



# Arsenic

## Toxicological Overview

### Key Points

#### Kinetics and metabolism

- arsenic is well absorbed through the GI tract and to a lesser extent via the lungs
- dermal absorption is considered low compared to other routes
- it is mainly excreted in the urine as a mixture of species, predominantly organic arsenic
- arsenic can accumulate in the placenta and may be transported to the fetus

#### Health effects of acute exposure

- arsenic is irritating to the upper respiratory tract
- GI effects and encephalopathy may result from ingestion or inhalation
- in severe cases peripheral neuropathy, multi-organ failure and death can follow ingestion
- arsenic is irritating to the eyes and skin

#### Health effects of chronic exposure

- skin lesions, vascular effects, peripheral neuropathy, neurobehavioral effects in children and other non-specific signs and symptoms may follow chronic arsenic exposure
- changes to the nasal mucosa as well as upper respiratory tract irritation and lung effects have been observed following chronic exposure to arsenic in air
- inorganic arsenic may promote carcinogenesis through indirect effects on DNA
- inorganic arsenic is a known human carcinogen

## Summary of Health Effects

Single doses of inorganic arsenic may be highly toxic by ingestion and inhalation. Ingestion of large doses of arsenic can rapidly lead gastrointestinal (GI) disturbance, encephalopathy and potentially peripheral neuropathies. In severe poisonings, multi-organ features will develop within hours, these include rhabdomyolysis, renal failure, respiratory failure, failure of vital cardiovascular and brain functions and death. The fatal dose for inorganic arsenic ingestion in humans is often quoted as 1-3 mg/kg, though survival at higher doses has been observed.

Acute inhalation of arsenic in dusts may cause; bronchitis, rhinitis and laryngitis with potential for tracheal and bronchial haemorrhage in severe cases. GI effects including nausea, vomiting, diarrhoea and abdominal pain as well as acute encephalopathy have been reported.

Peripheral neuropathy and skin lesions typical of chronic arsenic poisoning may occur weeks after the initial exposure. Single or multiple transverse white lines on the nails may appear. Death can later occur as a result of multiple organ damage.

Chronic exposure to inorganic arsenic has been extensively studied in areas of the world with naturally high levels. Chronic arsenic exposure may result in a wide range of signs and symptoms, many non-specific. Skin lesions including palmoplantar hyperkeratosis, hyperkeratinized warts or corns and hyper pigmentation (interspersed with areas of depigmentation) are thought to be the most sensitive indicator of chronic exposure to high levels. Other features include peripheral vascular effects such as “blackfoot disease” and Reynaud’s phenomenon, cardiovascular effects, peripheral neuropathy, neurobehavioral effects in children and GI irritation.

Chronic inhalation of inorganic arsenic has also been associated with upper respiratory tract irritation, changes to the nasal mucosa (in severe cases septum perforation) and lung effects. Arsenicals are irritating to the eyes and skin; chronic exposures may lead to allergic contact dermatitis and conjunctivitis.

Inorganic arsenic is believed to have little direct genotoxicity but has been shown to enhance mutagenesis at low chronic doses. The IARC has classified arsenic and inorganic arsenic as being carcinogenic (group 1). Occupational exposure studies show sufficient evidence to associate the inhalation of inorganic arsenic with lung cancer. Similarly, epidemiological studies in areas of the world with high levels of arsenic in drinking water provide evidence for a link between chronic consumption and skin, lung and bladder cancers.

There is some evidence of arsenic having teratogenic effect following chronic high level exposure from drinking water, however the threshold for an increased risk is unclear. Similar effects have been seen following inhalation, however these studies have not accounted for multiple chemical exposures. While early studies in experimental animals showed teratogenic effects only in the presence of maternal toxicity and through parenteral exposure, more recent studies have demonstrated effect in the absence of maternal toxicity.

## Kinetics and Metabolism

This document is primarily concerned with the toxicity of inorganic arsenic, which is found in two oxidation states, As<sup>III</sup> (arsenite) and As<sup>V</sup> (arsenate). The valence of arsenic influences its toxicokinetic profile. Arsenite species are considered more toxic than those of arsenate owing to their greater chemical reactivity and ability to enter cells more readily [1]. Use of the word “arsenic” in this document refers to inorganic arsenic unless otherwise specified.

Several human studies suggest that inorganic arsenic is well absorbed through the gastrointestinal (GI) tract, however absorption may be considerably lower for highly insoluble species such as arsenic triselenide (As<sub>2</sub>Se<sub>3</sub>). A study in which healthy volunteers were given water with high levels of arsenic reported that absorption was approximately 95%; similarly another reported that less than 5% of an oral dose of arsenite was recovered in the faeces [2].

