetime cancer per million exposed individuals. For non-carcinogenic water contaminants the RPHL and the MCL are identical. For carcinogens the MCL may exceed the RPHL based upon technical and economic limitations. The law is designed to improve water quality as technical and economic factors become more favorable. Also the toxicology and exposure data relating to the RPHL determination are to be reviewed and the standards revised as needed on a periodic basis. This report is based on a recent proposed RPHL and supporting documentation for arsenic [5].

2. Arsenic in California drinking water

According to the most recent survey data in California (1991), about a dozen counties contain water systems with arsenic concentrations above the 10 ppb reporting limit and about 15 water systems exceed the 50 ppb state and federal MCL. Of the latter, two large water systems, with greater than 200 service connections, are in Kings and Tulare Counties. The smaller water systems exceeding the MCL are in Kern, Kings, San Benito, San Joaquin and Sonoma counties.

This information was obtained from the California Department of Health Services' Division of Drinking Water and Environmental Management (DDEM) data base. DDEM staff estimate that about 35 000 people are exposed to drinking water exceeding the 50 ppb MCL (mostly in the City of Hanford), and perhaps as many as 5 000 000 could be exposed to concentrations above 5 ppb.

3. Toxicology

The acute toxicity of arsenic has long been recognized. Arsenic compounds may be absorbed from the lungs and the gastrointestinal tract. By ingestion as little as 10 mg

of arsenic may be life threatening to humans. Acute inhalation exposure to arsenic trioxide causes irritation of the eyes, nasal mucous and bronchi. Non-carcinogenic effects associated with chronic exposure to airborne arsenic include nasal septum ulceration and perforation, respiratory tract irritation, and peripheral neuropathy. The most sensitive non-carcinogenic end-points are probably vascular disorders, neurological disturbances and adverse reproductive effects. Chromosomal aberrations and sister chromatid exchanges have been observed in peripheral lymphocytes of people exposed to arsenic on the job or during pharmaceutical treatment. Occupational exposure of copper smelter employees to 50–500 μg As/m^3 was associated with blood pressure abnormalities, vascular constriction and decreased nerve conduction velocity [5].

Subacute and chronic oral exposures generally affect the same organs and systems as those affected by acute exposures. These include gastrointestinal tract, circulatory system, skin, liver, kidney, nervous system and heart. Adverse dermal effects, including hyperkeratosis, hyperpigmentation and depigmentation, are attributed to high arsenic levels in the drinking water. Palmoplantar keratoses are often surmounted by small, corn-like, elevated nodules up to 10 mm in diameter. Blackfoot disease, an endemic peripheral vascular disorder found in southwest Taiwan, is also associated with arsenic containing well water consumption although a causal connection with arsenic is disputed [6].

Arsenic compounds are fetotoxic and teratogenic in mice, rats and hamsters. Generally these effects are seen only at dose levels which also result in maternal toxicity. Common terata seen after administration of arsenic compounds to pregnant mammals include malformations of the brain, urogenital organs, skeleton, and ear and small or missing eyes. In general, deficiencies in study design and reporting documentation made it impossible to determine NOAEL or LOAEL values with confidence for developmental endpoints. Although conclusive evidence of human reproductive or developmental toxicity following arsenic exposure is lacking, adverse pregnancy outcomes have been observed among copper smelter employees and nearby residents. These effects included elevated incidence of malformed offspring [7, 8].

The non-carcinogenic adverse health effects noted above are unlikely to be caused by the concentrations of arsenic compounds currently found in drinking water or in ambient air. The US Environmental Protection Agency has identified a human chronic oral No-Observed-Adverse-Effect Level (NOAEL) of 0.8 μg/kg-d based on skin and vascular effects [2]. The reference dose based on this NOAEL is 0.3 μg/kg-d, or 10 ppb in drinking water for a 70 kg human consuming 2 l of water/day.

