Trivalent arsenites: Human health tier II assessment

28 June 2013

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Arsenic oxide (As2O3)	1327-53-3
Arsenenous acid, sodium salt	7784-46-5
Arsonic acid, calcium salt (1:1)	52740-16-6

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to

human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:**www.nicnas.gov.au**

Disclaimer

ACRONYMS & ABBREVIATIONS

Grouping Rationale

The chemicals in this group are arsenic oxo-compounds with arsenic in an oxidation state of +3. These chemicals have a similar molecular weight and are soluble in water.

Trivalent arsenics readily bind and react with sulfhydryl groups in proteins. Complexing to sulfhydryl groups in key enzymes can impair critical functions within the body (ATSDR, 2007). By targeting the mitochondria, the trivalent arsenics can bind and inhibit pyruvate dehydrogenase, causing a decrease in citric acid cycle activity and cellular adenosine-5'-triphosphate (ATP), impairing the metabolic pathway that results in the generation of glucose (gluconeogenesis). Furthermore, they are known to inhibit DNA repair by the inhibition of various other mitochondrial enzymes (Health Council of the Netherlands, 2012). Trivalent arsenics also inhibit the production of glutathione, which protects the cells against oxidative damage (Health Council of the Netherlands, 2012). As pentavalent arsenic may need to be reduced in the body to the trivalent state before it can exert these toxic effects, trivalent arsenics are considered more toxicologically potent than pentavalent arsenics (ATSDR, 2007).

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacture information have been identified for sodium arsenite (CAS No. 7784-46-5) or calcium arsenite (CAS No. 51740-16-6). The following Australian industrial uses were reported under previous mandatory and/or voluntary calls for information for arsenic trioxide (CAS No. 1327-53-3).

The chemicals have reported site-limited use including as an:

- impregnation agent;

- oxidising agent; and
- as a chemical intermediate.

The total volume introduced into Australia reported under previous mandatory and/or voluntary calls for information was between 1000 and 9999 tonnes.

International

For arsenic trioxide (CAS No. 1327-53-3) and sodium arsenite (CAS No. 7784-46-5), the following international uses have been identified through the European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers, Galleria Chemica, Substances in preparations in Nordic Countries (SPIN) database, and other data sources via eChemPortal, including the US Environmental Protection Agency (EPA) Aggregated Computational Toxicology Resource (ACToR), US Department of Health and Human Services Household Products Database and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemicals have reported commercial use including as a hide preservative.

The chemicals have reported site-limited use including:

- raw material in medicines; and
- scientific research and development.

The following non-industrial uses have been identified:

- therapeutic use in growth inhibitors, psoriasis and leukaemia treatment;
- agricultural use in herbicides and insecticides; and
- wood preservative.

The following additional international uses have been identified through Galleria Chemica, Substances in Preparations in Nordic Countries (SPIN) database for Arsenic trioxide (CAS No. 1327-53-3).

The chemical has reported commercial use including:

- ceramic enamels;
- flame retardants and extinguishing agents; and
- decolouring and refining agent in glass manufacturing.

The chemical has reported site-limited use including:

- preparation of other arsenic compounds; and
- glass manufacturing.

For calcium arsenite (CAS No. 51740-16-6), the following international uses have been identified through the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported non-industrial use including as a pesticide.

Restrictions

Australian

Trivalent arsenites, belonging to the group entry 'arsenic', are listed in the Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)) (SUSMP, 2012) in Schedule 7 with the following entry:

ARSENIC **except**:

(a) when separately specified in this Schedule;

(b) when included in Schedule 4 or 6;

(c) as selenium arsenide in photocopier drums;

(d) as 10,10'-oxydiphenoxarsine in silicone rubber mastic containing 120 mg/kg or less of arsenic;

(e) as 10,10'-oxydiphenoxarsine contained in polyvinyl chloride and polyurethane extruded and moulded articles containing 160 mg/kg or less of arsenic other than when included in articles:

(i) in contact with food stuffs, animal feeds or potable water;

(ii) of clothing and footwear in contact with the skin;

(iii) used as infant wear; or

(iv) intended for use as packaging materials;

(f) in animal feeds containing 75 g/tonne or less of arsenic; or

(g) in paints containing 0.1 % or less of arsenic calculated on the non-volatile content of the paint.'