Inorganic arsenic in air is bound in particulate matter; mostly particles less than 2 µm in diameter, which may reach the alveoli [2, 3]. Absorption is highly dependent on the solubility, chemical form/species and the size of particles [4]. Studies in humans suggest that between 30-60% of inhaled arsenic may be deposited in the lungs, the majority if not all of this fraction is then absorbed [2]. Dermal absorption of arsenic is considered low relative to the oral and inhalation routes [4].

Absorbed arsenic is widely distributed throughout the body via blood circulation. Data from autopsies suggest that muscle, bone, the kidneys, liver and the lungs accumulate the highest absolute amounts of arsenic [3]. Arsenite species reach higher levels in tissues than arsenate species following administration in experimental animals [5].

Arsenic metabolism is characterized by two processes; reduction and oxidation reactions that interconvert arsenate and arsenite, and methylation reactions which form mono-methylarsonic (MMA) and dimethylarsinic acid (DMA) from arsenite [2].

Ingested inorganic arsenic is predominantly excreted in the urine as a mixture of species. A study in pregnant women, exposed to arsenic in drinking water, measured the relative proportions to be 79-85%, 8-16% and 5-6% for DMA, inorganic species and MMA respectively [2]. Ingested inorganic arsenic has a half-life of 3-5 days, methylated compounds are excreted more rapidly [4]. Arsenite is more extensively methylated than arsenate, so despite it reaching higher concentrations in tissues, it shares a similar long term excretion rate with arsenate [5].

The vast majority of arsenic is excreted rapidly in the urine following inhalation; this is primarily as DMA and MMA, with inorganic arsenic composing less than 25% of species present [2].

Since the elimination of arsenic takes place mainly via the kidneys, the concentration of arsenic in the urine is a good indication of recent exposure to inorganic arsenic. Arsenic and its metabolites are cleared rapidly from the blood, limiting its usefulness for detecting arsenic exposure. However, blood should be collected in the absence of urine (and together with

urine) when acute exposure is suspected. It can be useful in the follow up of confirmed cases of significant chronic exposure [6].

Levels of arsenic in hair and nails are not considered useful for recent exposures, but may be used for past exposures [1, 6]. It is worth noting that recent consumption of sea food may be responsible for a significant rise in total urinary arsenic, sea food can be high in toxicologically insignificant organic arsenic species [6].

During pregnancy arsenic accumulates in the placenta, where it may impair function and lead to a reduction in the efficiency of nutrient transport to the fetus. Additionally, arsenic can cross the placental barrier and may cause toxic effects to the fetus [7]. Chronic exposure to high levels of arsenic in drinking water does not appear to correlate with high levels of arsenic in breast milk. The small amount arsenic which is present in breast milk is almost entirely inorganic, suggesting methylation may play a role in preventing greater accumulation [8, 9]. Inorganic arsenic was not detected (below limit of 0.3 µg/L) in 154 out of 187 samples of breast milk from women from regions of Germany where increased concentrations of arsenic were found in the soil and groundwater [8].

## Mechanism

Arsenites enter cells either by diffusion or by specific transporters. Once inside they react with sulphhydryl (ˉSH) groups of cellular proteins, this can lead to the disruption of enzymes such as pyruvate dehydrogenase which is key to oxidative phosphorylation. Arsenates may enter cells through phosphate transport proteins and are subsequently either reduced to arsenite or are substituted for phosphate in metabolic reactions such as glycolysis, resulting in further disruption of oxidative phosphorylation and the loss of ATP formation [6].

Following chronic exposure, inorganic arsenic and its metabolites will disrupt cell proliferation and cell signalling pathways, cause DNA damage and inhibition of DNA repair which may result in an increased risk of cancer [6].

## Sources and Route of Human Exposure

Arsenic is ubiquitous in soils, rocks and water bodies [8]. Dispersion of arsenic in the environment may occur as a result of volcanic activity, biological processes, volatilisation or movement of dusts [2]. Additional deposition of arsenic may also be the result of anthropogenic activities, past and present [4]. Smelting, metalliferous mining and coal burning are notable contributors to this [10].

