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Project Summary

Health Assessment Document for Inorganic Arsenic

Inorganic arsenic, predominantly the tri- and pentavalent forms, is emitted to the environment principally through primary smelting activity, biocide use, and glass manufacturing. Ambient air monitoring data indicate a concentration equal to or less than 0.1 $\mu g/m^3$ for most locations. Major routes of absorption of inorganic arsenic in the general population are inhalation and ingestion. Inhaled inorganic arsenic deposited in the lungs is eventually absorbed. Most ingested soluble inorganic arsenic is absorbed, whereas insoluble forms pass through the gastrointestinal tract with negligible absorption. Inorganic arsenic metabolism in man is complicated by biotransformation processes which include the methylation and oxidation reduction interconversion of inorganic arsenic. Long-term accumulation of inorganic arsenic does not generally occur in physiologically active compartments in the body; renal clearance appears to be the major route of excretion of absorbed inorganic arsenic. Acute symptoms of inorganic arsenic poisoning include severe gastrointestinal damage, facial edema, cardiovascular reactions, peripheral nervous system disturbances, and hematopoietic system effects. General population concerns arising from longterm exposures to moderate levels of inorganic arsenic include respiratory tract cancer, skin cancer, noncancerous skin lesions, peripheral neuropathological effects and cardiovascular effects. There appears to be a nutritional requirement for low levels of inorganic arsenic in certain experimental animals; however, this requirement has not yet been established in man.

This Project Summary was developed by EPA's Environmental Criteria and Assessment Office, Research Triangle Park, NC, to announce key findings of the research project that is fully documented in a separate report of the same title (see Project Report ordering information at back).

Introduction

As a toxic agent, inorganic arsenic possesses several unique properties. The element exists in various chemical states; e.g., tri- and pentavalent inorganic arsenic and methylated organic arsenic, with each having differing toxicological potential. In man, experimental animals, and other organisms, arsenic undergoes a variety of transformations, the full significance and mechanisms of which are, as yet, not well understood. Furthermore, there appears to be a nutritional requirement for low levels of arsenic in certain experimental animals, and this may also be the case for man. All of these factors complicate the analyses of the toxicological effects and the risk for human health associated with environmental exposure to arsenic compounds. The following sections summarize these factors which are presented in depth in the document text.

Chemical/Physical Aspects of Arsenic

Arsenic is encountered as a component of sulfidic ores of metals such as copper, cobalt, and nickel; the smelting of these ores is associated with arsenic release to the environment. Arsenic trioxide, As_2O_3, a toxicologically significant form, is a smelter product arising from air roasting of the sulfidic ores. It is only sparingly soluble in water and other solvents which do not promote chemical transformation. This arsenic compound dissolves in acidic or alkaline aqueous media to yield either the free acid or salts, soluble in a number of solvents. The oxide readily sublimes (135°C), a factor important in choosing analytical methods

for measuring levels of the compound. The pentavalent arsenic pentoxide, As_2O_5, may be prepared by nitric acid oxidation of the trioxide or the element itself. This form has high solubility in water (63 g/100 g water), forming the strongly oxidizing arsenic acid, H_3AsO_4 ($E^\circ = 0.56V$).

Stability of the valency forms of arsenic in solution depends on the nature of the medium. Oxygenated media and higher pH favor the pentavalent form, while reducing and/or acidic media favor the trivalent state.

The acids of both valency forms of arsenic readily form alkali and alkaline metal salts, with the former being more soluble than the latter. Organic ester derivatives of arsenic are quite labile to hydrolysis, and this chemical behavior has biochemical/toxicological implications in the postulated role of arsenate ion in interfering with phosphorylation reactions.

Arsine (arsenic trihydride, AsH_3) is the most poisonous of the arsenicals, being a strong hemolytic agent; it can be formed under certain restricted conditions, e.g., reduction of the oxy compounds in the presence of a strong hydrogen source.