Schedule 7 chemicals are labelled with 'Dangerous Poison'. These are substances with a high potential for causing harm at low exposure and which require special precautions during manufacture, handling or use. These poisons should be available only to specialised or authorised users who have the skills necessary to handle them safely. Special regulations restricting their availability, possession, storage or use may apply.

"Arsenic and its compounds " are restricted hazardous chemicals under Schedule 10 (Prohibited carcinogens, restricted carcinogens and restricted hazardous chemicals) of the Work Health and Safety (WHS) regulations (WHS, 2011). Specifically, use is restricted in:

- abrasive blasting at a concentration of greater than 0.1 % as arsenic; and
- for spray painting.

International

Trivalent arsenics appear on the following international restrictions:

- The Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products.
- Health Canada List of Prohibited and Restricted Cosmetic Ingredients (The "Hotlist").
- European Union (EU) Cosmetic Directive 76/768/EEC Annex II: List of Substances which must not form part of the composition of cosmetic products.
- New Zealand cosmetic products group standard—Schedule 4: Components cosmetic products must not contain.

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals in this group are classified as hazardous with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia).

Arsenic trioxide (CAS No. 1327-53-3)

Carc. Cat. 1; R45 (Carcinogenicity)

T; R28 (Acute toxicity)

C; R34 (Corrosive)

Sodium arsenite (CAS No. 7784-46-5) and calcium arsenite (CAS No. 52740-16-6)

Carc. Cat. 1; R45 (Carcinogenicity)

T; R23/25 (Acute toxicity)

Exposure Standards

Australian

The chemicals in this group have the following exposure standards on the Hazardous Substances Information System (HSIS) (Safe Work Australia):

Arsenic trioxide (CAS No. 1327-53-3)—exposure should be controlled to the lowest practicable level given that this chemical is an established human carcinogen.

Sodium arsenite (CAS No. 7784-46-5) and Calcium arsenite (CAS No. 52740-16-6)—the time weighted average (TWA) is 0.05 mg/m³ (arsenic and soluble compounds (as Arsenic)).

Short-term exposure limits (STEL)—no specific exposure standards are available.

International

The chemicals in this group have the following exposure standards identified internationally (Galleria Chemica):

An exposure limit TWA of 0.01 mg/m³ in different countries such as Canada (Alberta, Ontario, Saskatchewan), China, Denmark, Latvia, Malaysia and Norway.

An exposure limit TWA of 0.5 mg/m³ in different countries such as Canada (Yukon), Mexico and Philippines.

Health Hazard Information

Toxicokinetics

The chemicals in this group (i.e. trivalent arsenite compounds) may be absorbed from aerosols or ingested. Absorption depends on the size of particulates and the solubility of the chemical form of arsenic. Small particles are better absorbed than larger particles. The extent of absorption following inhalation is similar to that from ingestion, as non-respirable arsenic trioxide particles trapped in the upper airways are then deposited in the gastrointestinal tract by mucociliary clearance (IPCS, 1997a). Ninety five percent of the ingested trivalent arsenic is absorbed from the gastrointestinal tract. Sodium arsenite is highly soluble

compared with arsenic trioxide and represents a more acute toxic hazard than less soluble trivalent arsenic compounds (IPCS, 1997a).

Dermal absorption of chemicals in this group appears to be poor. An in vitro study conducted on human skin samples with the chemical, showed that in a 24-hour application, 1 % of the chemical was absorbed (REACH). Absorbed arsenic is then distributed to all body tissues.

Once absorbed, inorganic trivalent arsenites are oxidised to arsenates and are methylated in the liver, forming methylarsonic acid and dimethylarsinic acid (IPCS, 1997a).