A study by the British Geological Survey to define the normal background concentrations for soil contaminants in England found that arsenic concentrations throughout the majority (97%) of England were approximately 32 mg/kg, areas of iron lithology were typically 220 mg/kg and areas of mineralisation and mining had a higher arsenic concentration of 290 mg/kg. [10]. A similar study conducted in Wales found that the levels of arsenic in the urban areas (valleys draining the South Wales Coalfield), mineralisation areas and all other areas were approximately 250, 67 and 36 mg/kg respectively [11].

In certain areas of the world (such as Bengal, Bangladesh and Chile) arsenic concentrations are naturally high; populations may be chronically exposed to arsenic levels of up to 3000 µg/L by using ground wells for drinking water [7].

Arsenic in air has been reported at various levels; reports typically cite values of around 1-10 ng/m<sup>3</sup> in rural areas, 3-30 in unpolluted urban areas and potentially over 1 µg/m<sup>3</sup> in urban areas with an emission source (e.g. a smelter) [3]. Fossil fuel combustion and the metal industries (notably including smelting), are the major anthropogenic sources of emissions of arsenic to air [12]. Volcanic activity is an important natural emission source, while forest fires, mineral weathering and microbial activity represent minor sources [12]. Arsenic in air is largely inorganic [13].

In the UK, food is considered the main contributor to total arsenic exposure in non-occupationally exposed individuals. In regards to total dietary arsenic, fish may provide the greatest contribution; though this is largely in the form of organic arsenic. Inorganic arsenic is estimated to contribute to less than 12% of total dietary arsenic [14]. A recent European dietary survey suggested that dietary intake of inorganic arsenic was highest amongst infants and toddlers (<12 months and 12 to 36 months respectively) [8]. The greatest contribution to total dietary inorganic arsenic in this population was “milk and dairy products” while the greatest contribution to the remaining age range was “grain based processed products” [8]. Following a survey of total and inorganic arsenic in rice drinks, the Food Standards Agency (FSA) concluded that substituting formula, cow or breast milk with rice milk in a child or toddler’s diet could increase their total exposure to inorganic arsenic by up to four times [15]. It is possible that the major source of an individual’s inorganic arsenic intake may be drinking water (following high level intake from a contaminated water supply) [14]. Ambient air is considered a minor route for exposure to arsenic for the general public, typically contributing less than 1% of total exposure [1, 12]. A non-smoker may be exposed to around 1 µg/day of arsenic by inhalation, while a smoker may be exposed to approximately 10 µg/day [14].

Arsenic has been detected in traditional medicines and herbal supplements and use may lead to exposure [6]. Contaminated soils may represent another source of exposure [12, 14].

Workers at smelting plants may be exposed to higher than normal levels of arsenic by inhalation, with the predominant form in these settings being arsenic trioxide dust. Individuals sanding or burning wood preserved with inorganic arsenic may come into contact with vapours or dusts containing inorganic arsenic [2]. Workplace exposure limits (WELs) are enforced to protect workers from the harmful effects of arsenic; in the UK a the long-term WEL for “arsenic and compounds except arsine (as As)” is 1 ppm [16].

## Health Effects of Acute/Single Exposure

### Human data

#### Inhalation

Arsenic is irritating to the upper airways; bronchitis, rhinitis and laryngitis may follow inhalation [6]. Tracheal and bronchial haemorrhage may complicate severe cases [17]. GI effects (nausea, vomiting, diarrhoea and abdominal pain) as well as acute encephalopathy (hallucinations, increased excitability, emotional lability, memory loss, difficulties in learning new information) have been associated with inhalation of arsenic. However, it is possible that these effects are a result of ingestion of airborne arsenic dusts following mucociliary clearance [6].

#### Ingestion

Ingestion of arsenic causes gastrointestinal effects, with features developing 30 minutes to 2 hours after exposure. Symptoms may include abdominal pain, vomiting and diarrhoea. In severe cases fluid loss may be excessive, causing decreased blood volume, lowered blood pressure, electrolyte imbalance, hypovolaemic shock and acute tubular necrosis [6, 17].

In severe poisonings, patients progress to multi-organ involvement within hours; effects include rhabdomyolysis, renal failure, respiratory failure, failure of vital cardiovascular and brain functions and death [2, 5]. Peripheral neuropathies may also develop. The fatal dose for inorganic arsenic ingestion in humans is often quoted as 1-3 mg/kg, though survival at higher doses has been observed [2].

Inorganic arsenic crosses the placental barrier and fetal death has been reported following acute maternal intoxication [17]. A 22 year old, at 20 weeks gestation, attempted suicide by ingesting 340 mg of sodium arsenate. After intensive therapy, the fetus survived and was delivered at 36 weeks [18].

