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A review of the toxicity of arsenic in air

Science Report – SC020104/SR4

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Author(s):
Maud, J. & Rumsby, P.

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Environment Agency's Project Manager:
Jackie Maud, Science Department

Collaborator(s):
WRc NSF Ltd,
Henley Road,
Medmenham,
Marlow,
Bucks,
SL7 2HD.
Tel: + 44 (0) 1491 636500

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- **Delivering information, advice, tools and techniques**, by making appropriate products available to our policy and operations staff.

Steve Killeen

Head of Science

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Search strategy

A search for existing reviews was carried out from the following organisations:

Organisation/Review	Year
IEH Health Effects review: Review of incineration	2003
DEFRA/Environment Agency Contaminants in Soil: CLR TOX report - arsenic	2002
EU Risk Assessment Reports	-
WHO (Air Quality Guidelines for Europe)	2000
EC Working Group on As, Cd and Ni compounds, Position Paper	2000
ATSDR Toxicological Profiles	2000
US EPA (IRIS)	2001
HSE Toxicity Reviews	1989
CoC/CoT (not located)	-
CSTEE	2001
IARC Monographs	1987
WHO/IPCS (Environmental Health Criteria 224)	2001
JECFA	-
Health Effects Institute (HEI)	-
National Toxicology Program (NTP- NIEHS)	-

A search of the primary literature (from 2002 to the present) for the following search terms was undertaken in the PubMed, ToxLine, Medline and NIEHS – Environmental Health Perspectives websites;

“arsenic and health”

“arsenic and air”

“arsenic and toxic*”

“arsenic and epid*”

“arsenic and toxic* and human*”

“arsenic and epid* and air*”

It should be noted that the primary study references are cited in this document for the benefit of EPAQS members to aid their deliberations. They have not been specifically referred to during the preparation of the writing of this document, which is based on the reviews listed above.

Background

Arsenic is a metalloid with a complex chemistry, which can form a number of inorganic and organic compounds.

Inorganic arsenic occurs in many minerals and is widely found in rocks, soils and sediments. It can exist in several oxidation states, the most common being the pentavalent and trivalent forms. In minerals, the highest arsenic concentrations generally occur as the sulphide or oxide, or as the arsenides of copper, lead, silver or gold. The most important commercial compound, arsenic (III) oxide (also known as arsenic trioxide), is produced as a by-product in the smelting of copper and lead ores. A variety of arsenates (AsO_4^{3-}, pentavalent arsenic) and arsenites (AsO_3^{3-}, trivalent arsenic) are found in water, soil and food.

The organic chemistry of arsenic is extensive. Methylated arsenic compounds, such as di- and trimethylarsines, occur naturally in the environment as a result of biological activity. In water, these may undergo oxidation to methylarsinic acids, for example monomethylarsinic acid (MMA) and dimethylarsinic acid (DMA). However, the biomethylated forms of arsenic produced are subject to bacterial demethylation back to inorganic forms.

Currently, the principal use of arsenic (as arsenic trioxide) is in wood-preserving products. Otherwise it is used in agricultural chemicals, such as insecticides, herbicides, algicides and growth promoters. Smaller amounts are used in the production of some glasses and non-ferrous alloys, and in the electronics industry.

Arsenic is released into the general environment from a variety of natural and anthropogenic sources. On a global scale, releases to the air from natural sources such as volcanic eruptions and forest fires, and releases to water from weathering or leaching of arsenic-rich rocks and soils, may be the dominant sources. On a local scale, releases as a result of human activity, such as coal burning, industrial waste disposal, the application of agricultural chemicals containing arsenic, or the burning of wood treated with arsenic-containing preservatives, are likely to be more important (Department for Environment, Food and Rural Affairs (Defra) and Environment Agency, 2002).

Most of the toxicological literature on arsenic is based on oral exposure via drinking water, with few studies using inhalation as the route of exposure. Many of the human studies are related to some highly arsenic-polluted areas (such as Bangladesh and Taiwan) and the European Scientific Committee on Toxicity, Ecotoxicity and Environment (CSTEE) (2001) suggests that food and drinking water are the principal routes of exposure, with the exception of some industrial workers, and states the following calculated values for percentage of absorbed daily dose of inorganic arsenic:

Air	<1%
Cigarette smoke	0-16%
Drinking water	0-33%
Food	50-98%

However, CSTEE (2001) states that although air is not an important route of exposure in quantitative terms, it may be significant toxicologically since a principal site for

carcinogenicity is the lung. Furthermore, airborne levels of arsenic are ultimately likely to affect the levels of arsenic in food. Consequently, regulating ambient air levels of arsenic may affect concentrations of arsenic in food.

In the atmosphere, arsenic exists as particulate matter, mostly less than 2 µm in diameter. These particles are transported by air currents until they return to the ground via wet or dry deposition, where a certain amount of resuspension may occur (European Commission, 2000). However, an early occupational study suggests that 23 per cent of particles in samples of arsenic-polluted air were greater than 5.5µm (Pinto *et al*., 1953).