Intratracheal studies in rats and hamsters administered sodium arsenite and arsenic trioxide found 60–90% clearance within one day or less (ATSDR, 2007). After an oral administration of arsenic trioxide (CAS No. 1327-53-3) to rats, it was found that 95 % was cleared within a half life of 29 minutes. However, the remaining 5 % had a half life of 75 days (ATSDR, 2007). The half-life of inorganic arsenics is estimated to be 60 hours in humans with an average of 60 % of total arsenic intake assumed to be excreted in urine in the form of dimethylarsinic acid (DMA) and methylarsonic acid (MMA). Animal studies have found arsenic and its metabolites in faeces, suggesting biliary clearance as well (REACH).

Animal studies have shown that sodium arsenite (CAS No. 7784-46-5) crossed the placenta easily in pregnant mice. Furthermore, case reports of arsenic poisoning from arsenic trioxide (CAS No. 1327-53-3) in pregnant women resulting in the death of the foetus, demonstrated that arsenic trioxide passes readily through the human placenta (IPCS, 2001). Arsenic concentrations have been reported to be similar in cord blood and maternal blood (~9 µg/L) of maternal-infant pairs exposed to drinking water containing high levels of arsenic (~200 µg/L) (IPCS, 2001).

Acute Toxicity

Oral

Arsenic trioxide (CAS No. 1327-53-3) is classified as hazardous with the risk phrase ‘Very toxic if swallowed’ (T+; R28) in HSIS (Safe Work Australia), whereas sodium arsenite (CAS No. 7784-46-5) and calcium arsenite (CAS No. 52740-16-6) are classified with the risk phrase 'Toxic if swallowed' (T; R25). The available animal data and observations in humans, support an amendment to this classification (refer to **Recommendation** section) to reflect the findings reported below.

Arsenic trioxide (CAS No. 1327-53-3)

LD50 for rats was 14.6 mg/kg bw–385 mg/kg bw (IUCLID, 2000)

LD50 for mice was 31.5 mg/kg bw–500 mg/kg bw (IUCLID, 2000)

LD50 for rabbits was 20.19 mg/kg bw (IUCLID, 2000)

Sodium arsenite (CAS No. 7784-46-5)

LD50 for rats was 42 mg/kg bw (IPCS, 2001)

Reported signs of toxicity include convulsions, retching and haemorrhaging in the intestinal tract (IUCLID, 2000; IPCS, 2001).

Considering the higher solubility of sodium arsenite (CAS No. 7784-46-5) compared with arsenic trioxide (CAS No. 1327-53-3) and calcium arsenite (CAS No. 52740-16-6), it is expected to be more acutely toxic than arsenic trioxide (CAS No. 1327-53-3).

Dermal

The chemicals were reported to be acutely toxic in animal tests following dermal exposure. Due to limited information from studies, classification is not achievable.

The lowest published lethal dose (LDLo) in dogs is 2 mg/kg bw for arsenic oxide (CASNo. 1327-53-3). No other details were available (IUCLID, 2000).

In another dermal exposure study for arsenic oxide (CAS No. 1327-53-3) in rats, no deaths occurred up to a dose of 1000 mg arsenic/kg bw (ATSDR, 2007).

Inhalation

The chemicals sodium arsenite (CAS No. 7784-46-5) and calcium arsenite (CAS No. 52740-16-6) are classified as hazardous with the risk phrase 'Toxic by inhalation' (T; R23) in HSIS (Safe Work Australia). There are limited data regarding acute inhalation toxicity. The available data on arsenic trioxide support a similar hazard classification to other members of this group (refer to **Recommendation** section).

In a study where rats were exposed through intratracheal administration of arsenic trioxide (CAS No. 1327-53-3), an LD50 of 18.9 mg arsenic/kg was reported. No further details were given (NAC/AEGL, 2009).

