Chapter 6.1 Arsenic

General description

Arsenic (As) and its compounds are ubiquitous in nature and exhibit both metallic and nonmetallic properties. The trivalent and pentavalent forms are the most common oxidation states. From both the biological and the toxicological points of view, arsenic compounds can be classified into three major groups: inorganic arsenic compounds; organic arsenic compounds; and arsine gas. The most common trivalent inorganic arsenic compounds are arsenic trioxide, sodium arsenite and arsenic trichloride. Pentavalent inorganic compounds include arsenic pentoxide, arsenic acid and arsenates, e.g. lead arsenate and calcium arsenate. Common organic arsenic compounds are arsanilic acid, methylarsonic acid, dimethylarsinic acid (cacodylic acid) and arsenobetaine.

Arsenic trioxide is only slightly soluble in water; in sodium hydroxide it forms arsenite and with concentrated hydrochloric acid it forms arsenic trichloride. Sodium arsenite and sodium arsenate are highly soluble in water. Interchanges of valence state may occur in aqueous solutions, depending on the pH and on the presence of other substances which can be reduced or oxidized *(1)*.

Sources

Arsenic appears in nature primarily in the form of sulfides in association with the sulfides of ores of silver, lead, copper, nickel, antimony, cobalt and iron. Trace amounts of arsenic are found in soils and other environmental media.

Arsenic is mainly transported in the environment by water. In oxygenated water, arsenic usually occurs as arsenate, but under reducing conditions, for instance, in deep well-waters, arsenites predominate. In water, the methylation of inorganic arsenic to methyl- and dimethylarsenic acids is associated with biological activity. Some marine organisms have been shown to transform inorganic arsenic into more complex organic compounds, such as arsenobetaine, arsenocholine and arsoniumphospholipids. In oxygenated soil, inorganic arsenic is present in the pentavalent form. Under reducing conditions, it is in the trivalent form. Leaching of arsenate is slow because of binding to hydrous oxides of iron and aluminium. There is ample evidence of biomethylation in the soil and of the release of methylarsines into the air. However, airborne arsenic is mainly inorganic *(2)*.

Arsenic concentrations in uncontaminated soil are generally in the range 0.2–40 mg/kg *(2)*. However, levels of 100–2500 mg/kg have been found in the vicinity of copper smelters *(2,3)*. In the past, numerous arsenical pesticides were used widely and, as a result, arsenic concentrations of 200–2500 mg/kg occurred in the soil of orchards *(4)*.

Arsenic is released to the atmosphere from both natural and anthropogenic sources. The principal natural source is volcanic activity, with minor contributions by exudates from vegetation and wind-blown dusts. Man-made emissions to air arise from the smelting of metals, the combustion of fuels, especially of low-grade brown coal, and the use of pesticides *(5)*.

Global natural emissions have been estimated to be 7900 tonnes per year, while anthropogenic emissions are about three times higher, i.e. 23 600 tonnes per year *(6)*. Concentrations of arsenic in coal range from 1–10 mg/kg to 1500 mg/kg and in peat represent 16–340 mg/kg of dry mass *(2)*. These relatively high concentrations may result in substantial emission to air on combustion. White arsenic (arsenic (III) oxide) is principally obtained as a by-product in the smelting of copper, lead or gold ores. The arsenic then becomes gaseous and is collected on electrofilters, and serves as a basis for the manufacture of virtually all arsenicals.

World production of arsenic kept rising until about the mid-1940s (in 1943 it was estimated at some 70 000 tonnes annually). As arsenic pesticides, specifically insecticides, were gradually replaced by other preparations, the production of arsenic declined. World production of arsenic in 1975 was about 60 000 tonnes *(2)*. After 1985, arsenic trioxide was not produced in the United States of America and imports there rose to 33 000 tones in 1989 *(7)*. Arsenic is still used in the production of agricultural chemicals, although the amounts produced vary between countries, depending on the restrictions on this use that are in force (it is banned in the United States) *(8)*. Arsenic is an active component of antifungal wood preservatives (e.g. Wolman's salt, which contains 25% sodium arsenite). In the United States, 74% of arsenic is contained in products used for wood preservation *(7)*. It is also used in the pharmaceutical and glass industries, and in the manufacture of sheep-dips, leather preservatives and poisonous baits. Arsenicals are used in the manufacture of pigments while metallic arsenic is used in the manufacture of alloys. Gallium arsenide and indium arsenide are used in the production of certain semiconductor devices, such as field-effect transistors and microwave integrated circuits, and in optoelectronics.