There are various ambient air concentrations given for arsenic in literature. Bertorelli and Derwent (1995, cited in Defra and Environment Agency, 2002) report annual average concentrations in the range of 5 - 10 and 1 - 5 ng/m^3 arsenic in urban and rural areas, respectively in the UK. The World Health Organization (WHO) (2000) suggests concentrations of arsenic range from 1 - 10 ng/m^3 in rural areas, 3 - 30 ng/m^3 in non-contaminated urban areas, and can exceed 1 µg/l near emission sources (WHO, 2000: cited in Institute of Environment and Health (IEH), 2003). Schroeder *et al*. (1987) also report concentrations of 0.007 - 1.9 ng/m^3 in remote areas, 1 - 28ng/m^3 in rural locations and 2 – 2320 ng/m^3 in urban environments, with the highest concentrations occurring in the vicinity of non-ferrous-metal smelters.

1 Introduction

Any discussion of the toxicity of arsenic is complicated by the fact that arsenic can exist in several different oxidation states, and in many different inorganic and organic compounds. Most data on the human toxicity of arsenic are associated with exposure to inorganic arsenic compounds. The most common inorganic compounds in water, soil and food are probably arsenites and arsenates. A number of studies indicate that arsenites are generally the more toxic, but the differences in toxicity are usually small (a factor of two or three). Other inorganic arsenic compounds are expected to be approximately as toxic as, or less toxic than, the oxy compounds (Agency for Toxic Substances and Disease Registry (ATSDR), 2000). Organic arsenic compounds are generally considered to be less toxic than inorganic compounds, and those that accumulate in fish and shellfish (mainly arsenobetaine and arsenocholine, sometimes referred to as “fish arsenic”) have been shown to be virtually non-toxic.

Most laboratory animal species appear to be much less susceptible to arsenic toxicity than humans. For example, monkeys, dogs or rats, exposed to chronic oral doses of arsenic that would produce neurological or haematological effects in humans, showed no such effects (ATSDR, 2000). Furthermore, although there is good evidence that arsenic is carcinogenic to humans by both the inhalation and oral routes, the evidence for laboratory animals is mostly negative.

1.1 Toxicokinetics

1.1.1 Absorption

The extent of absorption of arsenic particles from the lungs depends upon the chemical form, particle size and solubility (WHO, 1997). Particle size and solubility are the main determinants of the fractional deposition and the fractional transfer of the deposited material to the systemic circulation, respectively. Studies on workers exposed to arsenic trioxide in smelters suggest that about half the inhaled arsenic is deposited (Defra and Environment Agency, 2002). Particles greater than 10µm are mainly deposited in the upper airways; 5-10µm particles can be cleansed by mucociliary transport, and it is particles <2 µm that are able to penetrate into the alveoli (WHO, 1997).

Autopsy data from retired smelter workers obtained several years after retirement, showed arsenic levels in the lungs at eight times higher than a control group. This suggests the existence of very low solubility arsenic compounds (WHO, 1997). Environment Agency, 2002). It appears as though Cr(VI) compounds have greater transfer rates than Cr(III) compounds (Defra and Environment Agency, 2002).

1.1.2 Distribution

Following absorption, arsenic is rapidly distributed throughout the body via the blood circulation. Autopsy data suggests that muscles, bones, kidneys, liver and lungs accumulate the highest absolute amounts; however skin, nails and hair have the highest concentrations (EC, 2000). Analysis of arsenic levels in nails, hair and urine have been used as biomarkers for exposure.

1.1.3 Metabolism

Two processes are involved in the metabolism of arsenic in humans: reduction and oxidation reactions, which interconvert arsenate and arsenite; and methylation reactions, which convert arsenite to monomethylarsinic acid (MMA) and dimethylarsinic acid (DMA) in the liver. These processes appear to be same whether exposure is by inhalation, oral or parenteral routes.

Most of the reviews claim that this process is an important form of detoxification and that the methylated species are less toxic than the inorganic forms. However, in recent years, research into the metabolism and biological effects of arsenic has profoundly changed the understanding of the role of metabolism. These effects are discussed in a number of papers, the most relevant of which are included below.

Styblo *et al*. (2002) conclude that there is new compelling evidence that biomethylation is a process which activates arsenic as a toxin and carcinogen. The production of methylated trivalent arsenic in particular, has been associated with a variety of adverse effects that have a profound impact on cell viability or proliferation. Known effects include the inhibition of several key enzymes, damage to DNA structure and activation of AP-1-dependent gene transcription.

Schoen *et al*. (2004) suggest that there is evidence that arsenic's trivalent methylated metabolites may induce comparable or greater toxicity than inorganic arsenic. However, there is limited evidence that these metabolites are present in sufficient quantities or for sufficient length of time to induce toxicity at target locations.

Other very recent studies published on biomethylation and the toxicity of metabolites include Yamanaka *et al.* (2004) and Wanibuchi *et al*. (2004). These studies present data confirming the carcinogenicity of dimethylarsenic acid (DMA), a major metabolite of ingested inorganic arsenics in mammals. Both studies also indicate that the adverse effects of arsenic may occur by initiation or promotion of carcinogenesis in a number of organs. Wanibuchi *et al*. also present data confirming DMA as a complete carcinogen in the rat urinary bladder at drinking water concentrations of 10 - 1000ppm over an exposure period of two years (Wanibuchi *et al*., 2004).