Observation in humans

Arsenic trioxide (CAS No. 1327-53-3) has been reported to be fatal to humans if swallowed. In one case, 26 hours after ingesting 2 g of the chemical, a 21-year-old male presented with gastrointestinal toxicity (nausea, vomiting, abdominal pain and diarrhoea) which led to gastrointestinal haemorrhaging, eventually cardiovascular shock, and death (IPCS, 1997a). Furthermore, in a case of poisoned chocolate, two patients presented with gastrointestinal toxicity developing to hyper-salivation and haematemesis. Further investigations revealed gastric ulcers, with severe gastritis and oesophagitis (IPCS, 1997a). Urine samples analysed on admission showed 5–6 mg/L of arsenic. Other reported symptoms include gastrointestinal haemorrhaging, cardiovascular collapse, renal failure, seizures, encephalopathy and rhabdomyolysis.

In a case of sodium arsenite (CAS No. 7784-46-5) poisoning, a 42 year-old agricultural worker presented with neuropathy and skin lesions. His urine contained 7000 µg of arsenic over a 24-hour period. On the 26th day after his hospital admission, he died from a cardiac arrest, triggered by fatal arrhythmia (IPCS, 1997b). From a case study of humans exposed to meat poisoned with sodium arsenite, abdominal pain and gastritis were reported in 30/85 individuals. Vomiting and nausea were more common in higher doses, with urine arsenic concentrations of 10000 µg/L. No adverse effects were observed after one month (IPCS, 1997b). In the US between 1949 and 1967, 65 % of human poisonings from ingested pesticides containing sodium arsenite resulted in fatalities (IPCS, 1997b).

No case studies of humans were reported after dermal exposure that caused fatalities (ATSDR, 2007). Similarly, no cases of lethality in humans has been found following acute inhalation exposure, at exposure levels of 1–100 mg As/m^3 (ATSDR, 2007).

An occupational case reported a fatality where a worker was buried by arsenic trioxide powder and died six hours later from inhalation exposure (IPCS, 1997a).

Corrosion / Irritation

Corrosivity

Arsenic trioxide (CAS No. 1327-53-3) is classified as hazardous with the risk phrase 'Causes burns' (C; R34) in HSIS (Safe Work Australia). The data available support this classification and provide evidence to support a recommendation to amend the classification of sodium arsenite (CAS No. 7784-46-5) and calcium arsenite (CAS No. 52740-16-6) to be classified similarly.

Reports of dermal exposure to arsenic trioxide (CAS No. 1327-53-3) indicate erythema, burning and itching, eczematous eruptions and folliculitis (IPCS, 1997a; IUCLID, 2000). In one case, skin lesions and nail thickening were observed after an individual applied caustic arsenic paste to his cheek (IPCS, 1997b).

Trivalent arsenic is also corrosive to the mouth, throat and mucous membranes causing oral burns, dysphagia, hyper-salivation and haemorrhagic gastroenteritis (HSDB, IPCS, 1997b).

Arsenic trioxide (CAS No. 1327-53-3) and sodium arsenite (CAS No. 7784-46-5) are reported to be corrosive to the eye. Most injuries result from exposure to dusts, causing conjunctivitis, lacrimation, photophobia, corneal damage and chemosis (IPCS,

1997a and IPCS, 1997b).

Arsenic trioxide (CAS No. 1327-53-3) and sodium arsenite (CAS No. 7784-46-5) are also known to be corrosive to metals such as stainless steel, galvanised steel, copper and aluminium, when in solution (National Physical Laboratory).

Sensitisation

Skin Sensitisation

The negative results observed for arsenic trioxide (CAS No. 1327-53-3) (REACH, ATSDR, 2007) and sodium arsenite (CAS No. 7784-46-5) (IPCS, 2001) in guinea pig maximisation tests support a conclusion that the chemicals in this group are not skin sensitisers.

Observation in humans

The available data do not permit a quantitative estimate of the concentration of arsenic on the skin that causes these effects, due to possible contaminations from other materials. The dose and time of exposure are not known.