Arsanilic acid and its derivatives 4-aminophenylarsonic and 3-nitro-4-hydroxyphenylarsonic acids are, in some countries, added to cattle and poultry feed at a concentration of 25–45 mg/kg for use as growth-stimulating agents *(9)*.

As a consequence of the many different uses of arsenic and arsenicals, there is a wide spectrum of situations in which humans may be exposed to this element.

Occurrence in air

Mean levels in ambient air in the United States range from <1 to 3 ng/m^3 in remote areas and from 20 to 30 ng/m^3 in urban areas *(7)*. Mean airborne concentration of arsenic in 11 Canadian cities and one rural site amounted to 1 ng/m^3 (range 0.5–17 ng/m^3) *(10)*. In England, the mean concentration was 5.4 ng/m^3, with a declining trend over the period 1957–1974 *(11)*.

Concentrations can reach several hundred nanograms per cubic metre in some cities and exceed 1000 ng/m^3 near nonferrous metal smelters *(2)* and some power plants, depending on the arsenic content in the coal that is burnt. For example, in Prague, airborne arsenic concentrations reported in the past were found to average 450 ng/m^3 in winter and 70 ng/m^3 in summer *(12)*.

Arsenic in air is present mainly in particulate forms as inorganic arsenic. It is assumed that methylated arsenic is a minor component in the air of suburban, urban and industrial areas, and that the major inorganic portion is a variable mixture of the trivalent and pentavalent forms *(9)*, the latter being predominant.

Analytical methods in air

Several methods for the collection and quantitative determination of arsenic in air have been developed.

Air samples can be collected on a cellulose acetate filter, porosity 0.8 µm, pretreated with sodium carbonate and glycerol 12 hours before use. A collection efficiency for the treated filters for arsenic trioxide dust and fumes exceeding 95% has been confirmed *(13)*. Arsine can be collected in solid sorbent tubes filled with coconut shell charcoal. A cellulose ester filter in front of a charcoal-filled tube may be used to remove aerosols *(14)*.

The molybdenum blue and silver diethyldithiocarbamate methods are two reasonably good quantitative colorimetric methods which have a limit of detection in the range of 1–50 µg/litre in a 5-ml solution. Neutron activation analysis (NAA) has a detection limit of 0.1 ng for total arsenic. Proton-induced X-ray emission (PIXE) analysis, with a detection limit of 0.1 mg/kg, has been used for simultaneous determination of arsenic and a number of other elements *(1)*. Atomic absorption spectrometry (AAS) is at present commonly used to determine arsenic in air in both the occupational and general environment. Electrothermal (ET-AAS) *(14)* and arsine generation (AG-AAS) techniques *(3,13)* have also been applied. AG-AAS has a detection limit of 200 ng/litre in a 5-ml solution *(15)*.

Routes of exposure

Air

Particulate arsenic compounds may be inhaled, deposited in the respiratory tract and absorbed into the blood. Inhalation of arsenic from ambient air is usually a minor exposure route for the general population. Assuming a breathing rate of 20 m^3/day, the estimated daily intake may amount to about 20–200 ng in rural areas and 400–600 ng in cities without substantial industrial emission of arsenic.

Tobacco smoke may contain arsenic, especially when the tobacco plants have been treated with lead arsenate insecticide. Although the use of arsenic pesticides is now prohibited in most countries, the natural content of arsenic in tobacco may still result in some exposure. It is estimated that the arsenic content of mainstream cigarette smoke is in the range 40–120 ng per cigarette. If consumption is 20 cigarettes per day, the daily intake from this source would amount to 0.8–2.4 µg *(10)*.

Occupational exposure to arsenic occurs primarily among workers in the copper smelting industry *(16)*, at power plants burning arsenic-rich coal *(9)*, and using or producing pesticides containing arsenic *(1)*. Inhalation exposure to arsenic can also take place during production of gallium arsenide in the microelectronics industry *(17)*, demolition of oil-fired boilers *(18)* and metal ore mining *(19)*.

