Arsenic, inorganic (CASRN 7440-38-2)

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[UPDATE] The (cancer) portion of this assessment is currently under development and the latest draft can be found at, IRIS Toxicological Review of Inorganic Arsenic (Cancer)(External Review Draft)

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Arsenic, inorganic; CASRN 7440-38-2 (04/10/1998)

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Arsenic, inorganic

File First On-Line 02/10/1988

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	02/01/1993
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	04/10/1998

_I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

_I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Arsenic, inorganic
CASRN — 7440-38-2

Last Revised — 02/01/1993

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

NOTE: There was not a clear consensus among Agency scientists on the oral RfD. Applying the Agency's RfD methodology, strong scientific arguments can be made for various values within a factor of 2 or 3 of the currently recommended RfD value, i.e., 0.1 to 0.8 ug/kg/day. It should be noted, however, that the RfD methodology, by definition, yields a number with inherent uncertainty spanning perhaps an order of magnitude. New data that possibly impact on the recommended RfD for arsenic will be evaluated by the Work Group as it becomes available. Risk managers should recognize the considerable flexibility afforded them in formulating regulatory decisions when uncertainty and lack of clear consensus are taken into account.

__I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Hyperpigmentation, keratosis and possible vascular complications Human Chronic oral exposure Tseng, 1977; Tseng et al., 1968	NOAEL: 0.009 mg/L converted to 0.0008 mg/kg-day LOAEL: 0.17 mg/L converted to 0.014 mg/kg-day	3	1	3E-4 mg/kg-day

*Conversion Factors -- NOAEL was based on an arithmetic mean of 0.009 mg/L in a range of arsenic concentration of 0.001 to 0.017 mg/L. This NOAEL also included estimation of arsenic from food. Since experimental data were missing, arsenic concentrations in sweet potatoes and rice were estimated as 0.002 mg/day. Other assumptions included consumption of 4.5 L water/day and 55 kg bw (Abernathy et al., 1989). NOAEL = [(0.009 mg/L x 4.5 L/day) + 0.002 mg/day] / 55 kg = 0.0008 mg/kg-day. The LOAEL dose was estimated using the same assumptions as the NOAEL starting with an arithmetic mean water concentration from Tseng (1977) of 0.17 mg/L. LOAEL = [(0.17 mg/L x 4.5 L/day) + 0.002 mg/day] / 55 kg = 0.014 mg/kg-day.

__I.A.2. Principal and Supporting Studies (Oral RfD)

Tseng, W.P. 1977. Effects and dose-response relationships of skin cancer and blackfoot disease with arsenic. Environ. Health Perspect. 19: 109-119.

Tseng, W.P., H.M. Chu, S.W. How, J.M. Fong, C.S. Lin and S. Yeh. 1968. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. J. Natl. Cancer Inst. 40: 453-463.

The data reported in Tseng (1977) show an increased incidence of blackfoot disease that increases with age and dose. Blackfoot disease is a significant adverse effect. The prevalences (males and females combined) at the low dose are 4.6 per 1000 for the 20-39 year group, 10.5 per 1000 for the 40-59 year group, and 20.3 per 1000 for the >60 year group. Moreover, the prevalence of blackfoot disease in each age group increases with increasing dose. However, a recent report indicates that it may not be strictly due to arsenic exposure (Lu, 1990). The data in Tseng et al. (1968) also show increased incidences of hyperpigmentation and keratosis with age. The overall prevalences of hyperpigmentation and keratosis in the exposed groups are 184 and 71 per 1000, respectively. The text states that the incidence increases with dose, but data for the individual doses are not shown. These data show that the skin lesions are the more sensitive endpoint. The low dose in the Tseng (1977) study is considered a LOAEL.

The control group described in Tseng et al. (1968; Table 3) shows no evidence of skin lesions and presumably blackfoot disease, although this latter point is not explicitly stated. This group is considered a NOAEL.

The arithmetic mean of the arsenic concentration in the wells used by the individuals in the NOAEL group is 9 ug/L (range: 1-17 ug/L) (Abernathy et al., 1989). The arithmetic mean of the arsenic concentration in the wells used by the individuals in the LOAEL group is 170 ug/L (Tseng, 1977; Figure 4). Using estimates provided by Abernathy et al. (1989), the NOAEL and LOAEL doses for both food and water are as follows: LOAEL - [170 ug/L x 4.5 L/day + 2 ug/day (contribution of food)] x (1/55 kg) = 14 ug/kg/day; NOAEL - [9 ug/L x 4.5 L/day + 2 ug/day (contribution of food)] x (1/55 kg) = 0.8 ug/kg/day.

Although the control group contained 2552 individuals, only 957 (approximately 38%) were older than 20, and only 431 (approximately 17%) were older than 40. The incidence of skin lesions increases sharply in individuals above 20; the incidence of blackfoot disease increases sharply in individuals above 40 (Tseng, 1968; Figures 5, 6 and 7). This study is less powerful than it appears at first glance. However, it is certainly the most powerful study available on arsenic exposure to people.