Dermal sensitisation has been reported from workers exposed to arsenic trioxide (CAS No. 1327-53-3) in a copper smelter where a positive patch test for arsenic was seen in 80 % of exposed workers compared with 30 % in a control population (ATSDR, 2007).

In another occupational study, an evaluation of 11 male workers exposed to arsenic trioxide levels ranging from 5.2 to 14.4 mg/m^3 found itching, dry and hyper-pigmented skin, folliculitis, superficial ulcerations and contact dermatitis (ATSDR, 2007). Furthermore, in an epicutaneous patch test with 0.1 % sodium arsenite applied to 379 dermatitis subjects, two subjects had a positive reaction (REACH).

Repeated Dose Toxicity

Oral

Chemicals in this group cause serious damage to health from repeated oral exposure with a lowest observed adverse effect level (LOAEL) of 1 and 1.5 mg/kg bw/day for arsenic trioxide (CAS No. 1327-53-3) and sodium arsenite (CAS No. 7784-46-5), respectively for treatment-related deaths in mice and rats. The available data warrant hazard classification of these chemicals.

The lowest oral sodium arsenite (CAS No. 7784-46-5) lethal level in pregnant rabbits dosed repeatedly throughout gestation was 1.5 mg arsenic/kg bw/day determined by the mortality of 7/20 rabbits. No rabbits died at 0.1–0.4 mg arsenic/kg bw/day (Health Council of the Netherlands, 2012; ATSDR, 2007).

Various chronic studies reported in the ATSDR (2007) observed treatment-related mortality in dogs exposed to 2.4 mg arsenic/kg bw/day as arsenic trioxide (CAS No. 1327- 53-3) and mice exposed to 1 mg arsenic/kg bw/day as arsenic trioxide (CAS No. 1327- 53-3). No details on clinical effects were provided.

Dermal

No data are available.

Inhalation

Chemicals in this group cause serious damage to health by repeated inhalation exposure with a lowest observed adverse effect concentration (LOAEC) of 20 mg arsenic/m³ as arsenic trioxide (CAS No. 1327-53-3) for treatment related deaths in rats. The available data warrant hazard classification of the chemicals.

In a repeated dose study, six Syrian golden hamsters were dosed twice a week for eight weeks with a single concentration of 1.3 mg/kg bw arsenic trioxide (CAS No. 1327-53-3) through intratracheal instillation. Although the body weight of the animals did not change compared to the control animals, relative lung weights were 20 % greater than the controls and the liver weights were 11 % lower. Microscopic evaluation of the lungs showed foci of mild to severe inflammatory response, consisting mainly of neutrophils, as well as mild hyperplasia of bronchiolar cells. No histopathological changes were seen in the spleen, liver or kidney (NAC/AEGL, 2009).

In a developmental toxicity study, 4/9 pregnant rats died between days 12 and 19 of gestation after 30–35 days of exposure to an aerosol of arsenic trioxide (CAS No. 1327-53-3) at an exposure concentration of 20 mg As/m³ (Health Council of the Netherlands, 2012). These animals exhibited severe hyperaemia and plasma discharge into the intestinal lumen at autopsy.

In another developmental study, groups of 24 female Crl:CD(SD)BR rats, were exposed (whole body) to arsenic trioxide (CAS No. 1327-53-3) at concentrations of 0, 0.32, 3.4, and 11 mg As/m³ for six hours a day from 14 days before mating until gestational day 19. There was no treatment-related mortality. Maternal toxicity was observed at the highest dose and observed as decreased food consumption and body weight gain. The no observed adverse effect concentration (NOAEC) for maternal toxicity was 3.4 mg As/m³ (NAC/AEGL, 2009) (refer to **Developmental toxicity** section).

Observation in humans

Case studies on arsenic exposure suggest that low levels (0.014–0.1 mg As/kg/day) of chemicals in this group could be fatal to humans when exposed orally over a period of time.

In a reported epidemiological study, five children between the ages of 2 and 7 years died from chronic arsenic poisoning after drinking contaminated water throughout their lives at estimated average doses of 0.05–0.1 mg As/kg/day (ATSDR, 2007).