Drinking-water

Drinking-water may contribute significantly to oral intake in regions where there are high arsenic concentrations in well-water or in mine drainage areas. More common drinking-water sources generally contain arsenic at concentrations of less than 10 µg/litre. The concentrations in groundwater depend on the arsenic content of the bed-rock. Unusually high levels have been reported in carbonate spring waters in New Zealand, Romania, the Russian Federation and the

United States (0.4–1.3 mg/litre), in artesian wells in Taiwan, China (up to 1.8 mg/litre) and in groundwater in Cordoba, Argentina (up to 3.4 mg/litre). In oxygenated water, arsenic occurs in pentavalent form, but under reducing conditions the trivalent form predominates *(2)*.

Flocculation treatment, using either aluminium or ferric salts, removes a high proportion, at least of pentavalent arsenic *(2)*.

Food

With the exception of some kinds of seafood, most foods contain low levels of arsenic, normally less than 0.25 mg/kg. Marine organisms may contain large amounts of organo-arsenicals (e.g. arsenobetaine). These arsenic derivatives are not acutely toxic because of their low biological reactivity and their rapid excretion in urine. Concentrations in seafood amount to 2.4–16.7 mg/kg in marine fish, 3.5 mg/kg in mussels *(20)* and more than 100 mg/kg in certain crustaceans *(1)*. Wine made from grapes sprayed with arsenic pesticides may contain appreciable levels of arsenic (up to 0.5 mg/litre) in the trivalent inorganic form *(10)*.

The amount of arsenic ingested daily by humans via food is greatly influenced by the amount of seafood in the diet. The intake in Japan, where the diet has a large seafood component, is higher than that in Europe and the United States (Table 1). The diet in Japan was found to contain 5.7–17% inorganic arsenic, 1.1–3.6% monomethylarsonate (MMA), 6.6–27% dimethylarsinate (DMA) and 47.9–75.2% arsenobetaine *(23)*.

Other routes of exposure

Certain pharmaceutical products contain arsenic (e.g. Fowler solution, which contains 1% potassium arsenite) and, for some individuals, the exposure from these source can be significant *(24)*. Soil and dust in the vicinity of copper smelters can contain arsenic in high concentrations .

Relative significance of different routes of exposure

In the general environment, the oral route constitutes the main route of absorption of arsenic (Table 1). In occupational exposures, arsenic is absorbed mainly through the lungs.

Table 1. Estimated daily intake of arsenic by the general population

Route	Daily intake (µg/day)	Reference
Air		
Rural areas	0.02–0.20	*(7,10,12)*
Cities	0.4–0.6	*(7)*
Food		
United States	60	*(21)*
Belgium	45	*(22)*
Canada	7 (inorganic)	*(10)*
Japan	126–273	*(23)*
Soil/dirt	0.14–0.28	*(10)*
Tobacco smoking (20 cigarettes	0.7–2.1	*(10)*
per day)	6	*(23)*

Population groups at higher probability of exposure

There are three population groups at high exposure risk: the occupationally exposed, people drinking water with abnormally high concentrations of arsenic, and children living in the close vicinity of copper smelters.

In the case of occupational exposure, workers employed in copper smelters where concentrations of arsenic in the air can range from 0.01 to 68 mg/m^3 represent the group with the highest health risk *(14,25)*. Unexpectedly high exposure (0.054 and 1.3 mg/m^3) was found in workers during the demolition of oil-fired boilers *(18)*.

Blackfoot disease and cancers of the skin, lung, bladder, kidney, liver and colon have been documented among residents of Taiwan, China, who consume arsenic-contaminated well-water *(24,26,27)*.

In the close vicinity of copper smelters, the soil can be heavily contaminated with arsenic. Around smelters in Butte and Anaconda, United States, more than 6500 acres are considered to be contaminated, with arsenic levels in the soil of more than 90 mg/kg *(28)*. Near a smelter in San Luis Potosi, Mexico, median concentrations of arsenic in soil and dust were 502 and 857 mg/kg. The median concentration of arsenic in the urine of children living nearby was 196 µg/g of creatinine (range 69–594 µg/g of creatinine). Arsenic in the soil could contribute from 30% to 88% of the total amount ingested *(3)*.