This study shows an increase in skin lesions, 22% (64/296) at the high dose vs. 2.2% (7/318) at the low dose. The average arsenic concentration in the wells at the high dose is 410 ug/L and at the low dose is 5 ug/L (Cebrian et al., 1983; Figure 2 and Table 1) or 7 ug/L (cited in the abstract). The average water consumption is 3.5 L/day for males and 2.5 L/day for females. There were about an equal number of males and females in the study. For the dose estimates given below we therefore assume an average of 3 L/day. No data are given on the arsenic exposure from food or the body weight of the participants (we therefore assume 55 kg). The paper states that exposure times are directly related to chronological age in 75% of the cases. Approximately 35% of the participants in the study are more than 20 years old (Figure 1).

Exposure estimates (water only) are: high dose - 410 ug/L x 3 L/day x (1/55 kg) = 22 ug/kg/day; low dose - 5-7 ug/L x 3 L/day x (1/55 kg) = 0.3-0.4 ug/kg/day.

The high-dose group shows a clear increase in skin lesions and is therefore designated a LOAEL. There is some question whether the low dose is a NOAEL or a LOAEL since there is no way of knowing what the incidence of skin lesions would be in a group where the exposure to

arsenic is zero. The 2.2% incidence of skin lesions in the low-dose group is higher than that reported in the Tseng et al. (1968) control group, but the dose is lower (0.4 vs. 0.8 ug/kg/day).

The Southwick et al. (1983) study shows a marginally increased incidence of a variety of skin lesions (palmar and plantar keratosis, diffuse palmar or plantar hyperkeratosis, diffuse pigmentation, and arterial insufficiency) in the individuals exposed to arsenic. The incidences are 2.9% (3/105) in the control group and 6.3% (9/144) in the exposed group. There is a slight, but not statistically significant increase in the percent of exposed individuals that have abnormal nerve conduction (8/67 vs. 13/83, or 12% vs. 16% (Southwick et al., 1983; Table 8). The investigators excluded all individuals older than 47 from the nerve conduction portion of the study. These are the individuals most likely to have the longest exposure to arsenic.

Although neither the increased incidence of skin lesions nor the increase in abnormal nerve conduction is statistically significant, these effects may be biologically significant because the same abnormalities occur at higher doses in other studies. The number of subjects in this study was insufficient to establish statistical significance.

Table 3 (Southwick et al., 1983) shows the annual arsenic exposure from drinking water. No data are given on arsenic exposure from food or the body weight (assume 70 kg). Exposure times are not clearly defined, but are > 5 years, and dose groups are ranges of exposure.

Exposure estimates (water only) are: dosed group - 152.4 mg/year x 1 year/365 days x (1/70) kg = 6 ug/kg/day; control group - 24.2 mg/year x year/365 days x (1/70) kg = 0.9 ug/kg/day.

Again because there are no data for a group not exposed to arsenic, there is some question if the control group is a NOAEL or a LOAEL. The incidence of skin lesions in this group is about the same as in the low-dose group from the Cebrian et al. (1983) study; the incidence of abnormal nerve conduction in the control group is higher than that from the low-dose group in the Hindmarsh et al. (1977) study described below. The control dose is comparable to the dose to the control group in the Tseng et al. (1968) and Hindmarsh et al. (1977) studies. The dosed group may or may not be a LOAEL, since it is does not report statisically significant effects when compared to the control.

This study shows an increased incidence of abnormal clinical findings and abnormal electromyographic findings with increasing dose of arsenic (Hindmarsh et al., 1977; Tables III and VI). However, the sample size is extremely small. Percentages of abnormal clinical signs possibly attributed to As were 10, 16, and 40% at the low, mid and high doses, respectively. Abnormal EMG were 0, 17 and 53% in the same three groups.

The exact doses are not given in the Hindmarsh et al. (1977) paper; however, some well data are reported in Table V. The arithmetic mean of the arsenic concentration in the high-dose and mid-dose wells is 680 and 70 ug/L, respectively. Figure 1 (Hindmarsh et al., 1977) shows that the average arsenic concentration of the low-dose wells is about 25 ug/L. No data are given on arsenic exposure from food. We assume daily water consumption of 2 liters and body weight of 70 kg. Exposure times are not clearly stated.

Exposure estimates (water only) are: low - 25 ug/L x 2 L/day x (1/70) kg = 0.7 ug/kg/day; mid - 70 ug/L x 2 L/day x (1/70) kg = 2 ug/kg/day; high - 680 ug/L x 2 L/day x (1/70) kg = 19 ug/kg/day.

The low dose is a no-effect level for abnormal EMG findings. However, because there is no information on the background incidence of abnormal clinical findings in a population with zero exposure to arsenic, there is no way of knowing if the low dose is a no-effect level or another marginal effect level for abnormal clinical findings. The low dose is comparable to the dose received by the control group in the Tseng (1977) and Southwick et al. (1983) studies.

The responses at the mid dose do not show a statistically significant increase but are part of a statistically significant trend and are biologically significant. This dose is an equivocal NOAEL/LOAEL. The high dose is a clear LOAEL for both responses.