1.1.4 Elimination

Most ingested inorganic arsenic is rapidly cleared from blood and excreted in the urine as inorganic arsenic or methylated arsenic (Health and Safety Executive (HSE), 2002b). Trace amounts of arsenic are incorporated in hair and nails. In terms of inhalation, a number of studies support the suggestion that urinary excretion of arsenic accounts for some 30-60 per cent of the inhaled dose (Holland *et al*., 1976; Pinto *et al*., 1976; Vahter *et al*., 1986; cited in ATSDR, 2000, WHO, 1997; cited in EC, 2000). As the deposition fraction also ranges from 30-60 per cent, it is suggested that nearly all arsenic that is deposited in the lung is excreted in the urine (US Environmental Protection Agency (EPA), 1989; cited in ATSDR, 2000).

Elimination appears to be fairly rapid, with both human and animal studies reporting significant decreases within days. Vahter (1986, cited in ATSDR, 2000) found that urinary levels of arsenic rose and fell over around the weekend when smelter workers weren't working; and rats showed a half-life whole body clearance of arsenic in less than one day (Rhoads and Sanders, 1985, cited in ATSDR, 2000).

2 Acute effects

There are few reports on the acute toxicity of arsenic via inhalation.

ATSDR (2000) suggests that no cases of mortality from exposure to arsenic in air have been reported. There are no other data on effects of acute inhalation exposures to arsenic in humans.

Acute lethal doses for oral exposure in humans estimated from poisoning incidents range from 70-190 mg arsenic (arsenic trioxide) (Vallee *et al.*, 1960, cited in Defra and Environment Agency, 2002) and 200-300 mg (Winship, 1984, cited in Defra and Environment Agency, 2002). An acute fatal dose of ingested arsenic trioxide for humans between 1-2.5 mg/kg bw has also been reported (WHO, 1981).

Ingestion of large doses can result in effects in 30-60 minutes, with the main effect being gastrointestinal damage leading to decreased blood volume, lowered blood pressure and electrolyte imbalance. These effects may lead to multiple organ failure and death.

3 Sub-chronic effects

There are no data reported on the sub-chronic effects of arsenic in humans.

In a single animal study, four out of nine pregnant rats died after 30-35 days exposure to 20 mg As/m^3 (Holson *et al*., 1999, cited in ATSDR, 2000).

High-dose acute and sub-chronic toxicity are reported to result from arsenic cytotoxicity. Reduced inorganic arsenic [As^{+3}] reacts strongly with sulfhydryl groups in proteins and inactivates many enzymes. Particular targets in the cell are the mitochondria, which accumulate arsenic (Goyer and Clarkson, 1991). Arsenic inhibits succinic dehydrogenase activity and can uncouple oxidative phosphorylation; the resulting fall in ATP levels affects virtually all cellular functions.

4 Chronic effects

Arsenic has been shown to be associated with various chronic effects in humans, including irritation of the respiratory system, respiratory disease, vascular disease, hypertension, diabetes, 'blackfoot disease' skin lesions, neurological effects, and cardiovascular disease. The majority of evidence for the chronic inhalation effects comes from occupational studies in smelter workers; however, there are also epidemiological studies of people living in the vicinity of these smelters. The effects of chronic oral exposure to arsenic, particularly 'blackfoot disease', have been intensively studied in a population in Taiwan where arsenic levels in drinking well water ranged from 0.01 to 1.82 mg/l.

Exposure to arsenic dusts may cause irritation of the mucous membranes of the nose and throat, possibly leading to laryngitis, bronchitis or rhinitis. Exposure levels of approximately 0.1-1 mg/m^3 appear to cause minor or unobservable effects, but the data are insufficient to set a No Observed Adverse Effect Level (NOAEL) (EC, 2000).

In a short review on the toxicity of arsenic, IEH (2003) discussed the effects of inhalation of arsenic compounds and the potential damage to the respiratory system. The review highlighted the following specific epidemiological studies:

Copper smelter workers exposed to a concentration not exceeding 0.5mg/m^3 arsenic. Changes in the nasal mucosa and signs of tracheobronchitis and pulmonary insufficiency were observed (WHO, 1981).

Copper smelter workers exposed to <13 µg/m^3 arsenic. Liver damage was implied due to elevated levels of the liver enzymes glutamate transaminase and lactate dehydrogenase in serum (WHO, 1981).

The WHO air quality guidelines report cases of peripheral neuropathy in arsenic smelter workers, where exposure to arsenic dust at a concentration of approximately 50 µg/m^3 resulted in a decrease in peripheral nerve conduction velocities (Lagerkvist & Zetterlund, 1994, cited in WHO, 2000).

The EC Working Group Position Paper discusses the effects of chronic exposures to arsenic. The studies reported in this review are summarised in Table 1.