Arsenic is genotoxic. Arsenic compounds inhibit DNA repair and induce chromosomal aberrations and sister chromatid exchanges. Although arsenic compounds usually show negative results in routine in vitro tests for mutagenicity, one assay in mammalian cells indicates that arsenic can inactivate genes by damaging chromosomes [9]. More recent findings suggest that inorganic arsenic may induce gene amplification in mammalian cells and possibly affect the later stages of carcinogenesis, specifically the progression from preneoplastic to malignant lesions [10]. However, the mechanism of arsenic induced cancer as its other toxic effects is largely unknown.

In general, when given orally to rodents, inorganic or organic arsenic failed to exhibit significant carcinogenic activity. The only exception is the study by Knoth [11], which reported adenomas of the skin, lung, peritoneum and lymph nodes in mice exposed to a total dose of seven mg/animal in five months. When arsenic in the form of sodium arsenate was given to pregnant mice by subcutaneous injection, increases in leukemia or lymphomas were demonstrated. Ishinishi et al. [12] and Pershagen et al. [13] have demonstrated increased incidence of lung tumors in hamsters given arsenic trioxide by intra-tracheal instillation. However, the tumor incidences were low (e.g., $\frac{3}{47}$). The applicability of these studies to human environmental exposure is questionable. In the case of arsenic, the lack of convincing carcinogenicity via the oral route in experimental animals is unique for a proven human carcinogen.

4. Risk assessment

4.1. Skin cancer

Reports of quantitative risk assessments of arsenic from inhalation exposures include the US Environmental Protection Agency's Health Assessment Document (HAD) for Inorganic Arsenic [14] and the California Department of Health Services' Health Effects of Arsenic Compounds [15]. In addition, the Special Report on Ingested Inorganic Arsenic: Skin Cancer: Nutritional Essentiality [16] provided a quantitative risk assessment applicable to drinking water exposure. The present OEHHA assessment [5] applied to drinking water is based on the Health Risk Assessment for Arsenic Ingestion produced by Smith and co-workers [6] under contract to the former OEHHA program within the California Department of Health Services, supplemented by an updated literature review.

As with previous quantitative risk assessments the most convincing data relating cancer incidence to arsenic ingestion via drinking water are found in humans. As noted above there is sufficient evidence from several epidemiological studies to demonstrate a causal association between arsenic exposure and human skin cancer. These studies have examined the effects of chronic ingestion of arsenic in drinking water, in arsenic-contaminated beverages and in medicinal products. Characteristic skin manifestations include hyperpigmentation, hyperkeratosis and carcinomas. Hyperkeratoses may represent premalignant lesions.

Of the human epidemiological studies of arsenic ingestion via drinking water, the most important are those of Tseng and co-workers [17, 18] which involved a large population in southwest Taiwan. The arsenic concentrations in the drinking water wells ranged from 1 to 1820 ppb of predominantly pentavalent inorganic arsenic. Tseng et al. conducted a house-to-house medical survey of 40 421 exposed individuals and demonstrated a dose–response relationship of increasing skin cancer prevalence and arsenic concentration in drinking water. A similar dose–response was noted for duration of water intake. The prevalence rates for skin cancer, hyperkeratosis, and hyperpigmentation were 10.6, 71.0, and 183.5 per 1000, respectively. Of the 428 skin cancers found, 238 from 153 patients were examined histologically. Of these 58% were

intraepidermal carcinomas, 19% squamous cell carcinomas and 15% basal cell carcinomas.

Additional studies which support an association between ingestion of arsenic in drinking water and the development of skin cancer and related disorders have been conducted in South America [19, 20], India [21], and Mexico [22]. A number of studies conducted in the United States, namely Oregon [23], Utah [24], Alaska [25], California [26], and Nevada [27] have shown no association between arsenic consumption via drinking water and adverse skin effects. These latter results are not necessarily at odds since in each of the US studies the populations were exposed to much less arsenic than in the Taiwan studies.