As discussed previously there is no way of knowing whether the low doses in the Cebrian et al. (1983), Southwick et al. (1983) and Hindmarsh et al. (1977) studies are NOAELs for skin lesions and/or abnormal nerve conduction. However, because the next higher dose in the Southwick and Hindmarsh studies only shows marginal effects at doses 3-7 times higher, the Agency feels comfortable in assigning the low doses in these studies as NOAELs.

The Tseng (1977) and Tseng et al. (1968) studies are therefore considered superior for the purposes of developing an RfD and show a NOAEL for a sensitive endpoint. Even discounting the people < 20 years of age, the control group consisted of 957 people that had a lengthy exposure to arsenic with no evidence of skin lesions.

The following is a summary of the defined doses in mg/kg-day from the principal and supporting studies:

1) Tseng (1977): NOAEL = 8E-4; LOAEL = 1.4E-2

2) Cebrian et al. (1983): NOAEL = 4E-4; LOAEL = 2.2E-2

3) Southwick et al. (1983): NOAEL = 9E-4; LOAEL = none (equivocal effects at 6E-3)

4) Hindmarsh et al., 1977: NOAEL = 7E-4; LOAEL = 1.9E-2 (equivocal effects at 2E-3)

__I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — The UF of 3 is to account for both the lack of data to preclude reproductive toxicity as a critical effect and to account for some uncertainty in whether the NOAEL of the critical study accounts for all sensitive individuals.

MF — None

__I.A.4. Additional Studies/Comments (Oral RfD)

Ferm and Carpenter (1968) produced malformations in 15-day hamster fetuses via intravenous injections of sodium arsenate into pregnant dams on day 8 of gestation at dose levels of 15, 17.5, or 20 mg/kg bw. Exencephaly, encephaloceles, skeletal defects and genitourinary systems defects were produced. These and other terata were produced in mice and rats all at levels around 20 mg/kg bw. Minimal effects or no effects on fetal development have been observed in studies on chronic oral exposure of pregnant rats or mice to relatively low levels of arsenic via drinking water (Schroeder and Mitchner, 1971). Nadeenko et al. (1978) reported that intubation of rats with arsenic solution at a dose level of 25 ug/kg/day for a period of 7 months, including pregnancy, produced no significant embryotoxic effects and only infrequent slight expansion of ventricles of the cerebrum, renal pelves and urinary

bladder. Hood et al. (1977) reported that very high single oral doses of arsenate solutions (120 mg/kg) to pregnant mice were necessary to cause prenatal fetal toxicity, while multiple doses of 60 mg/kg on 3 days had little effect.

Extensive human pharmacokinetic, metabolic, enzymic and long-term information is known about arsenic and its metabolism. Valentine et al. (1987) established that human blood arsenic levels did not increase until daily water ingestion of arsenic exceeded approximately 250 ug/day (approximately 120 ug of arsenic/L. Methylated species of arsenic are successively 1 order of magnitude less toxic and less teratogenic (Marcus and Rispin, 1988). Some evidence suggests that inorganic arsenic is an essential nutrient in goats, chicks, minipigs and rats (NRC, 1989). No comparable data are available for humans.

__I.A.5. Confidence in the Oral RfD

Study — Medium
Database — Medium
RfD — Medium

Confidence in the chosen study is considered medium. An extremely large number of people were included in the assessment (> 40,000) but the doses were not well-characterized and other contaminants were present. The supporting human toxicity database is extensive but somewhat flawed. Problems exist with all of the epidemiological studies. For example, the Tseng studies do not look at potential exposure from food or other source. A similar criticism can be made of the Cebrian et al. (1983) study. The U.S. studies are too small in number to resolve several issues. However, the database does support the choice of NOAEL. It garners medium confidence. Medium confidence in the RfD follows.

__I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — This assessment is not presented in any existing U.S. EPA document.

This analysis has been reviewed by EPA's Risk Assessment Council on 11/15/1990. This assessment was discussed by the Risk Assessment Council of EPA on 11/15/1990 and verified through a series of meetings during the 1st, 2nd and 3rd quarters of FY91.

Other EPA Documentation — U.S. EPA, 1984, 1988

Agency Work Group Review — 03/24/1988, 05/25/1988, 03/21/1989, 09/19/1989, 08/22/1990, 09/20/1990

Verification Date — 11/15/1990

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Arsenic (inorganic) conducted in September 2002 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

__I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

_I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Arsenic, inorganic
CASRN — 7440-38-2

Not available at this time.

_II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Arsenic, inorganic
CASRN — 7440-38-2
Last Revised — 04/10/1998

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

_II.A. Evidence for Human Carcinogenicity

__II.A.1. Weight-of-Evidence Characterization

Classification — A; human carcinogen

Basis — based on sufficient evidence from human data. An increased lung cancer mortality was observed in multiple human populations exposed primarily through inhalation. Also, increased mortality from multiple internal organ cancers (liver, kidney, lung, and bladder) and an increased incidence of skin cancer were observed in populations consuming drinking water high in inorganic arsenic.