Monomethyl and dimethyl arsenic arise by both environmental and *in vivo* transformation processes.

In high-temperature processes, arsenic is released as a vapor which is then adsorbed or condensed onto small particles. Such adherence to particles of 1-2 μm or less may result in enhanced health risk from the agent since particles in this size range are inhaled and deposited in the deepest part of the respiratory tract.

Arsenic compounds tend to form insoluble complexes with soils and sediments. In the case of soils, the interaction occurs with amorphous aluminum or iron oxides.

The Environmental Cycling of Arsenic

Primary smelting, biocide use, and glass manufacturing are major sources of arsenic in the environment. Of an estimated total release of approximately 10,000 short tons annually in the United States, smelter activity accounts for 50 percent; use of biocide (pesticide, fungicide, herbicide), 32 percent; and glass production contributes about 7.0 percent; various other sources release the remainder.

The atmosphere is a major conduit for arsenic emitted from anthropogenic sources via wet and dry precipitation processes to the other environmental media. Dry and wet arsenic falling on soils may be followed by movement through soils either into groundwater or surface water. Passage of arsenic into surface waters may be followed by its transfer to sediments. Such cycling is made complex by chemical and biological transformations, which have been reported as occurring in the various environmental compartments.

Trivalent arsenic in the atmosphere or in aerated surface waters can undergo oxidation to the pentavalent state, while pentavalent arsenic in media which are below pH 7.0 and contain oxidizable material can be reduced to the trivalent form.

Biological transformations of arsenic have been documented as occurring via both sedimentary bacteria and suspended marine algae. Reduction and mythylation of inorganic arsenic occur only to a limited extent in soils, one report noting a conversion of only 1-2 percent over a period of months.

The annual environmental burden of arsenic indicates that approximately 90 percent of arsenic is deposited on land, with the atmosphere accounting for eight percent and the smallest quantity deposited in waters.

Levels of Arsenic in Various Media

Available data on levels of arsenic in various media with which man interacts are generally presented as total arsenic, with limited information available for identifying specific chemical forms of arsenic.

Levels of Arsenic in Ambient Air

Based on the comprehensive data for U.S. air levels of arsenic obtained by the U.S. EPA's National Air Sampling Network, air levels of arsenic in the U.S. generally do not exceed 0.1 $\mu g/m^3$.

Generally, airborne arsenic adheres to particulate matter. Although the immediate areas around smelters may contain some arsenic in the vapor form, available data indicate rapid adherence to particulate matter when sampling 2-3 km from these emission sites.

The specific chemical form(s) of airborne arsenic is still unclear. Generally, in most urban/suburban areas, arsenic occurs mainly in the form of a mixture of inorganic arsenic in the tri- and pentavalent states. Only in areas where methylated arsenic is used agriculturally, or where biotic transformation can occur, has methylated arsenic been found in air samples.

Levels of Arsenic in Drinking Water

The National Interim Primary Drinking Water Regulations, promulgated under the Safe Drinking Water Act, set the Maximum Contaminant Level (MCL) for arsenic in U.S. public water supplies at 50 $\mu g/l$. I general, arsenic is not found in drinkin water at levels exceeding this MCL. We waters in the western U.S. and Alaska however, may have much higher levels ov ing to geochemical enrichment. In Lar County, Oregon, recent analyses repo levels up to 2.2 ppm (2.2 mg/liter), whi the highest figure in Alaska was 10 ppm (1 mg/liter), representing both natural an mining residue contributions.

It is reasonable to assume that the chi chemical form of arsenic in most publ water supplies would be the pentavalent i organic form, owing to both aeration an chlorination. Similarly, well waters i Alaska and the western U.S. are reporte to mainly contain pentavalent inorgan arsenic.