To evaluate the shape of the dose–response relation based on the Tseng data, Smith et al. [33] plotted the skin cancer data in terms of skin cancer prevalence by age group vs. estimated arsenic concentrations in drinking water. The average estimated arsenic concentrations for the low, mid, and high exposure groups were 170, 470 and 800 μg/l, respectively [16]. Straight lines, forced through the intercept of zero, were fitted to the data points by weighted least squares regression analysis. The lines were forced through zero since no skin cancers were reported for the control population.

In calculating an arsenic cancer potency from this dose–response relationship the following assumptions were made: (1) There is no threshold for cancer induction by arsenic; (2) The relationship between skin cancer risk and arsenic concentration in drinking water is linear; (3) There are no significant competing risks which would lead to an underestimation of the arsenic risk; (4) Those surveyed who did not have skin cancer never had it in the past; and (5) The lifetime risk of skin cancer in the Taiwan study is equal to the prevalence among those aged 60 and over.

While a nutritional role for arsenic in humans is still being sought it seems unlikely that a practical threshold for skin cancer exists in the current analytically detectable range of above 1 ppb in water. The assumption of linearity is prompted by the Tseng data, whereas EPA assumed sublinearity of low dose response based on theoretical considerations not supported by the data [16]. As noted in Section 4.2, there may be significant competing risks from internal cancers induced by arsenic. Since 72% of the males in the group aged 60 and over were under the age of 70, the usual criterion for lifetime risk, this assumption may underestimate the lifetime risk.

The slope of the regression line for males aged 60 and over was 0.32, i.e., the estimate of prevalence in this group was 0.32 per ppm of inorganic arsenic in drinking water. With the assumptions noted above, this is also the lifetime risk of contracting skin cancer from this concentration of arsenic in water. The upper bound on the slope which is usually identified with the cancer potency was 0.34/ppm. This value is converted to per mg/kg-d using water consumptions and body weight values for the test population. The potency estimate based on the upper bound of the slope is 5.3×10^{-3}/μg/kg-d or 5.3/mg/kg-d. Adjusting these figures for US body weight and water consumption values yields a unit risk value of 1.5×10^{-4}/μg/l. These values are about 3-fold higher than EPA potency estimate published in 1988 [16]. At 50 ppb and 2 l/d consumption the lifetime risk is calculated at up to 7.6/1000, or almost 1%.

4.2. Other cancers

The risk estimations and RPHL calculations above are based solely on skin cancer. Since 1985 studies of Chen et al. [28–30] and Chen and Wang [31] of populations in Taiwan exposed to high levels of arsenic in drinking water have found markedly elevated rates of cancers of the liver, lung, bladder and kidney, and smaller increases in the risks of colon and prostate cancers and cancers of the nasal cavity. From the most recent data [31], the multivariate-adjusted regression coefficients indicating an age adjusted mortality per 100 000 person-years for every 100 ppb increase in arsenic concentration of well water were 6.8 and 2.0 for male and female liver cancer; 0.7 and 0.4 for male and female nasal cavity; 5.3 and 5.3 for male and female lung cancer; 0.9 and 1.0 for male and female skin cancer; 3.9 and 4.2 for male and female bladder cancers; and 1.1 and 1.7 for male and female kidney cancer. The coefficient for prostate cancer was 0.5.

The magnitudes of these risk values, particularly the bladder and kidney cancers, are large enough that confounding or some other risk factor seems unlikely [32]. Although confirmatory evidence is so far lacking, it would be prudent to conclude that ingested arsenic is a cause of bladder, kidney, prostate, and nasal cavity cancers. The cumulative evidence supporting a causal relation between arsenic ingestion and lung and liver cancers is stronger. While the potency of arsenic for these internal cancer target sites is not as readily quantifiable as for skin cancer described above, some estimates based on relative risks have been made by Smith et al. [33]. If the 1990 Chen and Wang data are adjusted to 50 ppb, the current state and federal drinking water standard, then corrected to 2.0 l/day intake for males (vs. 3.5 in Taiwan), and applied to the background rates per 1000 for the tumor sites in the US population, the lifetime risks per 1000 exposed individuals consuming 2 l/day at 50 ppb can be estimated [5]. The highest risks estimates were for lung cancer, 11.0/1000 for females and 6.1/1000 for males. Bladder cancer estimates were 4.7/1000 and 2.2/1000 for females and males, respectively, and kidney cancer 3.4/1000 and 1.4/1000, respectively. These risks are numerically comparable with skin cancer discussed above. It is these preliminary risk estimates which have prompted OEHHA to initiate an accelerated review of California MCL for arsenic for which the proposed Recommended Public Health Level serves as a first step.