__II.A.2. Human Carcinogenicity Data

Sufficient. Studies of smelter worker populations (Tacoma, WA; Magma, UT; Anaconda, MT; Ronnskar, Sweden; Saganoseki-Machii, Japan) have all found an association between

occupational arsenic exposure and lung cancer mortality (Enterline and Marsh, 1982; Lee-Feldstein, 1983; Axelson et al., 1978; Tokudome and Kuratsune, 1976; Rencher et al., 1977). Both proportionate mortality and cohort studies of pesticide manufacturing workers have shown an excess of lung cancer deaths among exposed persons (Ott et al., 1974; Mabuchi et al., 1979). One study of a population residing near a pesticide manufacturing plant revealed that these residents were also at an excess risk of lung cancer (Matanoski et al., 1981). Case reports of arsenical pesticide applicators have also corroborated an association between arsenic exposure and lung cancer (Roth, 1958).

A cross-sectional study of 40,000 Taiwanese exposed to arsenic in drinking water found significant excess skin cancer prevalence by comparison to 7500 residents of Taiwan and Matsu who consumed relatively arsenic-free water (Tseng et al., 1968; Tseng, 1977). Although this study demonstrated an association between arsenic exposure and development of skin cancer, it has several weaknesses and uncertainties, including poor nutritional status of the exposed populations, their genetic susceptibility, and their exposure to inorganic arsenic from non-water sources, that limit the study's usefulness in risk estimation. Dietary inorganic arsenic was not considered nor was the potential confounding by contaminants other than arsenic in drinking water. There may have been bias of examiners in the original study since no skin cancer or preneoplastic lesions were seen in 7500 controls; prevalence rates rather than mortality rates are the endpoint; and furthermore there is concern of the applicability of extrapolating data from Taiwanese to the U.S. population because of different background rates of cancer, possibly genetically determined, and differences in diet other than arsenic (e.g., low protein and fat and high carbohydrate) (U.S. EPA, 1988).

A prevalence study of skin lesions was conducted in two towns in Mexico, one with 296 persons exposed to drinking water with 0.4 mg/L arsenic and a similar group with exposure at 0.005 mg/L. The more exposed group had an increased incidence of palmar keratosis, skin hyperpigmentation and hypopigmentation, and four skin cancers (histologically unconfirmed) (Cebrian et al. (1983). The association between skin cancer and arsenic is weak because of the small number of cases, small cohort size, and short duration follow-up; also there was no unexposed group in either town. No excess skin cancer incidence has been observed in U.S. residents consuming relatively high levels of arsenic in drinking water but the numbers of exposed persons were low (Morton et al., 1976; Southwick et al., 1981). Therapeutic use of Fowler's solution (potassium arsenite) has also been associated with development of skin cancer and hyperkeratosis (Sommers and McManus, 1953; Fierz, 1965); several case reports implicate exposure to Fowler's solution in skin cancer development (U.S. EPA, 1988).

Several follow-up studies of the Taiwanese population exposed to inorganic arsenic in drinking water showed an increase in fatal internal organ cancers as well as an increase in skin cancer. Chen et al. (1985) found that the standard mortality ratios (SMR) and cumulative mortality rates for cancers of the bladder, kidney, skin, lung and liver were significantly greater in the Blackfoot disease endemic area of Taiwan when compared with the age adjusted rates for the general population of Taiwan. Blackfoot disease (BFD, an endemic peripheral artery disease) and these cancers were all associated with high levels of arsenic in drinking water. In the endemic area, SMRs were greater in villages that used only artesian well water (high in arsenic) compared with villages that partially or completely used surface well water (low in arsenic). However, dose-response data were not developed (Chen et al. 1985).

A retrospective case-control study showed a significant association between duration of consuming high-arsenic well water and cancers of the liver, lung and bladder (Chen et al., 1986). In this study, cancer deaths in the Blackfoot disease endemic area between January

1980 and December 1982 were chosen for the case group. About 90% of the 86 lung cancers and 95 bladder cancers in the registry were histologically or cytologically confirmed and over 70% of the liver cancers were confirmed by biopsy or à-fetoprotein presence with a positive liver x-ray image. Only confirmed cancer cases were included in the study. A control group of 400 persons living in the same area was frequency-matched with cases by age and sex. Standardized questionnaires of the cases (by proxy) and controls determined the history of artesian well water use, socioeconomic variables, disease history, dietary habits, and lifestyle. For the cancer cases, the age-sex adjusted odds ratios were increased for bladder (3.90), lung (3.39), and liver (2.67) cancer for persons who had used artesian well water for 40 or more years when compared with controls who had never used artesian well water. Similarly, in a 15-year study of a cohort of 789 patients of Blackfoot disease, an increased mortality from cancers of the liver, lung, bladder and kidney was seen among BFD patients when compared with the general population in the endemic area or when compared with the general population of Taiwan. Multiple logistic regression analysis to adjust for other risk factors including cigarette smoking did not markedly affect the exposure-response relationships or odds ratios (Chen et al., 1988).