In another case study, a 26-year-old man died from swallowing approximately 10 g of arsenic trioxide (CAS No. 1327-53-3) over a two-week period. The individual developed severe toxic hepatitis and pancreatitis, and thereafter neurological disorders, respiratory distress, acute renal failure, cardiovascular disturbances and death (NAC/AEGL, 2009).

Genotoxicity

Chemicals in this group have a clastogenic potential based on in vitro and in vivo data. The available data warrant hazard classification.

Large number of studies have investigated the genotoxic potential of chemicals in this group. In vitro gene mutation studies were predominately negative (ATSDR, 2007). However, in vitro studies in human fibroblasts, lymphocytes, and leukocytes; and Chinese hamster ovary cells, Syrian hamster embryo cells and mouse lymphoma cells, demonstrated that chemicals in this group induce chromosomal aberrations and sister chromatid exchange. In vitro studies in human, mouse and hamster cells have also produced positive results for DNA damage, repair and enhancement, and DNA repair inhibition.

Studies in humans, and in vivo studies in mice (bone marrow cells, leukocytes) and rats (bone marrow cells) demonstrated that chemicals in this group cause chromosomal effects (ATSDR, 2007). There is, however, inadequate investigation in germ cell lines (Health Council of the Netherlands, 2012).

Carcinogenicity

Chemicals in this group are classified as hazardous—Category 1 carcinogenic substance—with the risk phrase ‘May cause cancer’ (T; R45) in HSIS (Safe Work Australia). The available data support this classification.

The International Agency for Research on Cancer (IARC) has classified arsenic and inorganic arsenic compounds, including arsenic trioxide (CAS No. 1327-53-3) and arsenites, as ‘carcinogenic to humans’ (Group 1) (IARC Monograph, 2012).

IARC (2012) concluded that there is sufficient evidence in humans for carcinogenicity in the lungs, urinary bladder and skin, and a positive association for cancer in the kidney, liver and prostate.

Reproductive and Developmental Toxicity

Animal data suggest that developmental toxicity was only observed secondary to maternal toxicity. Available epidemiological studies are inconclusive with respect to the reproductive and developmental toxicity of chemicals in this group. The available data do not warrant a hazard classification.

Reproductive toxicity was not seen in animal studies with chemicals in this group (ATSDR, 2007). A number of studies in rats, mice and hamsters demonstrated developmental toxicity at maternally toxic doses.

Several epidemiological studies suggested that inhalation exposure could result in congenital defects, abortion and low birth weights (ATSDR, 2007). However, these studies were not conclusive given a number of confounding factors in the studies. Some epidemiological studies found no significant association between levels of arsenic in drinking water and developmental toxicity.

Other Health Effects

Neurotoxicity

Clinical observations and neurological examinations of individuals have shown serious neurological effects from both inhalation and oral exposure to trivalent arsenics. Acute ingestion has caused muscle cramps, hearing problems, encephalopathy and seizures (IPCS, 1997a).

In one study, a 30-year-old male poisoned by arsenic trioxide (amount not stated) developed peripheral neuropathy and muscle weakness, which continued to increase, along with confusion and hallucination. Three weeks after admission, an electromyogram showed a polyneuropathy with axonal degeneration. Muscles in all limbs were a fifth of their previous power. Severe pins and needles in the hands and feet continued and the patient was confined to a wheelchair. Twenty-six months after intoxication, he was able to walk with an aid and had regained 70 % of his hand function (IPCS, 1997a).

Occupational trivalent arsenic exposure has also been linked to psychological impairment with defects of verbal learning ability, memory and personality changes. One case describes a 50-year-old chemical plant engineer who developed delirium, agitation and emotional instability after 20 years working in a smelting plant (IPCS, 1997a).

Endocrine Disruption

Epidemiological evidence from Taiwan, and an occupational study among smelter workers in Sweden have associated chronic arsenic exposure with the development of diabetes mellitus (IPCS, 1997a; IPCS, 1997b).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (carcinogenicity and genotoxicity), systemic acute effects (acute toxicity by oral and inhalation routes of exposure) and local effects (corrosivity). The chemicals also cause toxic effects following repeated exposure.