Table 1 Summary chronic effects from EC Working Group Position Paper (2000)

Effect	Details	Exposure level	Reference	Year
Respiratory tract	Irritation of mucous membranes; laryngitis, bronchitis or rhinitis – effects minor or absent at exposure level.	0.1-1 mg/m^3	ATSDR	1998
Nervous system	Peripheral neuropathy in arsenic smelter workers.	50 µg/m^3	Lagerkvist and Zetterlund	1994
Cardiovascular	Smelter workers' exposure to arsenic dust – higher incidence of Raynaud's disease and increased constriction of blood vessels in response to cold.	50-500 µg/m^3	Lagerkvist *et al*.	1986 1988

Arsenic has also been implicated in chronic effects from the burning of high-arsenic-containing coal (containing 100-9000 mg/kg) in China. Coal is burned inside the home in open pits for daily cooking and crop drying, resulting in arsenic-contaminated indoor air (20-400 µg/m^3). Effects include skin lesions, lung dysfunction, neuropathy, nephrotoxicity, hepatomegaly, cirrhosis and liver cancers, and some 200,000 people are thought to be at risk (Liu *et al*., 2002). Sun (2004) also reported these effects, but quoted arsenic concentrations of 160-760 µg/m^3 and refers to these effects as a serious environmental chemical disease known as "arsenicosis". These effects are also seen at lower coal-arsenic contents of 56-42 mg/kg with Shraim *et al.* (2003) reporting that over 30 per cent of study subjects burning coal in residences show symptoms of arsenicosis. However, specific air concentrations of arsenic were not stated.

The ATSDR Toxicological Profile (ATSDR, 2000) summarised the non-cancer effects of arsenic exposure in experimental animals. These results are outlined in Table 2 (taken from ATSDR, 2000).

Table 2 Levels of significant exposure to inorganic arsenic – inhalation (ATSDR, 2000)

Species	Exposure duration/ frequency	System	NOAEL	LOAEL (less serious) mg/m3	LOAEL (serious) mg/m3	Reference
Rat	14 d; pre-mating through Gd 19; 7d/wk, 6hr/d	respiratory	2	8 (rales, dried red material around nose)		Holson *et al.*, 1999
		body weight	2	8 (decreased body weight gain during gestation)		
Rat	14 d; pre-mating through Gd 19; 7d/wk, 6hr/d	respiratory	0.9	8	20 (laboured breathing, gasping)	Holson *et al.*, 1999
		gastro	8		20 (gross intestinal lesions)	
		body weight	8		20 (drastic decrease in body weight)	
Rat	4 wk; 5d/wk; 3hr/d		0.126	0.245 (decreased pulmonary bactericidal activity)		Aranyi *et al*., 1985
Human	23 yr (av)	cardio			0.36 (increased incidence of vasospasticity and clinical Raynaud's syndrome)	Lagerkvist *et al*., 1986
Human	6-8 yr (8hr/day)	dermal		0.007 (dermatitis)		Mohamed, 1998

Species	Exposure duration/ frequency	System	NOAEL	LOAEL (less serious) mg/m3	LOAEL (serious) mg/m3	Reference
Human	0.5-50 yr	respiratory	0.613			Perry *et al*., 1948
Human	0.5-50 yr	dermal		0.078 (mild pigmentation keratosis of the skin)		Perry *et al.,* 1948
Human	28 yr (av)			0.31 (decreased nerve condition velocity)		Lagerkvist and Zetterlund, 1994

It must be noted that animals do not appear to respond to arsenic toxicity in the same way as humans. However, the search for suitable animal models continues. A recent animal study investigated the systemic uptake of inhaled arsenic in rabbits at exposure levels of 0.05, 0.1, 0.22 or 1.1 mg/ m^3 for eight hours a day, seven days a week over a period of eight weeks. Significant increases in inorganic levels of arsenic in the plasma were only observed at the higher exposure levels (0.22 mg/m^3 and 1.1 mg/m^3). The study authors concluded that there was negligible impact of airborne arsenic to rabbits unless ambient levels were significantly elevated (Beck *et al*., 2002).

5 Genotoxicity

The genotoxicity of arsenic has been researched extensively. Although there appears to be some disagreement, the weight of evidence indicates that arsenic is genotoxic.

Although the UK Department for Environment, Food and Rural Affairs and the Environment Agency report several negative results obtained in assays to investigate gene mutation, they conclude that inorganic arsenic compounds have a clear mutagenic potential with evidence of clastogenicity in *in vitro* studies involving mammalian cells, *in vivo* assays in bone marrow of mice and limited evidence for effects in humans (Defra and Environment Agency, 2002).

The EU Scientific Committee on Toxicology, Ecotoxicity and the Environment (CSTEE, 2001) concluded that arsenic is genotoxic both *in vitro* and *in vivo*, and there is also evidence to suggest that it is genotoxic to humans. The Committee added that there was insufficient evidence to conclude that there is a threshold level below which arsenic would not induce cancer in humans, implying all routes of exposure could cause harm (CSTEE, 2001).

The ATSDR toxicological profile (ATSDR, 2000) concludes that although results are mixed, inorganic arsenicals appear to be either inactive or weak mutagens, but that they are able to produce chromosomal effects in most systems. A higher than average incidence of chromosomal aberrations in peripheral lymphocytes is found after both inhalation (Beckman *et al*., 1977; Nordenson *et al*., 1978; cited in ATSDR, 2000) and oral exposure (Burgdorf *et al*., 1977; Nordenson *et al*.,1979; cited in ATSDR, 2000).

The EC Working Group (EC, 2000) discusses a review of the dose-response relationships observed in arsenic genotoxicity assays published by Rudel *et al*. (1996). With the exception of sister chromatid exchanges, sublinear dose-response relationships for arsenic (V)-induced chromosomal aberrations were observed repeatedly in different mammalian and human cell systems. For arsenic (III) effects, sublinearity is questionable. Arsenic also enhanced the clastogenicity and mutagenicity of other DNA-damaging agents with a sublinear dose response.