A significant dose-response relationship was found between arsenic levels in artesian well water in 42 villages in the southwestern Taiwan and age- adjusted mortality rates from cancers at all sites, cancers of the bladder, kidney, skin, lung, liver and prostate (Wu et al., 1989). An ecological study of cancer mortality rates and arsenic levels in drinking water in 314 townships in Taiwan also corroborated the association between arsenic levels and mortality from the internal cancers (Chen and Wang, 1990).

Chen et al.(1992) conducted a recent analysis of cancer mortality data from the arsenic-exposed population to compare risk of various internal cancers and compare risk between males and females. The study area and population have been described by Wu et al. (1989). It is limited to 42 southwestern coastal villages where residents have used water high in arsenic from deep artesian wells for more than 70 years. Arsenic levels in drinking water ranged from 0.010 to 1.752 ppm. The study population had 898,806 person-years of observation and 202 liver cancer, 304 lung cancer, 202 bladder cancer and 64 kidney cancer deaths. The study population was stratified into four groups according to median arsenic level in well water (< 0.10 ppm, 0.10- 0.29 ppm, 0.30-0.59 ppm and 60+ ppm), and also stratified into four age groups (< 30 years, 30-49 years, 50-69 years and 70+ years). Mortality rates were found to increase significantly with age for all cancers and significant dose- response relationships were observed between arsenic level and mortality from cancer of the liver, lung, bladder and kidney in most age groups of both males and females. The data generated by Chen et al. (1992) provide evidence for an association of the levels of arsenic in drinking water and duration of exposure with the rate of mortality from cancers of the liver, lung, bladder, and kidney. Dose-response relationships are clearly shown by the tabulated data (Tables II-V of Chen et al., 1992). Previous studies summarized in U.S. EPA (1988) showed a similar association in the same Taiwanese population with the prevalence of skin cancers (which are often non-fatal). Bates et al. (1992) and Smith et al. (1992) have recently reviewed and evaluated the evidence for arsenic ingestion and internal cancers.

__II.A.3. Animal Carcinogenicity Data

Inadequate. There has not been consistent demonstration of carcinogenicity in test animals for various chemical forms of arsenic administered by different routes to several species (IARC, 1980). Furst (1983) has cited or reviewed animal carcinogenicity testing studies of nine inorganic arsenic compounds in over nine strains of mice, five strains of rats, in dogs, rabbits, swine and chickens. Testing was by the oral, dermal, inhalation, and parenteral

routes. All oxidation states of arsenic were tested. No study demonstrated that inorganic arsenic was carcinogenic in animals. Dimethylarsonic acid (DMA), the end metabolite predominant in humans and animals, has been tested for carcinogenicity in two strains of mice and was not found positive (Innes et al., 1969); however, this was a screening study and no data were provided. The meaning of non-positive data for carcinogenicity of inorganic arsenic is uncertain, the mechanism of action in causing human cancer is not known, and rodents may not be a good model for arsenic carcinogenicity testing. There are some data to indicate that arsenic may produce animal lung tumors if retention time in the lung can be increased (Pershagen et al., 1982, 1984).

__II.A.4. Supporting Data for Carcinogenicity

A retrospective cohort mortality study was conducted on 478 British patients treated between 1945-1969 with Fowler's solution (potassium arsenite). The mean duration of treatment was 8.9 months and the average total oral consumption of arsenic was about 1890 mg (daily dose x duration). In 1980, 139 deaths had occurred. No excess deaths from internal cancers were seen after this 20-year follow-up. Three bladder cancer deaths were observed (1.19 expected, SMR 2.5) (Cuzick et al., 1982). A recent follow-up (Cuzick et al., 1992) indicated no increased mortality from all cancers but a significant excess from bladder cancer (5 cases observed/1.6 expected; SMR of 3.07). A subset of the original cohort (143 persons) had been examined by a dermatologist in 1970 for signs of arsenicism (palmar keratosis). In 1990, there were 80 deaths in the subcohort and 11 deaths from internal cancers. All 11 subjects had skin signs (keratosis-10, hyperpigmentation-5 and skin cancer-3). A case-control study of the prevalence of palmar keratoses in 69 bladder cancer patients, 66 lung cancer patients and 218 hospital controls (Cuzick et al., 1984), indicated an association between skin keratosis (as an indicator of arsenic exposure) and lung and bladder cancer. Above the age of 50, 87% of bladder cancer patients and 71% of lung cancer patients but only 36% of controls had one or more keratoses. Several case reports implicate internal cancers with arsenic ingestion or specifically with use of Fowler's solution but the associations are tentative (U.S. EPA, 1988).

Sodium arsenate has been shown to transform Syrian hamster embryo cells (Dipaolo and Casto, 1979) and to produce sister chromatid-exchange in DON cells, CHO cells, and human peripheral lymphocytes exposed in vitro (Wan et al., 1982; Ohno et al., 1982; Larramendy et al., 1981; Andersen, 1983; Crossen, 1983). Jacobson-Kram and Montalbano (1985) have reviewed the mutagenicity of inorganic arsenic and concluded that inorganic arsenic is inactive or very weak for induction of gene mutations in vitro but it is clastogenic with trivalent arsenic being an order of magnitude more potent than pentavalent arsenic.