#### Dermal/ocular exposure

Arsenic compounds are skin irritants, effects include erythema, swelling with papules and blisters (in more severe cases) [6]. Contact dermatitis has been reported in occupational exposure to arsenic dusts (often arsenic trioxide) [2, 6].

Pain, lacrimation, blepharospasm, conjunctivitis, photophobia, visual disturbance and corneal damage may occur after ocular exposure to dusts or vapours containing inorganic arsenic [6].

#### Delayed effects following an acute exposure

After acute exposure, death may be delayed and occur as a result of multiple organ damage [2].

Peripheral neuropathy may develop up to 5 weeks after the initial exposure; this typically takes the form of a symmetrical sensorimotor neuropathy [6]. Skin lesions typical of chronic arsenic poisoning may also occur; hyperkeratosis and “rain-drop” pigmentation. Single or multiple transverse white lines on the nails (“Mee’s lines”) may appear several weeks after absorption [17].

## Animal and in-vitro data

### General Toxicity

Most laboratory animal species appear to be far less sensitive to arsenic toxicity than humans; for instance chronic oral doses that would cause marked effects in humans cause no effect in monkey’s, dogs or rats [4].

### Inhalation

In one study, rats were dosed with gallium arsenide and arsenic trioxide (100 and 17 mg/kg, respectively) via the trachea to simulate inhalation. Findings included a significantly increased wet and dry lung weight, increased wet lung weight/body weight ratio and an elevation in total pulmonary protein, 4-hydroxyproline content and DNA; all suggestive of an acutely fibrogenic effect in the lung. Histopathological analysis of the lungs showed that there was an inflammatory response and pneumocyte hyperplasia, which resulted in thickening of the alveolar walls [5].

### Ingestion

The oral LD<sub>50</sub> of arsenic ranges from 15 to 293 mg/kg in rats, and from 11 to 150 mg/kg in other experimental animals [19]. Symptoms observed from arsenic trioxide intoxication in the rat include convulsions, retching and haemorrhaging in the intestinal tract [5].

### Dermal/ocular exposure

No significant dermal irritation was observed in guinea pigs exposed to 4000 mg As/L as arsenate or 580 mg As/L as arsenite in solution. Studies in guinea pigs also did not yield evidence of a sensitization reactions to inorganic arsenic [2].

## Health Effects of Chronic/Repeated Exposure

### Human data

It is pertinent to note that many of the chronic arsenic exposure studies in humans focus on areas of the world where arsenic occurs at high concentrations in drinking water (tens, hundreds or even thousands of micrograms per litre) [1].

### General Toxicity

A number of body systems are affected following chronic exposure to inorganic arsenic, resulting in a wide range of signs and symptoms; many of which are non-specific; such as abdominal pain, diarrhoea, vomiting, anorexia, weight loss and sore throat. However there are some features, such as the development of skin lesions (palmoplantar hyperkeratosis, hyperkeratinized warts or corns and hyperpigmentation interspersed with areas of hypopigmentation) which are considered highly characteristic of chronic arsenic exposure. These skin lesions are reported to be sensitive indicators of arsenic toxicity in individuals chronically exposed to high levels in drinking water; dermal effects are also seen following inhalation exposure though they are not as diagnostic as for oral exposure [2, 4].

Effects on the peripheral vascular system following chronic exposure to arsenic by inhalation have been reported; effects include cyanosis, Raynaud's phenomenon and in extreme cases progression to endarteritis obliterans and gangrene of the lower extremities ("Black foot disease") [2, 5].

There is some evidence that chronic exposure to arsenic may cause central and peripheral neurotoxicity [20]. Signs and symptoms may include decreases in peripheral nerve conduction velocities (and other nerve function tests), tingling of the skin of extremities, motor paralysis foot and wrist drop, tremors, severe pain and ataxia [19].

There is some evidence for chronic exposure to arsenic in early life having neurobehavioral effects in children. A number of studies (though not all) have found associations between decrements in scores for intelligence, motor and behavioural test scores and higher levels of arsenic in drinking water [9].

Anaemia and leucopenia may occur together with disturbances in haem synthesis. An increased incidence of myocardial injury, cardiac arrhythmias, cardiomyopathy and cerebrovascular disease (especially cerebral infarction) have been associated with exposure to arsenic [5].

There is suggestive evidence of an increase in the incidence of diabetes mellitus in response to chronic arsenic exposure [2].