Available data on reproductive and developmental toxicity are equivocal. However, risk management controls to mitigate risk from the above hazards would be sufficient for reproductive and developmental toxicity.

Public Risk Characterisation

In Australia, chemicals in this group are used for site-limited uses. Use of these chemicals for non-industrial uses such as herbicides, insecticides and fungicides in agriculture are outside the scope of this assessment.

Given the uses identified for the chemicals in this group, it is unlikely that the public will be exposed. Hence, the public risk from the industrial use of chemicals is not considered to be unreasonable.

These chemicals are currently listed on Schedule 7 of the SUSMP. Schedule 7 chemicals are not available for general public use. The current controls are considered adequate to minimise the risk to public health.

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation exposure of workers to chemicals in this group may occur, particularly where manual or open processes are used. These may include transfer and blending activities, quality control analysis, and cleaning and maintenance of equipment. Worker exposure to these chemicals at lower concentrations may also occur while using formulated products containing the chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic long-term, systemic acute and local health effects, these chemicals may pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposure to the chemical are implemented. The chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU), e.g. employer, at a workplace, has adequate information to determine appropriate controls.

The data available support an amendment to the hazard classification in HSIS (refer to **Recommendation** section).

NICNAS Recommendation

Assessment of chemicals in this group is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Work Health and Safety

The chemicals in this group are recommended for classification and labelling under the current approved criteria and adopted GHS as below. This does not consider classification of physical hazards and environmental hazards.

Based on the hazard data or classifications available for some chemicals in this group (refer above), all chemicals in this group are classified as below.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Very toxic if swallowed (T+; R28) Toxic by inhalation (T; R23)	Fatal if swallowed - Cat. 2 (H300) Toxic if inhaled - Cat. 3 (H331)
Irritation / Corrosivity	Causes burns (C; R34)	Causes severe skin burns and eye damage - Cat. 1 (H314)

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Repeat Dose Toxicity	Toxic: danger of serious damage to health by prolonged exposure through inhalation (T; R48/23) Toxic: Danger of serious damage to health by prolonged exposure if swallowed (T; R48/25)	Causes damage to organs through prolonged or repeated exposure - Cat. 1 (H372)
Genotoxicity	Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68)	Suspected of causing genetic defects - Cat. 2 (H341)
Carcinogenicity	Carc. Cat 1 - May cause cancer (T; R45)*	May cause cancer - Cat. 1A (H350)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for industry

Control measures

Control measures to minimise the risk from dermal/ocular/inhalation exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures which may minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemical if valid techniques are available to monitor the effect on the worker's health;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing Risks of Hazardous Chemicals in the Workplace—Code of Practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to assist with meeting obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((m)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of Safety Data Sheets for Hazardous Chemicals— Code of Practice* and *Labelling of Workplace Hazardous Chemicals—Code of Practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