Both the pentavalent and trivalent forms of inorganic arsenic are found in drinking water. In both animals and humans, arsenate (As+5) is reduced to arsenite (As+3) and the trivalent form is methylated to give the metabolites mononomethylarsinic acid (MMA) and dimethylarsonic acid (DMA) (Vahter and Marafante, 1988). The genotoxicity of arsenate (As+5) and arsenite (As+3) and the two methylated metabolites, MMA and DMA were compared in the thymidine kinase forward mutation assay in mouse lymphoma cells (Harrington-Brock et al. 1993; Moore et al., 1995, in press). Sodium arsenite (+3) and sodium arsenate (+5) were mutagenic at concentration of 1-2 ug/mL and 10-14 ug/mL, respectively, whereas MMA and DMA were significantly less potent, requiring 2.5-5 mg/mL and 10 mg/mL, respectively, to induce a genotoxic response. Based on small colony size the mutations induced were judged chromosomal rather than point mutations. The authors have previously shown that for chemicals having clastogenic activity (i.e., cause chromosomal mutations), the mutated cells grow more slowly than cells with single gene mutations and

this results in small colony size. In the mouse lymphoma assay, chromosomal abberations were seen at approximately the same arsenic levels as TK forward mutations. Arsenate, arsenite and MMA were considered clastogenic but the abberation response with DMA was insufficient to consider it a clastogen. Since arsenic exerts its genotoxicity by causing chromosomal mutations, it has been suggested by the above authors that it may act in a latter stage of carcinogenesis as a progressor, rather than as a classical initiator or promotor (Moore et al., 1994). A finding which supports this process is that arsenate (8-16 uM) and arsenite (3 uM) have been shown to induce 2-10 fold amplification of the dihydrofolate reductase gene in culture in methotrexate resistant 3T6 mouse cells (Lee et al., 1988). Although the mechanism of induction in rodent cells is not known, gene amplification of oncogenes is observed in many human tumors. Inorganic arsenic has not been shown to mutate bacterial strains, it produces preferential killing of repair deficient strains (Rossman, 1981). Sodium arsenite (As+3) induces DNA-strand breaks which are associated with DNA-protein crosslinks in cultured human fibroblasts at 3 mM but not 10 mM (Dong and Luo, 1993) and it appears that arsenite inhibits the DNA repair process by inhibiting both excision and ligation (Jha et al., 1992; Lee-Chen et al., 1993).

The inhibitory effect of arsenite on strand-break rejoining during DNA repair was found to be reduced by adding glutathione to cell cultures (Huang et al., 1993). The cytotoxic effects of sodium arsenite in Chinese hamster ovary cells also has also found to correlate with the intracellular glutathione levels (Lee et al., 1989).

In vivo studies in rodents have shown that oral exposure of rats to arsenate (As+5) for 2-3 weeks resulted in major chromosomal abnormalities in bone marrow (Datta et al., 1986) and exposure of mice to As (+3) in drinking water for 4 weeks (250 mg As/L as arsenic trioxide) caused chromosomal aberrations in bone marrow cells but not spermatogonia (Poma et al., 1987); micronuclei in bone marrow cells were also induced by intraperitoneal dosing of mice with arsenate (DeKnudt et al., 1986; Tinwell et al., 1991). Chromosomal aberrations and sister chromatid exchange have been seen in patients exposed to arsenic from treatment with Fowler's solution (Burgdorf et al., 1977) and subjects exposed occupationally (Beckman et al., 1977) but no increase in either endpoint was seen in lymphocytes of subjects exposed to arsenic in drinking water (Vig et al., 1984).

_II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

__II.B.1. Summary of Risk Estimates

Oral Slope Factor — 1.5E+0 per (mg/kg)/day

Drinking Water Unit Risk — 5E-5 per (ug/L)

Extrapolation Method — Time- and dose-related formulation of the multistage model (U.S. EPA, 1988)

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	2E+0 ug/L
E-5 (1 in 100,000)	2E-1 ug/L

E-6 (1 in 1,000,000)	2E-2 ug/L

__II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

The Risk Assessment Forum has completed a reassessment of the carcinogenicity risk associated with ingestion of inorganic arsenic (U.S. EPA, 1988). The data provided in Tseng et al., 1968 and Tseng, 1977 on about 40,000 persons exposed to arsenic in drinking water and 7500 relatively unexposed controls were used to develop dose-response data. The number of persons at risk over three dose intervals and four exposure durations, for males and females separately, were estimated from the reported prevalence rates as percentages. It was assumed that the Taiwanese persons had a constant exposure from birth, and that males consumed 3.5 L drinking water/day and females consumed 2.0 L/day. Doses were converted to equivalent doses for U.S. males and females based on differences in body weights and differences in water consumption and it was assumed that skin cancer risk in the U.S. population would be similar to the Taiwanese population. The multistage model with time was used to predict dose-specific and age-specific skin cancer prevalance rates associated with ingestion of inorganic arsenic; both linear and quadratic model fitting of the data were conducted. The maximum likelihood estimate (MLE) of skin cancer risk for a 70 kg person drinking 2 L of water per day ranged from 1E-3 to 2E-3 for an arsenic intake of 1 ug/kg/day. Expressed as a single value, the cancer unit risk for drinking water is 5E-5 per (ug/L). Details of the assessment are in U.S. EPA (1988).