### Inhalation

Irritation of the upper respiratory tract has been observed in workers chronically exposed to inorganic arsenic dusts. Effects include laryngitis, bronchitis, rhinitis and at high exposures, perforation of the septum [2]. Studies of copper smelter workers chronically exposed



arsenic (up to 0.5 mg/m<sup>3</sup>) in air have shown changes in nasal mucosa, signs of tracheobronchitis and pulmonary insufficiency [3].

### Ingestion

Nausea, vomiting and diarrhoea are common after repeat low dose exposures to arsenic as well as acute, likely due to direct irritation of the GI tract following ingestion [2].

### Dermal/ocular exposure

Allergic contact dermatitis may occur from repeated dermal exposure to arsenic and is frequently seen among workers who are exposed to arsenic trioxide. A study of 11 workers at a tin smelting factory where arsenic trioxide levels ranged from 5.2 to 14.4 mg/m<sup>3</sup> showed generalized itch, dry and hyper-pigmented skin, folliculitis, and superficial ulcerations. The development of contact dermatitis may be due to the arsenic dust collecting on the workers' skin. Chemical conjunctivitis with redness, swelling and pain has also been observed in workers exposed to arsenic dusts in air and is usually accompanied by facial dermatitis [2].

### Genotoxicity

Studies in humans exposed to high levels of arsenic in drinking water have reported an increase in micronuclei in peripheral lymphocytes, urothelial cells and buccal mucosa cells and some in cases higher incidences of chromosome aberrations and sister chromatid exchange have been observed in whole blood lymphocyte cultures [1, 9].

Recently, some authoritative expert groups have considered that inorganic arsenic does not interact directly with DNA. Potential mechanisms of carcinogenicity include oxidative damage, epigenetic effects and interference with DNA repair mechanisms [1, 9, 20]. This implies that there may be a threshold dose below which inorganic arsenic does not cause mutation or cancer. However, so far no reliable threshold for an absence of adverse health effects has been identified.

### Carcinogenicity

The International Agency for Research on Cancer (IARC) have classified arsenic and inorganic arsenic compounds as known human carcinogens (Group 1). This classification does not differentiate based on arsenic species [1].

There is consistent epidemiological evidence of an association between inhalation exposure to inorganic arsenic mixtures and lung cancer. Evidence of a dose-response relationship was observed in the exposed populations. Much of the evidence for this role comes from occupational exposures in miners and smelter workers; such environments may lead to exposure to other airborne carcinogens and potentially result in confounding [1]. Studies in smelter workers have also suggested increased risks for stomach and colon cancer and possibly bone and kidney cancer [3].

Ecological studies centred on regions with naturally high levels of arsenic have provided a sufficient body of evidence for the association of exposure to arsenic in drinking water and cancers of the lung, bladder and skin (primarily squamous cell carcinoma). Evidence of a

dose-response relationship was observed in the exposed populations. There is also some evidence for an increased risk of liver, kidney and prostate cancer; however chance or bias cannot be ruled out for these endpoints [1].

In its 2011 evaluation of arsenic, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) considered a follow up study on a cohort of 8,086 people in Taiwan, which looked at the relative risk for urinary tract cancer in relation to the concentration of arsenic in drinking water. The study showed an elevated but non-significant relative risk for those individuals exposed to concentrations of arsenic below 100 µg/l, but a significant five-fold increase for those exposed to levels above 100 µg/L. Another follow up study from the same cohort demonstrated a significant exposure response trend for lung cancer at exposures of 100-300 µg/L but not between 10 and 100 µg/L. Synergy was observed between cigarette smoking and squamous and small cell lung cancer but not adenocarcinomas [20].

The skin cancers induced by arsenic are characteristically of the non-melanoma type such as a squamous cell carcinomas arising in keratoses (including Bowen's disease) and multiple basal cell carcinomas [1]. The development of skin lesions has been associated with an increased risk of skin cancers, such as squamous cell carcinoma [4].

### Reproductive and developmental toxicity

Exposure to high concentrations of arsenic in drinking water during pregnancy has been associated with spontaneous abortion, fetal death, preterm birth, neonatal morbidity and intrauterine growth restriction in some but not all studies. However, confounding factors including malnutrition and poverty complicate the analysis of environmental exposures. The UK Teratology Information Service has noted that although the available evidence indicates a potential for an increased risk for adverse fetal effects following exposure to inorganic arsenic in drinking water during pregnancy, the threshold dose above which an increased risk occurs has not been identified [7].