Toxicokinetics

Absorption

The major routes of arsenic absorption in the general population are ingestion and inhalation.

Human and animal data indicate that over 90% of the ingested dose of dissolved inorganic trivalent or pentavalent arsenic is absorbed from the gastrointestinal tract. Organic arsenic compounds in seafood are also readily absorbed (75–85%). Absorption of less soluble forms, e.g. arsenic trioxide, is much lower *(1)*. The bioavailability of arsenic in soil contaminated by smelter activities, following oral administration in rabbits, is about 25% *(29)*.

Factors affecting the extent of absorption from the lungs include the chemical form, particle size and solubility. Particles of more than 10 µm in aerodynamic diameter are predominantly deposited in the upper airways (nasopharynx), particles of between 5 and 10 µm are deposited in the airways cleansed by mucociliary action, and particles with diameters of less than 2 µm penetrate significantly into the alveoli. Airborne arsenic is usually in the form of arsenic trioxide. More than 23% of the particles in samples of arsenic-polluted air in occupational settings were reported to be larger than 5.5 µm *(30)*. Analysis of arsenic in airborne fly ash from coal-fired power plants indicated that 76% of the arsenic was recovered from particles with a diameter of less than 7.3 µm *(31)*.

In eight terminal lung cancer patients exposed to arsenic in cigarette smoke, deposition was estimated to be about 40% and absorption was 75–85% *(32)*. Thus, overall absorption (as a proportion of the inhaled dose) was about 30–35%. In workers exposed to arsenic trioxide dusts in

smelters, the amount of arsenic excreted in urine was about 40–60 % of the estimated inhaled dose *(7)*.

Distribution

Blood is the main vehicle for the transport of arsenic following absorption, and arsenic is cleared relatively rapidly from it. Arsenic movement from the blood appears to conform to a three-compartment model, which must reflect in part the biomethylation of inorganic arsenic.

In humans, information on tissue-partitioning is mainly available from autopsy data. The muscles, bones, kidneys and lungs have the highest absolute amounts of arsenic, but skin and excretory/storage organs, such as nails and hair, have the highest concentrations. Transplacental transfer of arsenic appears to occur in humans. This finding is based on autopsy data and on reports showing that blood levels in the cords of neonates approximate those of their mothers *(2)*. Data on the effects of valency and exposure level on the tissue distribution of arsenic indicate that levels of arsenic in the kidneys, liver, bile, brain, skeleton, skin and blood are 2–25 times higher for the trivalent than for the pentavalent form and are greatly increased at higher doses *(9)*. Autopsy data from retired metal-smelter workers, obtained several years after cessation of occupational exposure, showed that arsenic levels in the lung were eight times higher than in a control group *(33)*. This suggests the existence of arsenic compounds of very low solubility in the smelter environment.

Metabolism and elimination

Trivalent inorganic arsenic is oxidized *in vivo* in animals and humans exposed to arsenite. The opposite reaction, the reduction of arsenate to arsenite, has also been demonstrated in mice and rabbits. Both arsenite and arsenate, after reduction to arsenite, are methylated in the liver. Both methylated species, MMA and DMA, are considered to be less toxic and to bind less to tissues, and are eliminated more rapidly than the unmethylated form. There is a great variation between species in the urinary excretion of the different arsenic metabolites. The marmoset monkey is the only species which has been shown to be unable to methylate inorganic arsenic. The low urinary excretion of methylated arsenic metabolites in the rat is not an indication of low methylating capacity, but is due to the specific retention of DMA in the erythrocytes. An interesting feature is that only humans excrete significant amounts of MMA following exposure to inorganic arsenic. The rabbit seems to be the species most similar to humans with regard to the methylation of arsenic *(34)*. In human volunteers who ingested a single oral dose of arsenic (500 µg) either as sodium arsenite, MMA or DMA, the excretion rate increased in order, inorganic arsenic (In-As)<MMA<DMA *(35)*. Assuming that methylation is the detoxifiyng mechanism for In-As, it has been suggested that when uptake exceeds a certain value, the methylation mechanism becomes saturated, and its efficiency declines as exposure increases. However, analysis of excretion of In-As, MMA and DMA in the urine of different groups of people, nonexposed, occupationally exposed and volunteers, did not support this methylation threshold hypothesis. On average, 20–25% of In-As remains unmethylated regardless of exposure level. In population groups receiving background exposure, 21%, 15% and 64% of the arsenic was excreted as In-As, MMA and DMA, respectively (average urinary arsenic concentration 4.4–57.2 g/litre). Respective values in an occupationally exposed group (average urinary arsenic concentration 10.2–245 µg/litre) were 19%, 15% and 65% *(36)*. According to Offergelt et al. *(13)* occupational exposure to concentrations of up to 300 µg/m^3 does not inhibit the methylation of arsenic.