Dose response data have not been developed for internal cancers for the Taiwanese population. The data of Chen et al. (1992) are considered inadequate at present.

__II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

Eastern Research Group, under contract to EPA, convened an Expert Panel on Arsenic Carcinogenicity on May 21 and 22, 1997 (Eastern Research Group, 1997). The Expert Panel believed that, "it is clear from epidemiological studies that arsenic is a human carcinogen via the oral and inhalation routes (p. 20)." They also concluded, "that one important mode of action is unlikely to be operative for arsenic". The panel agreed that arsenic and its metabolites do not appear to directly interact with DNA (pp. 30-31)." In addition, the panel agreed that, "for each of the modes of action regarded as plausible, the dose-response would either show a threshold or would be nonlinear (p. 31)". The panel agreed, however, "that the dose-response for arsenic at low doses would likely be truly nonlinear, i.e., with a decreasing slope as the dose decreased. However, at very low doses such a curve might be linear but with a very shallow slope, probably indistinguishable from a threshold (p. 31)."

__II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

This assessment is based on prevalence of skin cancer rather than mortality because the types of skin cancer studied are not normally fatal. However, competing mortality from Blackfoot disease in the endemic area of Taiwan would cause the risk of skin cancer to be underestimated. Other sources of inorganic arsenic, in particular those in food sources have not been considered because of lack of reliable information. There is also uncertainty on the amount of water consumed/day by Taiwanese males (3.5 L or 4.5 L) and the temporal variability of arsenic concentrations in specific wells was not known. The concentrations of arsenic in the wells was measured in the early 1960s and varied between 0.01 and 1.82 ppm. For many villages 2 to 5 analyses were conducted on well water and for other villages only

one analysis was performed; ranges of values were not provided. Since tap water was supplied to many areas after 1966, the arsenic-containing wells were only used in dry periods. Because of the study design, particular wells used by those developing skin cancer could not be identified and arsenic intake could not be assigned except by village. Several uncertainties in exposure measurement reliability existed and subsequent analysis of drinking water found fluorescent substances in water that are possible confounders or caused synergistic effects. Uncertainties have been discussed in detail in U.S. EPA (1988). Uncertainties in exposure measurement can affect the outcome of dose- response estimation.

_II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

__II.C.1. Summary of Risk Estimates

Inhalation Unit Risk — 4.3E-3 per (ug/cu.m)

Extrapolation Method — absolute-risk linear model

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	2E-2 ug/cu.m
E-5 (1 in 100,000)	2E-3 ug/cu.m
E-6 (1 in 1,000,000)	2E-4 ug/cu.m

__II.C.2. Dose-Response Data for Carcinogenicity, Inhalation Exposure

Tumor Type — lung cancer
Test animals — human, male
Route — inhalation, occupational exposure
Reference — Brown and Chu, 1983a,b,c; Lee-Feldstein, 1983; Higgins, 1982; Enterline and Marsh, 1982

Ambient Unit Risk Estimates (per µg/cu.m)				
Exposure Source	**Study**	**Unit Risk**	**Geometric Mean Unit Risk**	**Final Estimated Geometric Mean Unit Risk**
Anaconda smelter	Brown and Chu Lee-Feldstein Higgins et al.	1.25E-3 2.80E-3 4.90E-3	2.56E-3	4.29E-3
ASARCO smelter	Enterline & Marsh	6.81E-3 7.60E-3	7.19E-3	4.29E-3

__II.C.3. Additional Comments (Carcinogenicity, Inhalation Exposure)

A geometric mean was obtained for data sets obtained with distinct exposed populations (U.S. EPA, 1984). The final estimate is the geometric mean of those two values. It was assumed that the increase in age-specific mortality rate of lung cancer was a function only of cumulative exposures.

The unit risk should not be used if the air concentration exceeds 2 ug/cu.m, since above this concentration the unit risk may not be appropriate.

__II.C.4. Discussion of Confidence (Carcinogenicity, Inhalation Exposure)

Overall a large study population was observed. Exposure assessments included air measurements for the Anaconda smelter and both air measurements and urinary arsenic for the ASARCO smelter. Observed lung cancer incidence was significantly increased over expected values. The range of the estimates derived from data from two different exposure areas was within a factor of 6.

_II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

__II.D.1. EPA Documentation

U.S. EPA. 1984, 1988, 1993

A draft of the 1984 Health Assessment Document for Inorganic Arsenic was independently reviewed in public session by the Environmental Health Committee of the U.S. EPA Science Advisory Board on September 22-23, 1983. A draft of the 1988 Special Report on Ingested Inorganic Arsenic; Skin Cancer; Nutritional Essentiality was externally peer reviewed at a two -day workshop of scientific experts on December 2-3, 1986. A draft of the Drinking Water Criteria Document for Arsenic was reviewed by the Drinking Water Committee of the U.S. EPA Science Advisory Board on March 10, 1993. The comments from these reviews were evaluated and considered in the revision and finalization of these reports.