In 1994, the UK CoC (Committee on Carcinogenicity of Chemicals in Food, Consumer products and the Environment) considered arsenic in drinking water and concluded that “inorganic arsenic compounds have clastogenic potential and are human carcinogens”. They also stated “it is prudent, in the absence of further data, to assume that they are genotoxic carcinogens and that there is no threshold for such effects” (cited in Defra and Environment Agency, 2002).

The genotoxicity of organic arsenicals has not been well studied, however some tests suggest that DMA may be capable of causing mutations and DNA strand breaks (EC, 2000).

Szymanska-Chabowska *et al.,* (2002) reports that the probable mutagenic activity and proved carcinogenicity caused by clastogenesis in peripheral lymphocytes and sister chromatid exchange are one of the most important aspects of arsenic toxicity. The paper goes on to state that arsenic’s carcinogenic activity results mainly from inhalation exposure.

One paper states that arsenic is not mutagenic and does not directly interact with DNA (Schoen *et al*., 2004).

Chromium contact hypersensitivity is the main form of sensitisation that occurs, and has been reported for both the general population and occupational settings (Defra and Environment Agency, 2002). Symptoms seen include erythema, swelling, papules, small vesicles, dryness, scaling, fissuring (Adams, 1990; MacKie, 1981 both cited in US EPA, 1998a), dermatitis (a diffuse erythematous type, which may progress to an exudative stage) and eczema, as well as the primary irritation and ulceration effects (WHO, 1988). It is thought that Cr(VI)-related allergic contact dermatitis occurs in less than 1 per cent of the general population (Defra and Environment Agency, 2002), which is a slight underestimation compared to that of Paustenbach *et al.* (1992). These authors estimate chromium (VI) skin sensitisation in the general population in North America to be 1.6 per cent (Paustenbach *et al.*, 1992 cited in CEPA, 1994). Items responsible for the reaction in the general population include Cr(VI) in tattoo pigments, tanned leather and matches (Defra and Environment Agency, 2002). Water soluble Cr(VI) compounds are also responsible for cases of occupational allergic contact dermatitis (Defra and Environment Agency, 2002). Occupational causes include dichromate-containing detergent and bleach, welding, printing, glues, wood ash, foundry sand, match heads, machine oils, timber preservative, boiler linings, manufacture of television screens, magnetic tapes, tyre fitting, chrome plating, the wood and paper industries and milk testing (Wahba and Cohen, 1979; Burrows, 1983 both cited in WHO, 1988).

HSE states that respiratory sensitisation is a critical effect, which occurs at ambient concentrations, but especially so at occupational levels (HSE, 2002; WHO 1987 cited in IEH, 2003). Indeed, inhaled occupational exposure to chromium compounds is a well known cause of asthmatic attacks in humans (US EPA, 1998a; ATSDR, 2000; WHO, 1988). These attacks can last for 24-36 hours without treatment (Langard and Norseth, 1979 cited in WHO, 1988), and can recur with subsequent exposures to much lower concentrations (US National Academy of Sciences, 1974 cited in WHO, 1988). However, ATSDR states that the number of sensitised individuals is low and the evidence for chromium being the direct cause of occupational respiratory sensitisation is weak (ATSDR, 2000).

6 Carcinogenicity

Arsenic has been classified as carcinogenic to humans by the International Agency for Research on Cancer (IARC) (Group 1) and by the US EPA (Group A), (IARC, 1987; US EPA, 2001). Lung cancer in particular is implicated in arsenic exposure by inhalation and is considered to be the critical effect. This conclusion is supported by various investigations involving smelter workers in the USA, Sweden, and Japan. There is also evidence for an increased risk of lung cancer in people living near industries where arsenic is emitted. It is also important to note that only inorganic arsenic is clearly implicated as a carcinogen; there are no studies concerning cancer in humans from the ingestion or inhalation of organic arsenic (Defra and Environment Agency, 2002).

The human evidence on cancer and arsenic exposure centres on detailed epidemiological studies on workers in three copper smelters. The works are in Rönnskar in Sweden, Tacoma in Washington and Anaconda in Montana, both in the USA (see Table 3 for references). These studies indicated an increased risk of respiratory cancers in workers exposed to arsenic over time, and unit risk estimates for increased lung cancer per 1µg/m^3 air exposure to arsenic have been calculated and updated with time. The data for the three smelters have been pooled and a composite unit risk for cancer risk estimate for arsenic has been produced (see Table 3). These studies have been discussed in a number of different reviews (EC, 2000; WHO, 2000; IEH, 2003; ATSDR, 2000) and the figure has been used in the WHO Air Quality Guidelines for Europe (WHO, 2000) and in the Index Dose for inhalation produced by Defra and the Environment Agency (2002).

The different occupational studies on copper smelter works are outlined in Table 3 below (EC, 2000).