Arsenic in Food

The most recent data base for the arseni content of foods is the 1975-1976 surve carried out by the U.S. Food and Drug Ac ministration. Shellfish and other marir foods have the highest levels on a foo category basis. Overall, the total dietary i take of arsenic in 1975-1976 was appro imately 50 μg (elemental arsenic), repr senting an increase from the precedin years. Whether this increase represents trend or merely reflects analytical variatic in sampling from year to year is still to b determined.

The chemical forms of arsenic in fooc are varied and complex. Crustaceans ar other marine life store arsenic in comple organoarsenical forms which, based on r cent reports, are assimilated by man ar generally excreted intact. Toxicologicall these forms are comparatively inert.

Arsenic in Soils

Background soil arsenic levels ran from less than 1 ppm to over 40 ppm, th latter reflecting agricultural practices a well as air fallout. Soil arsenic is usual bound to clay surfaces, and its mobility is function of soil pH, phosphate levels, irc and aluminum content, and soil type. Th mobile fraction, usually in the pentavale form, is of concern in terms of moveme to plants and water. Little reducti methylation occurs in most soils.

Other Sources of Arsenic

Limited data on arsenic content of toba co suggest that more recent values ran from around 1.5 ppm or less, while in th past (1945), values up to 40 ppm we measured. This decrease reflects reduc use of arsenical biocides in tobacco produ tion.

Aggregate Exposure Levels to Arsenic in the U.S. Population

Among individuals of the general population (not occupationally exposed to arsenic), the main routes of exposure to arsenic are typically via ingestion of food and water, with lesser exposures occurring via inhalation. Representative intake figures are presented in Table 1. Intake by inhalation is augmented among smokers in proportion to the level of smoking.

Assuming a daily ventilation rate of 20 m^3, and a national population inhalation average of 0.006 $\mu g/m^3$/As, the total daily inhalation exposure for arsenic can be projected to be approximately 0.12 μg. Assuming 30 percent absorption, approximately 0.03 μg of arsenic would be absorbed on a daily average.

Contribution of tobacco-borne arsenic to the respiratory burden would depend upon the rate of cigarette smoking. Assuming a mass of 1 gram/cigarette and an average tobacco value of 1.5 ppm, this yields 1.5 μg arsenic/cigarette. With 20 percent of this amount in mainstream smoke, the inhaled amount for each pack of cigarettes would be approximately 6 μg arsenic, and of this amount, 40 percent would be deposited in the respiratory tract. Assuming an absorption of 75 percent of the deposited fraction, approximately 2 g/pack of cigarettes would be absorbed. This represents a factor of 10 to 100 times greater than intake for nonsmokers in given ambient air settings. The rates of absorption for trivalent and pentavalent arsenic in the respiratory tract are assumed to be equivalent.

Since drinking water arsenic is mainly in a soluble form (arsenate or arsenite), virtually all of it is absorbed in the GI tract. Thus, assuming an average daily consumption of two liters of water containing at most 10 μg As/liter as an outside high figure, it can be estimated that the total arsenic absorbed from drinking water would be approximately 20 μg/day. Most individuals would, in reality, take in much less than this amount, while those in the Western U.S. with well water supplies much higher in arsenic content would assimilate proportionately more.

Food arsenic values taken from the 1976 FDA survey indicate a daily total dietary intake of approximately 50 μg elemental arsenic. The major portion (80 percent) of food arsenic would be absorbed, resulting in a net daily food arsenic absorption of 40 μg total.

Thus, a nonsmoker would have a total daily absorption from all exposure media of approximately 60 μg arsenic/day or less. Of this, the diet would be the major contributor, assuming levels in water much below 10 μg/liter. For cigarette smokers, 2 μg/arsenic/pack of cigarettes smoked daily would have to be added.