__II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 01/13/1988, 12/07/1989, 02/03/1994

Verification Date — 02/03/1994

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Arsenic (inorganic) conducted in September 2002 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

__II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

_III. [reserved]
_IV. [reserved]
_V. [reserved]

_VI. Bibliography

Substance Name — Arsenic, inorganic
CASRN — 7440-38-2
Last Revised — 04/10/1998

_VI.A. Oral RfD References

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_VI.B. Inhalation RfD References

None

_VI.C. Carcinogenicity Assessment References

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_VII. Revision History

Substance Name — Arsenic, inorganic
CASRN — 7440-38-2

Date	Section	Description

06/30/1988	II.B.	Revised last paragraph
06/30/1988	II.C.1.	Inhalation slope factor changed
06/30/1988	II.C.3.	Paragraph 2 added
09/07/1988	II.B.	Major text changes
12/01/1988	II.A.2.	Mabuchi et al. citation year corrected
12/01/1988	II.A.3.	Pershagen et al. citation year corrected
09/01/1989	II.C.2.	Citations added to anacondor smelter
09/01/1989	VI.	Bibliography on-line
06/01/1990	II.A.2.	2nd and 3rd paragraph - Text revised
06/01/1990	II.A.4.	Text corrected
06/01/1990	II.C.1.	Inhalation slope factor removed (format change)
06/01/1990	IV.F.1.	EPA contact changed
06/01/1990	VI.C.	References added
12/01/1990	II.B.	Changed slope factor to "unit risk", 2nd para, 1st sen
02/01/1991	II.C.3.	Text edited
09/01/1991	I.A.	Oral RfD summary now on-line
09/01/1991	I.A.	Oral RfD bibliography added
10/01/1991	I.A.1.	Conversion factor text clarified
10/01/1991	IV.B.1.	MCLG noted as pending change
01/01/1992	IV.	Regulatory actions updated
08/01/1992	II.	Note added to indicate text in oral quant. estimate
10/01/1992	VI.C.	Missing reference added to bibliography
02/01/1993	I.A.4.	Citations added to second paragraph
02/01/1993	VI.A.	References added to bibliography
03/01/1993	VI.A.	Corrections to references
03/01/1994	II.D.2.	Work group review date added
06/01/1994	II.	Carcinogen assessment noted as pending change
01/01/1995	II.	Pending change note revised
01/01/1995	II.B.	Dates and document no. added to oral quant. estimate
06/01/1995	II.	Carcinogenicity assessment replaced
06/01/1995	VI.C.	Carcinogenicity references replaced
07/01/1995	II.D.1.	Documentation year corrected; review statement revised
07/01/1995	VI.C.	U.S. EPA, 1994 corrected to 1993
08/01/1995	II.D.2.	EPA's RfD/RfC and CRAVE workgroups were discontinued in May, 1995. Chemical substance reviews that were not completed by September 1995 were taken out of IRIS review. The IRIS Pilot

		Program replaced the workgroup functions beginning in September, 1995.
04/01/1997	III., IV., V.	Drinking Water Health Advisories, EPA Regulatory Actions, and Supplementary Data were removed from IRIS on or before April 1997. IRIS users were directed to the appropriate EPA Program Offices for this information.
04/10/1998	II.B.3	Added discussion on expert panel workshop
02/11/2000	II.C.2	Corrected alignment of unit risks in table with corresponding studies
12/03/2002	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.
02/05/2003	I., II.	This chemical is being reassessed under the IRIS Program.

_VIII. Synonyms

Substance Name — Arsenic, inorganic
CASRN — 7440-38-2
Last Revised — 02/10/1988

- 7440-38-2
- Arsenic
- Arsenic, inorganic
- gray-arsenic

IRIS Home

Chronic Health Hazards for Non-Carcinogenic Effects

Reference Dose for Chronic Oral Exposure (RfD)

- Oral RfD Summary
- Principal and Supporting Studies
- Uncertainty and Modifying Factors
- Additional Studies/Comments
- Confidence in the Oral RfD
- EPA Documentation and Review

Reference Concentration for Chronic Inhalation Exposure (RfC)

- Inhalation RfC Summary

- Principal and Supporting Studies
- Uncertainty and Modifying Factors
- Additional Studies/Comments
- Confidence in the Inhalation RfC
- EPA Documentation and Review

Carcinogenicity Assessment for Lifetime Exposure

Evidence for Human Carcinogenicity

- Weight-of-Evidence Characterization
- Human Carcinogenicity Data
- Animal Carcinogenicity Data
- Supporting Data for Carcinogenicity

Quantitative Estimate of Carcinogenic Risk from Oral Exposure

- Summary of Risk Estimates
- Dose-Response Data
- Additional Comments
- Discussion of Confidence

Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

- Summary of Risk Estimates
- Dose-Response Data
- Additional Comments
- Discussion of Confidence
- EPA Documentation, Review and, Contacts

Bibliography

Revision History

Synonyms