Table 3 Summarised studies following occupational exposure to arsenic

Site	Exposure level	Unit risk estimate* (per 1µg/m^3)	Reference
Tacoma smelter, WA	50 µg/m^3 (over 25 years)	7.50 x 10^{-3}	Pinto *et al*., 1977
Tacoma smelter, WA	-	7.20 x 10^{-3}	Enterline and Marsh, 1982
Tacoma smelter, WA	-	1.28 x 10^{-3}	Enterline *et al*., 1987
Anaconda smelter, Montana	11.27 µg/m^3 (heavy) 0.58 µg/m^3 (medium) 0.27 µg/m^3 (light) (over 15 years)	3.90 x 10^{-3} 5.10 x 10^{-3} 3.10 x 10^{-3}	Lee-Feldstein, 1983
Rönnskar smelter, Sweden	0.05 mg/ m^3 0.15 mg/ m^3 0.30 mg/ m^3	3.77 x 10^{-3} 3.10 x 10^{-3} 2.40 x 10^{-3}	WHO, 1994
Pooled estimate based on Tacoma, Montana and Rönnskar estimates	-	1.50 x 10^{-3}	Viren and Silvers, 1994

Notes: * Unit Risk Estimate: The risk estimate for lifetime exposure to a concentration of arsenic of 1 µg/m³.

Arsenic inhalation may also be associated with other cancers. Copper smelter workers have been shown to have an increased risk of stomach cancer and possibly bone

cancer and kidney cancer (Enterline *et al*., 1995; cited in EC, 2000), and Lagerkvist and Zetterlund (1994) found an increase in the risk of colon cancer amongst Swedish smelter workers (cited in EC, 2000).

6.1 Lung cancer in the vicinity of arsenic-emitting industry

The WHO (2001) reported moderate increases in lung cancer mortality in populations living near copper smelters and other point sources of arsenic (Blot *et al*., 1975; and Matanoski *et al*., 1981, cited in WHO, 2001). Pershagen (1985, cited in WHO, 2001) reported a relative risk of 2.0 for lung cancer amongst men living up to 20 km from a copper smelter in Sweden, which could not be explained by smoking or occupational background. However, this effect is not observed in other studies (Greaves *et al*., 1981 and Rom *et al*., 1982, cited in WHO, 2001).

Various studies are described in the WHO/IPCS Environmental Health Criteria review (WHO, 2001). Seven out of 12 studies reviewed showed little or no evidence of a positive association between lung cancer and residential exposure to arsenic emissions (Frost *et al*., 1987; Greaves *et al*., 1981; Pershagen *et al*., 1977; Pershagen, 1985; Rom *et al*., 1982 and Marsh *et al*., 1997 and 1998, cited in WHO, 2001). The remaining studies (Blot & Fraumei, 1975; Brown *et al*., 1984; Cordier & Multigner, 2005; Matanoski *et al*., 1981; Xu *et al*., 1989) found some increased evidence for elevated risks of lung cancer. The review noted that epidemiological studies designed to detect lung cancer risk and other health effects in communities surrounding arsenic-producing smelters usually have insufficient statistical power to detect small increases in risk that may occur (Hughes *et al.,* 1988).

Schoen *et al.* (2004) summarised various epidemiological studies of populations exposed to arsenic. A Belgian study concluded that moderate exposure to arsenic via drinking water and smelter emissions (annual mean concentration of 0.3µg/m^3) was not associated with an increased cancer risk (Buchet and Lison, 1998, cited in Schoen *et al.*, 2004). Tollestrup (article in press, cited in Schoen *et al.*, 2004) reported that childhood exposures to arsenic from a copper smelter in Ruston, WA did not result in increased rates of bladder or lung cancer during adulthood. Additionally, a 1987 study of the same area found no evidence of increased lung cancer risk to women living near the smelter, (Frost *et al*., 1987, cited in Schoen *et al.*, 2004). No arsenic concentrations were quantified in this study. Schoen *et al.* (2004) concluded that current epidemiological studies provide evidence that the dose-response relationship for carcinogenicity of arsenic is nonlinear and that current approaches that use linear extrapolation may overestimate arsenic cancer risk for US populations.

Bessö *et al*., (2003) conducted a case-control study of deceased men and women who had lived in the vicinity of the Rönnskar smelter and had been diagnosed with lung cancer. Arsenic concentrations were stated to be 0.5µg/m^3 as a weekly average, but some weeks exceeded 1µg/m^3. The findings, although not significant, indicated an increased risk of lung cancer among men, especially those that were exposed at the beginning of operations (1930). No overall increased risk of lung cancer was observed among women.

The EC Position Paper (EC, 2000) discussed investigations of populations living near smelters and concluded that these studies lacked reliable exposure data and that they were not adequate to confirm or disprove any association between ambient exposure to arsenic and health effects, especially cancer.

7 Reproductive and developmental effects

The available literature indicates that exposure to arsenic via the air can have reproductive and developmental effects.

The IEH review (2003) suggested that several epidemiological studies found associations between increased spontaneous abortions, still births and foetal mortality, lowered birth weight and congenital malformations and arsenic in drinking water, air-borne dust and smelter environments; but that there was no consistent evidence for any specific end-point (DeSesso *et al*., 1998; WHO, 2001, cited in IEH, 2003).

The Defra and Environment Agency document highlighted an epidemiological study of a population living in the vicinity of a copper smelter (Zelikoff *et al.*, 1995, cited in Defra and Environment Agency, 2002). In this study, the concentration of arsenic in the placenta, the incidence of pregnancy complications and the rate of mortality at birth due to congenital malformations were all significantly higher in the smelter area. However, it was not possible to suggest a LOAEL or NOAEL from this study. The report also suggests that developmental effects are unlikely to be of concern at levels lower than those that cause maternal toxicity.