Table 1. Routes of Daily Human Arsenic Intake

Route/Level	Rate	Total Intake	Absorbed Amount
Ambient air/0.006 $\mu g/m^3$ [a]	20 m^3	0.12 μg	0.036 μg [b]
Drinking water/$\leq$ 10 μg/liter	2 liters	$\leq$20 μg	$\leq$20 μg [c]
Food/50 μg daily (elemental As)	—	50 μg	40 μg [d]
Cigarettes/6 μg in mainstream smoke/pack [e]	½ pack	3 μg	0.9 μg [f]
	1 pack	6 μg	1.8 μg [f]
	2 pack	12 μg	2.7 μg [f]
Total: $\leq$ 60 μg nonsmokers			

[a] National Average for 1981.
[b] Assumes 30 percent respiratory absorption.
[c] Assumes total absorption.
[d] Assumes 80 percent absorption.
[e] Assumes 20 percent of cigarette content in inhaled smoke.
[f] Assumes 30 percent absorption of inhaled amount.

If aggregate intake is viewed not in terms of total arsenic intake but in terms of toxicologically significant forms of the element, then much of the dietary fraction, for reasons given earlier, such as complex organoarsenicals being present, becomes relatively less important than the forms in water and air as well as in cigarette smoke. Arsenic forms in such media include pentavalent arsenic in most water supplies, variable mixtures of tri- and pentavalent arsenic in ambient air, and probably an arsenic oxide in cigarette smoke. From this viewpoint, utilizing the examples already given above, nonsmokers would absorb 20 μg or less daily of toxicologically significant arsenic. Heavy smokers having otherwise very low air and water exposure, conceivably could receive their major exposure via cigarettes.

Significant Human Health Effects Associated With Ambient Exposure Acute Exposure Effects

Serious acute effects and late sequelae from exposure to arsenic will appear after single or short-term respiratory or oral exposures to large amounts of arsenic. Available data indicate that inorganic trivalent compounds of arsenic are generally more acutely toxic than inorganic pentavalent compounds, which in turn are more toxic than organic arsenic compounds. Serious effects will also appear after long-term exposure to respiratory or oral doses of arsenic.

The acute symptoms following oral exposure consist of gastrointestinal disturbances, which may be so severe that secondary cardiovascular effects and shock may result and cause death. Also, direct toxic effects on the liver, blood-forming organs, the central and pheripheral nervous systems, and the cardiovascular system may appear. Some symptoms, especially those from the nervous system, may appear a long time after exposure has ceased and may not be reversible, whereas the other effects seem to be reversible. Infants and young children especially are susceptible with regard to effects on the central nervous system. A Japanese study on milk poisoned with arsenic showed that persisting damage, especially mental retardation and epilepsy, is a late sequela in children of short-term oral exposure to large doses of inorganic arsenic. Among adults, the central nervous system is not as susceptible, but peripheral neuropathy has been a common finding.

Both in adults and children, acute oral exposure has resulted in dermal changes, especially hyperpigmentation and keratosis, as a late sequela.

Acute inhalation exposures have also resulted in irritation of the upper respiratory tract, even leading to nasal perforations.

Direct dermal exposure to arsenic may lead to dermal changes; allergic reactions may also be involved.

Chronic Exposure Effects

Both carcinogenic and non-carcinogenic effects are associated with long-term exposures, which do not cause any obvious immediate effects. Chronic effects germane to the general population can be ranked as follows:

1. Respiratory tract cancer
2. Skin cancer
3. Non-cancerous skin lesions
4. Peripheral neuropathological effects
5. Cardiovascular changes

Cancer of the respiratory system is clearly associated with exposure to arsenic via inhalation. This association has been especially noted among smelter workers where there is a consistency of findings across different studies in different countries, high relative risk, and dose-response by length and intensity of exposure. Excess risk of lung cancer has also been found among arsenical pesticide manufacturing workers. Based on this information, the Carcinogen Assessment Group (CAG) of the U.S. Environmental Protection Agency has concluded that there is sufficient evidence that inorganic arsenic compounds are lung carcinogens in humans.