A cohort study of 1,578 in Bangladesh demonstrated a significant negative association between birthweight of head and chest circumference and maternal urinary arsenic concentration (where the concentration was below 100 µg/L). Birthweight was estimated to decrease by 1.68 g for every 1 µg/L of arsenic in the mother's urine [9, 20]. However another study in Mongolia in which levels of arsenic in drinking water were up to 100 µg/L found no adverse birth outcomes or significant increases in neonatal death rate. Other cohort studies of infants born to mothers consuming inorganic arsenic in drinking water have shown a significant increase in first-year mortality where the mothers drank from sources containing 164-275 µg/L arsenic [20].

Chronic exposure to inorganic arsenic in drinking water may negatively impact on the development of intellectual function in children. Studies in children in areas with high levels of arsenic in drinking water have suggested an inverse relationship between arsenic exposure and intelligence scores [4, 9].

An association between inhalation exposure to arsenic and an increased risk of adverse developmental effects (fetal, neonatal and postnatal mortality, spontaneous abortions,

lowered birth weight, congenital malformations and stillbirths) as well as pre-eclampsia has been reported in several epidemiological studies. In all of these, there were also exposures to other chemicals and risk factors, which could have contributed towards the observed effects and there is no consistent evidence for any one particular end-point [4, 5, 20].

Fetal death has been reported following acute maternal intoxication, maternal toxicity is likely to be a major determinant of risk to the fetus [7].

## Animal and in-vitro data

### General Toxicity

Chronic oral exposure to arsenic has been associated with effects on a number of systems including the cardiovascular, respiratory, gastrointestinal, haematological, immune, reproductive, and nervous in experimental animal studies [20]. There are limited data available on chronic exposure by inhalation in experimental animals.

### Genotoxicity

Studies demonstrate that inorganic arsenic does not directly bind to DNA. The main mechanisms of the genotoxicity of inorganic arsenic are considered to be induction of oxidative DNA damage, DNA repair inhibition, changes in DNA methylation, gene amplification and aneuploidy. Gene amplification, changes in DNA methylation and aneuploidy can lead to altered gene expression and genomic instability [1, 9, 20].

Point mutations were not induced in bacterial or mammalian test systems. Studies in mammalian cells have reported the induction of DNA damage (strand breaks, oxidative base modifications and DNA protein crosslinks) at chronic low non-cytotoxic exposure concentrations of inorganic arsenic [1, 9, 20].

At higher concentrations, arsenic compounds induced micronuclei and chromosome aberrations, aneuploidy and sister chromatid exchanges in mammalian cells and deletion mutations in human-hamster hybrid cells. Arsenic has also been reported to cause gene amplification in mouse 3T6 cells [1, 9, 20].

In vivo, oral administration of arsenic resulted in the induction of micronuclei and chromosomal aberrations in mouse peripheral blood lymphocytes and mouse bone marrow [1, 9, 20].

Inorganic arsenic enhances the mutagenicity of other DNA damaging agents including UV radiation, BaP and alkylating agents. This may occur via interference with DNA damage repair processes [1, 9, 20].

### Carcinogenicity

IARC has stated that there is sufficient evidence for the carcinogenicity of inorganic arsenic compounds calcium arsenate and sodium arsenite in experimental animals. Various tumours including lung, liver, ovary and adrenal gland have been observed in the offspring of mice orally administered sodium arsenite. IARC concluded that early life transplacental and perinatal exposure seems to be a period of particular sensitivity in terms of arsenic carcinogenesis. Calcium arsenate caused an increase in lung tumours in hamsters following oral or intratracheal administration [1].

For sodium arsenate, gallium arsenide and arsenic trioxide the evidence is limited and insufficient for arsenic trisulphide [1].

IARC concluded that overall there is sufficient evidence for the carcinogenicity of inorganic arsenic compounds in experimental animals [1].

### Reproductive and developmental toxicity

Early experimental animal studies reported teratogenic effects in the offspring of mothers exposed to arsenic. However, these studies were designed to produce neural tube defects, exposure was intraperitoneal or intravenous and effects were observed in the presence of maternal toxicity or death [7].

More recent experiments involving maternal exposure to arsenic through oral routes have shown neural tube defects, foetal growth retardation and neurotoxicity at doses which do not cause maternal toxicity. Neural tube defects increased with dose (4.8-14.4 mg/kg bw/day) in mice administered sodium arsenite by oral gavage [20].

No increase in adverse reproductive outcomes were observed when rats were exposed to 0.2–8 mg/m<sup>3</sup> As as arsenic trioxide for 6 hours a day for 14 days prior to mating through to gestation day 19 [2].

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