In animal experiments, arsenic compounds have been found to be fetotoxic and teratogenic. The common developmental effects seen include malformations of the brain, uro-genital organs, skeleton, ear and small or missing eyes (Tchounwou *et al*., 2004).

The results of various experimental animal studies are included in Table 4 below (taken from ATSDR, 2000).

Table 4 Reproductive toxicity data for exposure of experimental animals to arsenic (ATSDR, 2000).

Species	Exposure duration/ frequency	NOAEL (mg/m^3)	LOAEL (serious) mg/m3	Reference
Rat	14 d; pre-mating through Gd 19; 7d/wk, 6hr/d	8		Holson *et al.*, 1999
Rat	14 d; pre-mating through Gd 19; 7d/wk, 6hr/d	20		Holson *et al.*, 1999
Rat	14 d; pre-mating through Gd 19; 7d/wk, 6hr/d	8		Holson *et al.*, 1999
Rat	14 d; pre-mating through Gd 19; 7d/wk, 6hr/d	8	20 (marked increase in post-implantation loss and marked decrease in viable foetuses	Holson *et al.*, 1999
Human	NS	5.5E-5	0.0007 (increased risk of stillbirth)	Ihrig *et al*., 1998

8 Evaluation and recommendations by other authoritative bodies

The following text summarises the air quality evaluations by various organisations that have reviewed the toxicology of arsenic.

WHO Air Quality Guidelines for Europe

As a known human carcinogen, the WHO has not recommended safe levels for inhalation exposure.

The WHO has considered lung cancer to be the critical effect after inhalation of arsenic, and as such has based its air quality guideline on unit risk estimates, specifically the pooled unit risk estimates on the three copper smelting works mentioned in Section 7 and in other evaluations (Rönnskar in Sweden, Tacoma in Washington and Anaconda in Montana in the USA) to yield a composite unit risk of 1.43×10^{-3} (see Table 3).

The WHO states that, assuming a linear-dose response relationship, a safe level for inhalation exposure cannot be recommended, and has quoted that at an air concentration of 1µg/m^3 the estimate of lifetime risk is 1.5×10^{-3}. This translates to an excess lifetime risk of 1×10^{-4}, 1×10^{-5} and 1×10^{-6} at an air concentration of 66 ng/m^3, 6.6 ng/m^3 or 0.66 ng/m^3 respectively.

Defra and Environment Agency

The Defra and the Environment Agency (2002) have recently adopted an Index Dose for inorganic arsenic derived from both oral and inhalation studies (ID_{oral} and ID_{inh}) for the purposes of deriving a Soil Guideline Value for contaminated land. The Index Dose represents a dose that poses a minimal risk level from possible exposure to a particular chemical, with the additional requirement that exposure from all routes needs to be as low as reasonably practicable (ALARP), so that even this minimal risk is further diminished. It was considered that there was clear evidence of carcinogenic and genotoxic potential for inorganic arsenic and as such there was no threshold of effect, so an Index Dose rather than a tolerable daily intake (TDI) was derived.

Defra and the Environment Agency derived the ID_{inh} for arsenic based on the WHO air quality guideline of 6.6 ng/m³ for a 1×10^{-5} excess lifetime lung cancer risk (WHO, 2000). Here, assuming a 70kg adult inhales 20 m³ air per day, the ID_{inh} is calculated to be 0.002 µg/kg bw/day.

EC Working Group on Arsenic, Cadmium and Nickel compounds

The EC Position Paper on Ambient Air Pollution from arsenic, cadmium and nickel (2000) has derived a limit value for both non-cancer and cancer effects (EC, 2000).

Non-cancer effects: this limit is based on a LOAEL of 0.50 µg/l (irritation of upper respiratory tract, peripheral neuropathy and cardiovascular effects and increased blood pressure).

Uncertainty factors of 5, 10 and 10 have been applied to this LOAEL (to account for chronic exposure of the general population; to extrapolate from a LOAEL to a NOAEL and to account for variability within the human population).

Therefore a limit value for non-cancer effects has been proposed of 100 ng As/m^3).

Carcinogenic effects: the report discusses the "unit risk approach" and the "threshold approach" to setting limits. Here the UK (threshold) approach takes the midpoints of the lowest dose levels from the Rönnskar and Anaconda cohort studies on copper smelter workers (125 µg/m^3 x years and 415 µg/m^3 x years). In fact, the latest Defra and Environment Agency evaluation of arsenic took the 'unit risk approach', which has been accepted by Department of Health as good quality human epidemiology data, rather than a threshold approach (Defra and Environment Agency, 2002).

Safety factors were applied to obtain a level at which one would expect that increased risks would be difficult to detect in a reasonably sized epidemiology study, to adjust for the general population and to account for sensitive groups (factors of 10, 4.5 and 10 respectively).

This resulted in a proposed limit value of 4-13 As ng/m^3**.**

The European Environment Bureau (EEB), however, regards a value of 3 As ng/m^3 as a suitable future revision of the 4-13 ng/m^3 figure following the discussion on the genotoxicity of arsenic.

Industry argued that a limit value of 50 As µg/m^3 would provide sufficient protection with respect to cancer and non-cancer endpoints (EC, 2000).