After oral intake in humans of radiolabelled pentavalent arsenic, 66% was excreted with a half-time of 2.1 days, 30% with a half-time of 9.5 days and 3.7% with a half-time of 38 days *(37)*. In another human experiment, following an arsenic dose of 3 mg in the form of sodium arsenite, 48% of the dose was excreted within five days with a biological half-life of 30 hours. Arsenobetaine present in seafood is apparently not metabolized *in vivo* and is eliminated rapidly via the kidneys (half-time 18 hours) *(38)*.

Biomarkers of exposure

After exposure to inorganic arsenic, the only significant arsenic species excreted in urine are In-As, MMA and DMA. In non-occupationally exposed subjects, the sum of the concentration of the three metabolites in urine is usually less than 10 µg/g of creatinine. For occupational exposures, significant (logarithmic scales) correlation was found between airborne time-weighted average exposure to arsenic trioxide at arsenic concentrations of 6–502 µg/m^3 and the inorganic arsenic metabolites in urine collected immediately after a shift, or just before the next shift. At a concentration of 50 µg/m^3, the mean concentration of arsenic derived from the sum of the three inorganic arsenic metabolites in a postshift urine sample was 55 µg/g of creatinine *(13)*.

AG-AAS is the method of choice for biological monitoring of exposure to inorganic arsenic because it allows the simultaneous determination of In-As, MMA and DMA, eliminating the possible influence of organo-arsenicals, such as arsenobetaine, of dietary origin *(38)*. Recent data suggest, however, that because of possible direct release of DMA from organo-arsenicals during digestion, it is still justified to instruct workers to refrain from eating marine organisms for at least 48 hours before urine is collected for the assessment of exposure to inorganic arsenic *(20)*.

Health effects

Effects on experimental animals and *in vitro* test systems

There has been no consistent demonstration of carcinogenicity in test animals for various chemical forms of arsenic administered by different routes to several species *(4,39)*. There are some data to indicate that arsenic may produce animal tumours if retention time in the lung is increased *(40)*. Two studies suggest a positive interaction between arsenic trioxide and benzo[*a*]pyrene in relation to pulmonary tumours, but the evidence is not conclusive *(40,41)*. According to the International Agency for Research on Cancer, there is inadequate evidence for the carcinogenicity of arsenic compounds in animals *(4,39)*.

Arsenic is clastogenic and induces sister chromatid exchanges in a variety of mammalian cells *in vitro (42)*; trivalent arsenic is approximately one order of magnitude more potent than pentavalent arsenic *(43)*. Sodium arsenite caused a slight increase in chromosomal aberrations in the bone-marrow cells of mice treated *in vivo (4)*.

Several studies have suggested that inorganic arsenic affects DNA repair mechanisms and acts as a co-mutagen in bacterial test systems by inhibiting the repair of damage to DNA caused by another agent *(44)*.

At relatively high exposure levels, arsenic is teratogenic in a number of animal species, including hamster, rat and mouse *(1)*. Such effects have generally been observed after parenteral

administration of either arsenite or arsenate. Oral exposures have not produced any notable effects on reproduction or development.