References

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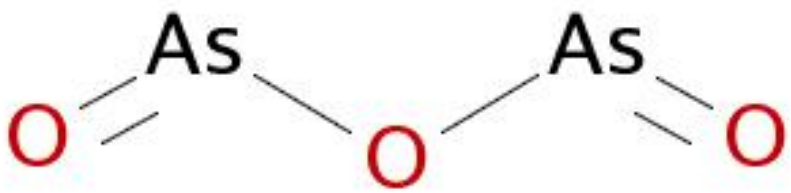
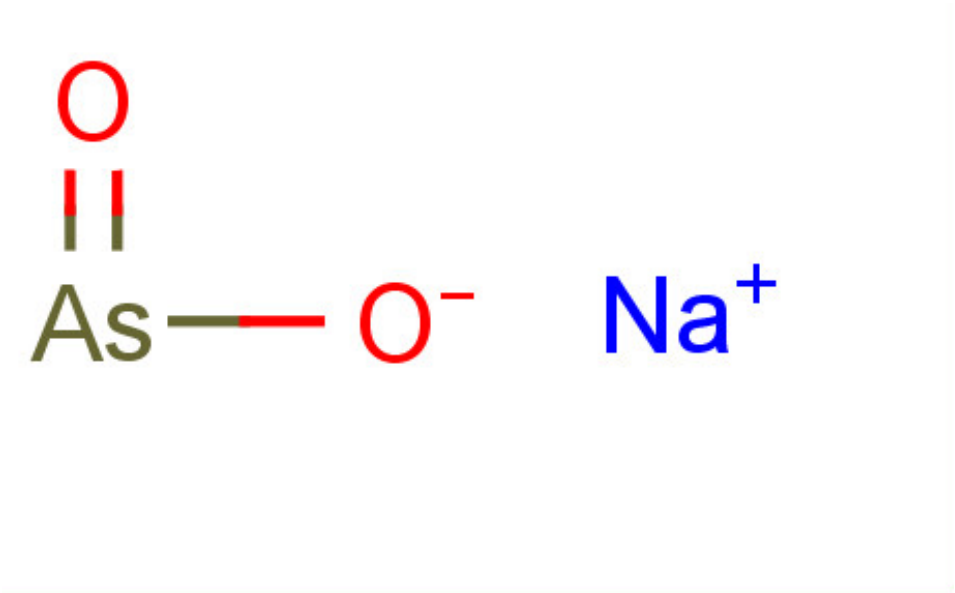
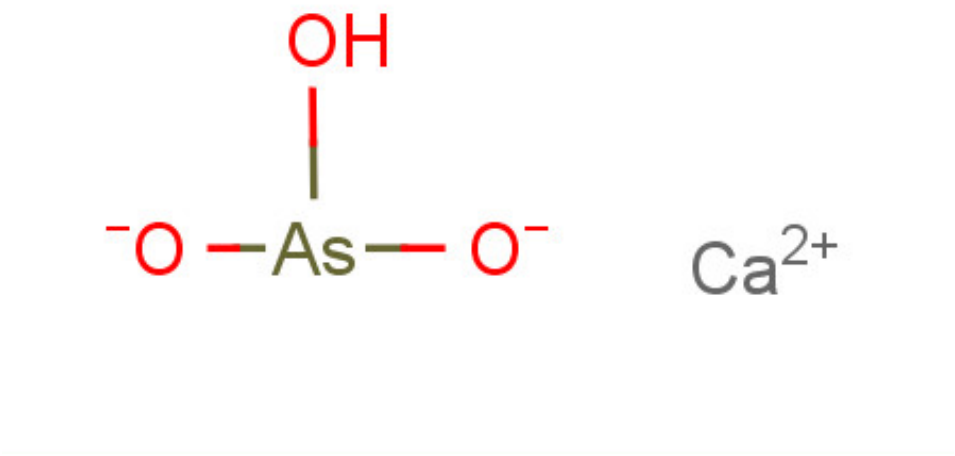
Last Update 28 June 2013

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Arsenic oxide (As2O3)** Arsenic trioxide Arsenious Acid Anhydride Arsenite Arsenolite Trisenox
CAS Number	1327-53-3
Structural Formula	
Molecular Formula	As2O3
Molecular Weight	197.84

Chemical Name in the Inventory and Synonyms	**Arsenenous acid, sodium salt** Sodium arsenite Arsenious acid, monosodium salt Sodium metaarsenite Sodium dioxoarsenate

CAS Number	7784-46-5
Structural Formula	
Molecular Formula	AsHO2.Na
Molecular Weight	130.92

Chemical Name in the Inventory and Synonyms	**Arsonic acid, calcium salt (1:1)** Calcium arsenite Calcium arsenicosum Calcium meta-arsenite Mono-calcium arsenite
CAS Number	52740-16-6
Structural Formula	
Molecular Formula	AsH3O3.Ca
Molecular Weight	165.02

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