Cancer of the skin was found to have a dose-related effect in a population in Taiwan who had lifetime exposure to arsenic in well water. Cancer of the skin has also been found among people treated with large doses of arsenite for skin disorders. The CAG has concluded that there is sufficient evidence that inorganic arsenic compounds are skin carcinogens in humans.

Hyperkeratosis and hyperpigmentation, sometimes with precancerous changes, have been a common finding in persons ingesting arsenic. These skin lesions, as well as the manifest cancer, develop on skin surfaces usually unexposed to sunlight. In studies in the United States, an association between skin lesions or skin cancer has not been demonstrated. These studies have been limited, however, by sample sizes too small to be able to detect the dose response seen in studies outside the U.S.

The effects on the peripheral nervous system range from sensory disturbances to motor weakness and even paralysis. The more severe signs have been noted in subacute poisonings, but more subtle changes after long-term low-level exposure have been found by using electromyography or measuring nerve conduction velocity. These subclinical effects are slow in recovery and may persist for years after cessation of exposure. In a study in Canada, electromyographic (EMG) changes were noted when water concentrations of arsenic exceeded 0.05 mg/l.

Cardiovascular effects have been noted especially in Taiwan, where Blackfoot disease (peripheral vasculopathy) occurred after long-term exposure to arsenic in well water. However, the presence of ergotamine-like compounds raises the possibility of vascular effects from these agents. Peripheral vascular changes were also found among German vintners who were exposed both occupationally, by spraying arsenic-containing pesticides, and orally, by drinking wine with elevated arsenic levels. Studies on occupationally exposed persons have been inconclusive in showing that arsenic causes an increase in mortality from cardiac disease.

Dose-Effect/Dose-Response Relationships

The general question of how to define and employ a dose factor in attempts at quantitative assessments of human health risk for any toxicant is highly dependent upon: 1) the available information on the body's ability to metabolize the agent, and 2) the assessment of the relative utility of various internal indices of exposure.

The time period over which a given total intake occurs is highly important. For example, intake of one gram of arsenic over a period of years would be quite different pathophysiologically from assimilating this amount at one time, the latter probably having a lethal outcome. This time-dependent behavior is related in part to the relative ability of the body to detoxify inorganic arsenic by methylation as a function of both dose and time.

In cases of acute and subacute exposure, indicators of internal exposure such as blood or urine arsenic levels are probably appropriate for assessing the intensity of exposure.

With chronic, low-level exposure, however, the available data would indicate that the total amount assimilated is probably more important than an indicator concentration without knowledge of the total exposure period. An added problem is the background level of arsenic found in these indicators due to dietary habits. For example, in acute exposures, levels in blood or urine would be greatly elevated over background values while low-level chronic exposures would only result in moderate increases over background.

In regard to hair arsenic levels as an indicator of internal arsenic exposure, no reliable methods exist for distinguishing external contamination levels from those accumulated via absorption and metabolic distribution. Hair arsenic levels cannot, therefore, be employed as reliable indicators of either current or cumulative long-term exposures for individual subjects, but rather may provide only a rough overall indication of group exposure situations.

Given the above considerations and limitations concerning the use of blood, urinary, or hair arsenic concentrations as internal indices of cumulative, long-term low-level arsenic exposures of concern here, the dose-effect/dose-response relationships summarized below are done so mainly in terms of external arsenic exposure levels v either inhalation or ingestion.

It is difficult to define a precise acut lethal dose of arsenic for man, becaus such exposure situations rarely allow ac curate determination of the effectiv amounts. However, for trivalent arseni the figure is believed to range from 70 t 180 milligrams.

For subacute exposure, it appears th for children, about one gram assimilate over a period of 3-4 weeks will induce deat with severe effects in survivors, while fc adults, that dose will occasion significar clinical effects. In one poisoning episod intake of approximately 50 milligrams over period as short as two weeks resulted i clinically demonstrable effects in adults.