UK Health and Safety Executive

The HSE has set a maximum exposure limit (MEL) long-term exposure limit (eight-hour TWA) reference period of 0.1mg/m^3 for arsenic and its compounds. This number was based on a figure that was considered to be well below that at which raised incidence of respiratory tract cancer had been observed and below the no effect level for respiratory tract irritation (HSE, 2002b).

US Environmental Protection Agency

The US EPA IRIS database details the Reference Dose for chronic oral exposure (RfD) and Reference Concentration for chronic inhalation exposure (RfC) for various chemicals based on non-cancer effects (US EPA, 2001). These reference values are an estimate 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, and modified to take account of various uncertainty factors (UF).

Although an RfD has been determined for arsenic (0.3 µg/kg bw day per day), an RfC is currently not available. Table 5 lists the NOAELs considered during the derivation of the RfD.

Table 5 NOAELS derived from various studies (Defra and Environment Agency, 2002)

Study	NOAEL (µg/kg bw per day)	Reported adverse effect used to derive NOAEL
Tseng (1977)	0.8	Skin lesions
Cebrian *et al.* (1983)	0.4	Skin lesions
Southwick *et al.* (1983)	0.9	Skin lesions
Hindmarsh *et al.* (1977)	0.7	Neurological effects

ATSDR – Toxicological Profile: Arsenic (ATSDR, 2000)

The ATSDR toxicological profile for arsenic has not determined an inhalation Minimal Risk Level (MRL). However, the profile indicates that the effects of greatest concern are lung cancer, respiratory irritation, nausea and skin problems. A single LOAEL of 0.1 mg As/m³ was reported for skin changes in humans, but due to a lack of supporting data, no conclusions were made.

WHO/IPCS (Environmental Health Criteria) Document (WHO, 2001)

This review did not derive any health protection guideline value for arsenic. However, it does provide a brief conclusion that occupational exposure to airborne arsenic is causally related to lung cancer, and that cumulative exposure to a level greater than or equal to 0.75 mg/m^3 is associated with an increased risk of lung cancer.

9 Key studies

Non-cancer endpoints

The EC Working Group Position Paper (EC, 2000) highlighted two key studies in proposing a LOAEL for non-cancer endpoints. Lagerkvist and Zetterlund (1994) found exposure to arsenic dust at 50µg/m^3 led to a significant decrease in peripheral nerve conduction velocity. These results supported an earlier study by Blom *et al.* (1985), which observed effects at the same concentration.

Cancer endpoints

The key studies identified in the evaluations of Defra and the Environment Agency, WHO and others are those on the copper smelting works: Rönnskar in Sweden, Tacoma in Washington and Anaconda in Montana in USA (Enterline and Marsh, 1982; Enterline *et al*., 1987, 1995; Pinto et al., 1977; Lee-Feldstein, 1983; Viren & Silvers, 1994). There have been a series of studies over time on cancers in these workers and the unit risk estimates for lung cancer have been updated with time. The WHO has pooled these data and produced a composite unit risk, and this figure has been used in their Air Quality Guidelines for Europe (WHO, 2000) and in the Index Dose for inhalation produced by Defra and the Environment Agency (2002).

In the evaluation by European Commission Working Group, two studies are highlighted for what the Group called 'the UK threshold approach to setting a Limit Value for arsenic'. Järup *et al*. (1989) discusses the Rönnskar cohort and takes a midpoint dose level of 125µg/m^3 x years (<250µg/m^3 x years) and Lee-Feldstein (1986) reports on the Anaconda cohort with a midpoint taken as 415µg/m^3 (<10µg/m^3 x months or <833µg/m^3 x years). However, the UK used a risk estimate approach when setting an Index Dose for inhalation of arsenic for use in deriving a Soils Guidance Value, rather than a threshold approach.

10 Preliminary evaluation of data for EPAQS

There are enough human data on exposure by inhalation upon which to set a guideline value for arsenic. All the evaluations to date have used the studies on workers exposed to airborne arsenic in copper smelters in Sweden and the USA. These data have been used to derive lifetime unit cancer risks for each site, and these results have been pooled to give a composite unit risk of 1.5×10^{-3} per µg/m^3. This translates to an excess lifetime risk of 1×10^{-4}, 1×10^{-5} and 1×10^{-6} at an air concentration of about 66 ng/m^3, 6.6 ng/m^3 or 0.66 ng/m^3 respectively. These are figures given by the WHO in its Air Quality Guidelines for Europe (WHO, 2000).

The Environment Agency and Defra have recently evaluated the data for arsenic (Defra and Environment Agency, 2002) and derived an Index Dose for inhalation ($ID_{inh)}$ for arsenic based on the WHO air quality guideline of 6.6 ng/m³ for a 1×10^{-5} excess lifetime lung cancer risk. Here, assuming a 70kg adult inhales 20 m³ air per day, the ID_{inh} was calculated to be 0.002 µg/kg bw/day. This figure was agreed by all the relevant UK government departments before publication (Environment Agency, Defra, Food Standards Agency and Department of Health) and as such is the most recent UK guideline value set for arsenic. It is accompanied by an ALARP (as low as reasonably practicable) notation. Although set for soil, with the ALARP intended for controlling intake by food and air, the same reasoning is applicable for air alone, that is, no consideration is necessary for 'background' mean daily intake (MDI).

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