Effects on humans

Toxicological effects

The clinical picture of chronic poisoning with arsenic varies widely. It is usually dominated by changes in the skin and mucous membranes and by neurological, vascular and haematological lesions. Involvement of the gastrointestinal tract, increased salivation, irregular dyspepsia, abdominal cramps and loss of weight may also occur. Reports of diminished sexual activity in persons with chronic arsenic exposure are frequent *(1,2)*.

Arsenic and its inorganic compounds have long been known to be neurotoxic. Peripheral neuropathy in arsenic smelter workers has been reported. Chronic exposure to arsenic dust caused a decrease in peripheral nerve conduction velocities *(45)*.

The skin is a common critical organ in people exposed to inorganic arsenical compounds. Eczematoid symptoms develop with varying degrees of severity. Hyperkeratosis, warts and melanosis of the skin are the most commonly observed lesions in chronic exposure.

Increased mortality from cardiovascular diseases has been observed in epidemiological investigations of smelter workers exposed to high levels of airborne arsenic. A peripheral vascular disorder leading to gangrene of the extremities, known as blackfoot disease, has been observed.

Inorganic arsenic has an inhibitory effect on haematopoiesis, giving rise to anaemia, most commonly of the hypoplastic type. In severe cases of arsenical poisoning, agranulocytosis or thrombopenia may develop.

An increased rate of spontaneous abortions and lower mean birth weights has been reported among Swedish smelter workers and among subjects living in the vicinity of the smelter. The rate of congenital malformations in the offspring of women working at the smelter was also higher. However, it is not possible to link these effects with exposure to any specific compound in the smelter environment *(1,2)*. The United States Environmental Protection Agency (EPA), considering hyperpigmentation, keratosis and possible vascular complications (blackfoot disease) as the critical effects, accepted the value of 0.3 µg/kg per day (no-observed-adverse-effect level (NOAEL) 0.009 mg/litre, converted to 0.0008 mg/kg per day; uncertainty factor 3) as the reference dose in the case of human chronic oral exposure *(46)*.

Carcinogenic effects

There is sufficient evidence that inorganic arsenic compounds are skin and lung carcinogens in humans *(4,39)*.

Several studies show that exposure to inorganic compounds can increase the risk of lung cancer in smelter workers, those involved in the production of arsenic-containing pesticides and metal ore miners *(16,25,47–56)*. The data often indicate positive dose–response relationships. Both trivalent and pentavalent arsenic compounds have occurred in these exposure situations and at present the possibility cannot be ruled out that any form of inorganic arsenic may be carcinogenic. Results of

studies on the interaction between inorganic arsenic and smoking are conflicting: one study provided evidence of a multiplicative interaction *(57);* according to another, the interaction between arsenic and smoking was intermediate between additive and multiplicative and appeared to be less pronounced among heavy smokers *(58)*.

Some investigations of populations living near copper smelters and other point sources of arsenic emission to the air have revealed moderate increases in lung cancer mortality *(59–61)*. Other studies have failed to detect an effect in such situations *(62,63)*. Significantly elevated standard mortality ratios for cancer of the bladder, lung, liver, kidney, skin and colon were found in the population living in an area of Taiwan, China where arsenic contamination of the water supply was endemic *(24,26,64)*. Lung cancer is considered as the critical effect following exposure via inhalation. Consequently, cancer at other sites, e.g. skin cancer, will not be discussed in detail here. An increased frequency of chromosomal aberrations has been found in peripheral blood lymphocytes of wine-growers exposed to arsenic, in psoriasis patients treated with arsenic, and in arsenic-exposed copper smelter workers. Sodium arsenate inhibits DNA repair in human skin biopsy cells and in lymphocytes *(2)*.

Evaluation of human health risks

Exposure

There are many arsenic compounds, both organic and inorganic, in the environment. Airborne concentrations of arsenic range from 1 ng/m^3 to 10 ng/m^3 in rural areas and from a few nanograms per cubic metre to about 30 ng/m^3 in noncontaminated urban areas. Near emission sources, such as nonferrous metal smelters and power plants burning arsenic-rich coal, concentrations of airborne arsenic can exceed 1 µg/m^3.