From available data, the Carcinoge Assessment Group (CAG) has estimate carcinogenic unit risks for both air an water exposures to arsenic. The quar titative aspect of carcinogen risk asses ment is included here because it may be c use in setting regulatory priorities evaluating the adequacy of technology based controls, and other aspects of th regulatory decision-making process However, the imprecision of present available technology for estimating cance risks to humans at low levels of exposur should be recognized. At best, the linea extrapolation model used provides a roug but plausible estimate of the upper limit c risk—that is, with this model it is not likel that the true risk would be much more tha the estimated risk, but it could be cor siderably lower. The risk estimate presented below should not be regarded therefore, as accurate representations c true cancer risks even when the exposure involved are accurately defined. Th estimates presented may, however, be fa tored into regulatory decisions to the exter that the concept of upper-risk limits found to be useful.

The air estimates were based on dat obtained in five separate studies involvin three independently exposed worker pop ulations. Both linear and quadratic absc lute risk and relative risk models wer fitted to the data. It was found that for th models that fit the data at the $p = 0.01$ c better level, the corresponding unit ris estimates ranged from 1.05×10^{-4} to 1.3×10^{-2}. Linear models were found to f better than quadratic models, and absc lute risk models better than relative ris models. Restricting their unit risk est imates to those obtained from linea absolute risk models gave a range of 1.2×10^{-3} to 7.6×10^{-3}. A weighted average c the five estimates in this range gave composite estimate of 4.3×10^{-3}.

The unit risk estimates for water were based on an extensive drinking water study which was conducted in a rural area of Taiwan. An association between arsenic in well water and skin cancer was observed in the study population. Using the male population, who appeared to be more susceptible, the CAG estimated that the unit risk associated with drinking water contaminated with 1 $\mu g/l$ of arsenic was 4.3×10^{-4}.

To compare the air and water unit risks, the CAG converted the exposure units in both cases to mg/kg/day absorbed doses, which resulted in unit risk estimates of 50.1 and 15.0, respectively.

The potency of arsenic compared to other carcinogens was evaluated by noting that an arsenic potency of $2.25 \times 10^{+3}$ $(mMol/kg/day)^{-1}$ lies in the first quartile of the 52 suspect carcinogens that have been evaluated by the CAG.

The U.S. EPA is presently examining information from studies on both patient and general populations which have been exposed to arsenic via medicinals or drinking water, respectively, in order to determine whether quantitative dose-response relationships can be established for non-cancerous skin lesions.

While the qualitative evidence for peripheral neurological effects and cardiovascular changes in arsenic-exposed populations is well established, the data are insufficient for determining quantitative dose-response relationships at the present time.

Populations at Special Risk to Health Effects of Arsenic

From a Japanese study, which reported on the poisoning of children exposed to arsenic in infant milk formula, young children may be considered at risk for acute exposure to arsenic. From the clinical reports published at the time of the mass poisoning, as well as those from follow-up studies, a number of signs of central nervous system involvement were noted at both the time of the episode and much later, with the follow-up studies showing behavioral problems, abnormal brain wave patterns, marked cognitive deficits, and severe hearing loss.

Because children consume more water per unit body weight than do adults, the daily intake of arsenic via drinking water per kilogram body weight would be greater in children. This might have implications regarding chronic exposure effects in children. However, it should be noted that serious health effects due to chronic exposure of arsenic in drinking water have not been found at a greater frequency in children than adults.

Individuals residing in the vicinity of certain arsenic-emitting sources, e.g., certain types of smelters, may be at risk for increased arsenic intake because of both direct exposure to arsenic in air and indirect exposure via arsenic secondarily deposited from air onto soil or other human exposure media. The relative contribution from such indirect exposures to increased risk would be difficult to define, however.

A less defined group at risk would be cigarette smokers due to some arsenic in tobacco, but it is not clear just what the quantitative increase in risk would be.

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The complete report, entitled "Health Assessment Document for Inorganic Arsenic," (Order No. PB 84-190 891; Cost: $23.50, subject to change) will be available only from:

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