4.3. Non-cancer endpoints

As noted above the only non-cancer toxicity possibly associated with chronic exposures to arsenic in drinking water are skin and vascular effects. EPAs oral NOAEL of 0.0008 mg/kg-d based on observations of these effects in human epidemiological studies indicates that the 50 μg/l standard may be insufficiently protective of these effects as well as the carcinogenic effects noted above. At 2 l/day water ingestion and 70 kg body weight the NOAEL is equivalent to 28 μg/l. Incorporating an uncertainty factor of 3 to 10 for human heterogeneity would indicate a safe concentration range of 3–10 μg/l.

5. Calculation of the RPHL

To calculate the RPHL we use the formula shown below. The calculated value is 1.3 ppt. Because of uncertainty in the relative source contribution we have adopted the value of 2.0 ppt. This value is close to the EPA ambient water quality standard for water and fish consumption of 2.2 ppt.

$$C = \frac{(R)(\mathrm{BW})(F)\,\mu\mathrm{g/l}}{(q_1^*,\ \text{human})\ (W)},$$

where

$R = 10^{-6}$ or 1 extra lifetime cancer case per million exposed individuals,

BW = 70 kg standard human body weight,

F = relative source contribution or the % of environmental As exposure due to drinking water, assumed to be 0.2 or 20% for arsenic (may be higher),

q_1^* = human cancer potency or slope factor, 5.3×10^{-3} $(\mu\mathrm{g/kg\text{-}d})^{-1}$,

W = daily water consumption, 2.0 l/d (0.029 l/kg-d),

$$C = \frac{(10^{-6})\ (70\ \mathrm{kg})\ (0.2)}{(5.3 \times 10^{-3})\ (2.0)} = 1.3 \times 10^{-3}\ \mu\mathrm{g/l},$$

$$= 1.3\ \mathrm{ppt},$$

RPHL = 2.0 ppt (0.000002 mg/l).

6. Uncertainties and future work

A number of controversial issues surrounding arsenic carcinogenicity and toxicity remain to be resolved. The related issues of low dose threshold and sub-linear dose–response are important both from the theoretical and practical view points. The lack of domestic epidemiologic evidence can be explained at least partly by the relatively small numbers of people exposed to high arsenic concentrations in the US, however, there may be opportunities for epidemiological investigations and these should be taken advantage of.

The lack of convincing animal carcinogenicity data is troubling to many scientists although great differences are known to exist between toxicity and metabolism of arsenic in man and experimental rodent species, and even among rodent species. New and more sensitive animal models may be feasible and can aid in the study of the mechanism of arsenic carcinogenesis, but the lack of an animal model presently should not prevent us from taking regulatory action based on human data.

The negative findings seen in animal carcinogenicity experiments and a lack of a mutagenic effect in gene mutation assays have generated suggestions that arsenic might act as a co-carcinogen, or tumor promoter, rather than a direct carcinogen. A possible threshold dose has been postulated by US EPA [16], Marcus and Rispin

Table 1

Physiologically-based pharmacokinetic model comparisons of 5.0 mg/kg oral doses of inorganic arsenic in three species