Health risk evaluation

Inorganic arsenic can have acute, subacute and chronic effects which may be either local or systemic. Lung cancer is considered to be the critical effect following inhalation. An increased incidence of lung cancer has been seen in several occupational groups exposed to inorganic arsenic compounds. Some studies also show that populations near emission sources of inorganic arsenic, such as smelters, have a moderately elevated risk of lung cancer. Information on the carcinogenicity of arsenic compounds in experimental animals was considered inadequate to make an evaluation *(6, 39)*.

A significant number of studies concerning occupational exposure to arsenic and the occurrence of cancer have been described. Unit risks derived by the EPA Carcinogen Assessment Group in 1984 *(9)* were not changed until 1994 *(46)*. They form five sets of data involving two independently exposed worker populations in Montana and Tacoma smelters in the United States, ranging from 1.25×10^{-3} to 7.6×10^{-3}, a weighted average of these five estimates giving a composite estimate of 4.29×10^{-3}.

Table 2. Updated unit risk estimates

		Estimated unit risk		
Risk update	**Smelter population**	**Study**	**Cohort**	**Pooled unit risk**
Pooled estimate using updated Swedish and Tacoma cohorts	Tacoma 1987	1.28×10^{-3}	1.28×10^{-3}	$\}1.07 \times 10^{-3}$
	Ronnskar, 1989			
	– workers hired pre-1940	0.46×10^{-3}	0.89×10^{-3}	
	– workers hired post-1939	1.71×10^{-3}		
Updated Tacoma cohort with original EPA estimates for Montana cohort	Tacoma 1987 (updated results supersede earlier estimates)	–	1.28×10^{-3}	$\}1.28 \times 10^{-3}$
	Montana 1984 (EPA) (new estimates not available, 1984 EPA estimates apply)	–	2.56×10^{-3}	
Pooled across all smelter cohorts	Ronnskar, 1989	–	0.89×10^{-3}	
	Tacoma, 1987	–	1.28×10^{-3}	$\}1.43 \times 10^{-3}$
	Montana, 1984 (EPA)	–	2.56×10^{-3}	

Source: Viren & Silvers *(65)*.

A WHO Working Group on Arsenic *(2)* conducted a quantitative risk assessment for arsenic, assuming a linear relationship between the cumulative arsenic dose and the relative risk of developing lung cancer. Risk estimates for lung cancer from inorganic arsenic exposure were based on the study by Pinto et al. *(49)* of workers at the Tacoma smelter. The lifetime risk of lung cancer was calculated to be 7.5×10^{-3} per microgram of airborne arsenic per cubic metre.

The second study relating to the quantitative risk assessment included a large number of the 8047 males employed as smelting workers at the Montana copper smelter *(48)*. Exposure to airborne arsenic levels were estimated to average 11.17, 0.58 and 0.27 mg/m^3 in the high-, medium- and low-exposure areas. Unit risks for these three groups were calculated to be 3.9×10^{-3}, 5.1×10^{-3} and 3.1×10^{-3}, respectively.

Assuming that the risk estimation based on the Tacoma study was higher because of the urine measurements made, it may have underestimated the actual inhalation exposure; the unit risk was considered to be 4×10^{-3}.

In 1994, Viren & Silvers *(65)*, using updated results from the cohort mortality study in the Tacoma smelter workers together with findings from a cohort study of 3619 Swedish smelter workers, developed other unit risk estimates. A unit risk of 1.28×10^{-3} was estimated for the Tacoma smelter cohort and 0.89×10^{-3} for the Swedish cohort. Pooling these new estimates with the EPA's earlier estimates from the Montana smelter yielded a composite unit risk of 1.43×10^{-3} (Table 1). This value is three times lower than the EPA estimate *(46)* and two times lower than the value assumed in the 1987 edition of *Air quality guidelines for Europe (64)*.

Guidelines

Arsenic is a human carcinogen. Present risk estimates have been derived from studies in exposed human populations in the United States and Sweden. When assuming a linear dose–response relation, a safe level for inhalation exposure cannot be recommended. At an air concentration of 1 $\mu g/m^3$ an estimate of lifetime risk is 1.5×10^{-3}. This means that the excess lifetime risk level is 1:10 000, 1:100 000 or 1:1 000 000 at an air concentration of about 66 ng/m^3, 6.6 ng/m^3 or 0.66 ng/m^3, respectively.

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