Tissue/excreta	Mouse[a]			Rat			Human		
	Peak[b] concentration	% Dose	% Dose	Peak concentration	% Dose	% Dose	Peak concentration	% Dose	% Dose
Blood	10.2	–[c]	–[d]	13.2	–	–	73	–	–
Liver	46.2	0.008	ND	65.1	2.03	1.44	367	5.8	3.7
Lung	20.3	0.008	ND	26.5	0.14	0.10	153	2.2	1.4
Kidney VRG[d]	34.9	0.13	ND	37.4	5.33	3.98	292	2.7	1.8
Muscle	25.0	1.7	ND	64.8	59.3	41.4	105	49.2	31.6
Skin	24.2	0.17	ND	32.5	2.81	2.03	94	4.2	2.8
Fat	NA	NA	NA	3.3	0.26	0.18	20	1.9	1.2
Intestine	44.1	0.18	ND	66.8	1.47	1.03	590	4.2	2.7
Urine (Asi)	–	15.9	16.4	–	7.79	13.0	–	5.6	9.2
MMA	–	11.8	12.2	–	0.53	0.96	–	8.1	14.9
DMA	–	45.1	46.8	–	2.10	3.85	–	16.1	34.4
Feces (Asi)	–	24.8	25.3	–	18.1	30.4	–	NA	NA
Total		99.8	101.7		99.9	98.4		100.0	103.7

Asi = inorganic arsenic, MMA = monomethylated arsenic, DMA = dimethylated arsenic; ND = not detectable; NA = not applicable.

[a] Body weights; mouse, 0.0285 kg; rat, 0.23 kg; human, 16.3 kg (based on post-mortem analysis of fatal poisoning of a 16.3 kg child).

[b] Peak tissue concentration in μmoles (μg atoms) Asi/l tissue.

[c] % of model dose at 24 h of simulation (tabular output).

[d] % of model dose at 48 h of simulation (estimates from graphical output).

[34] and Stohrer [35]. While a methylation threshold hypothesis has been discussed by Petito and Bech [36], it has been challenged by Hopenhayn-Rich et al. [37]. On the other hand, recent observations reported by Hertz-Picciotto and Smith [38] following evaluation of six studies on occupational arsenic exposure and lung cancer suggested that the use of linear models applied to epidemiological data may result in in an underestimation of the true risk at lower exposures.

Arsenic may play a trace nutrient role similar to selenium at doses far lower than those which cause cancer. Presently, there are no data in humans supporting the idea of nutritional essentiality for arsenic in the human diet.

In order to better understand the toxicokinetic differences between species that could lead to such dramatic differences in toxicity and carcinogenicity, a series of pharmacokinetic models is being developed. Physiologically based pharmacokinetic models employ compartment volumes and flows based on actual anatomical and physiological parameters and are calibrated with kinetic and other data from one or more sources. Preliminary efforts of PBPK modeling of arsenic has been directed towards determining interspecies differences in target organ concentrations of inorganic arsenic and its methylated metabolites that might aid in explaining differences in toxicity and carcinogenic activity.

A 13 compartment PBPK model was constructed using STELLA simulation software (High Performance Systems, Inc.) and typical anatomical and physiological values for mouse, rat, and a human child. The model was calibrated using experimental data for absorption, distribution, metabolism, and excretion of inorganic arsenic (As V) and its metabolites in rodents [39] and from a human child fatal poisoning postmortem analysis [40]. The results of preliminary simulations using a 5.0 mg/kg oral gavage dose are summarized in Table 1. Model predictions were usually within one standard deviation of the supporting experimental data. The PBPK models predict significant interspecies differences in peak blood and tissue concentrations and in rates of tissue elimination for inorganic arsenic. The greatest differences were seen in human/mouse comparisons e.g., peak concentration in mixed venous blood, 7; liver, 8; lung, 8; kidney-vessel rich group, 8; muscle, 4; and perfused skin, 4. By contrast rat/mouse tissue concentrations ratios ranged from 1 to 3. The preliminary model is being extended to accommodate reduction of As(V) to As(III) by chemical reaction with tissue glutathione and the distribution of methylated metabolites. The extended model, which attempts to predict both As(III) and As(V) concentrations in target tissues, also allows for differential excretion and metabolism of the two oxidation states [41]. While results from these models are preliminary and do not fully account for the complexity of As metabolism in mammals, they indicate that further PBPK investigations are warranted.

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