Arsine: Human health tier II assessment

28 June 2013

CAS Number: 7784-42-1

- Preface
- Chemical Identity
- Import, Manufacture and Use
- Restrictions
- Existing Work Health and Safety Controls
- Health Hazard Information
- Risk Characterisation
- NICNAS Recommendation
- References

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.

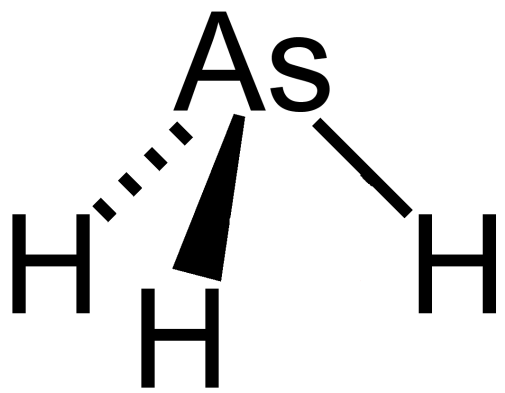
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	Arsenic hydride Hydrogen arsenide Agent SA Arseniuretted hydrogen
Structural Formula	
Molecular Formula	AsH3
Molecular Weight (g/mol)	77.95
Appearance and Odour (where available)	Colourless gas with a garlic odour.
SMILES	[As]

Import, Manufacture and Use

Australian

The following Australian uses were reported under previous mandatory and/or voluntary calls for information (NICNAS, 2013).

The chemical has reported site-limited use including:

- in semi-conductors manufacturing; and
- as a laboratory reagent.

International

The following international uses have been identified through the Substances in Preparations in Nordic Countries (SPIN) database and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported site-limited use including:

- as a laboratory reagent;
- gallium arsenide manufacturing for use in the microelectronic industry;
- glass dyes manufacturing; and
- as a doping agent in the crystal manufacturing for computer chips and fibre optics.

Restrictions

Australian

The chemical, belonging to the group entry 'arsenic', is listed in the Poisons Standard (Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)) 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

International restrictions include:

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.
- Health Canada List of Prohibited and Restricted Cosmetic Ingredients ("Hotlist").

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

T+; R26 (Acute toxicity)

Xn; R48/20 (Repeat dose toxicity)

Exposure Standards

Australian

The chemical has an exposure standard of 0.16 mg/m³ (0.05 ppm) time weighted average (TWA).

International

The following exposure standards are identified (Galleria Chemica):

- An exposure limit (TWA) of 0.01–0.5 mg/m³ in different countries such as USA (Alaska, Hawaii), Canada (Yukon), Norway and Switzerland.

Health Hazard Information

Toxicokinetics

The chemical is rapidly absorbed by inhalation and easily crosses the alveolo-capillary membrane and the red blood cell membrane (IPCS, 1997). On average, 64 % of inhaled arsine was absorbed in mice when exposed by inhalation to concentrations of 25–2500 mg/m³ for periods ranging from one hour to 24 hours (CICAD, 2002). After exposure to the chemical, blood concentrations rise rapidly, but accumulation in other organs such as the liver or kidneys is slow (Pakulska and Czerczak, 2006). The chemical is metabolised to arsenite, monomethylarsonic and dimethylarsinic acids (IPCS, 1997). The metabolites arsenite (20 %), monomethylarsonic (20 %) and dimethylarsinic acids (60 %) are excreted in urine (IPCS, 1997).

Acute Toxicity

Oral

No data are available. The chemical is a gas at room temperature and ingestion is unlikely.

Dermal

No data are available.

Inhalation

The chemical is currently classified as hazardous with the risk phrase ‘Very toxic by inhalation’ (T+; R26) in the HSIS (Safe Work Australia). The available data support this classification.

The acute toxicity of the chemical is a result of its haemolytic effects (CICAD, 2002). Female B6C3F1 mice exposed for one hour to 5–26 parts per million (ppm) of the chemical had a linear decrease (with respect to dose) in haematocrit values 24 hours after exposure. In another study, 100 % mortality was observed across four animal species (Fischer 344 rats, B6C3F1 and C57BL/6 mice, and Syrian Golden hamsters) after exposure to 81 mg/m³ arsine gas for six hours (CICAD, 2002)

Observation in humans

Human cases of accidental poisoning indicate that the chemical causes a rapid and severe Coombs-negative haemolytic anaemia, which is a specific adverse effect of arsine gas exposure (HSDB). Further symptoms of acute toxicity include malaise, abdominal cramps, nausea and vomiting, red staining of conjunctivae and dark red urine (HSDB). Other symptoms include bronzing of the skin, pyrexia, and severe anaemia (IPCS, 1997).

Corrosion / Irritation

Skin Irritation

No animal data are available.

Eye Irritation

No animal data are available.

Observation in humans

Contact with the gaseous form of the chemical has been reported to cause chemical burns, and contact with liquid arsine may cause tissue to freeze (frostbite) (IPCS, 1997). Accidental human exposure to the chemical has been reported to cause redness of the skin. Eye effects include watering, photophobia, blurred vision and red staining of the conjunctivae (HSDB).

Sensitisation

Skin Sensitisation

No data are available.

Repeated Dose Toxicity

Oral

No data are available.

Dermal

No data are available.

Inhalation

The chemical is currently classified as hazardous with the risk phrase ‘Danger of serious damage to health by prolonged exposure through inhalation’ (Xn; R48/20) in the HSIS (Safe Work Australia). The available data support an amendment to this classification.

In general, across all repeated dose toxicity studies conducted in animals (rats, mice and hamsters), the major organ system affected is the blood, characterised through haemolysis, decrease in red blood cell count, and changes in haemoglobin levels (CICAD, 2002).

In a 12-week repeated dose inhalation toxicity study, exposure to 0.08, 1.6, or 8.1 mg/m³ for 12 weeks resulted in anaemia in animals exposed to 8.1 mg/m³. At the lowest dose (0.08 mg/m³), a 2 % increase in mean red blood cell volume was observed. Furthermore, an increase in spleen weights (25 %) was also observed at the lowest concentration—0.08 mg/m³ (CICAD, 2002). Histopathological investigation of the spleen was not reported. The derived lowest observed adverse effect concentration (LOAEC) for this study is 0.08 mg/m³.

Observation in humans

In humans, long-term and/or occupational exposure may cause symptoms similar to those observed in cases of accidental poisoning (refer above). Symptoms and related system organ failure may be delayed until toxic concentrations are reached in the body. An example of concentration-dependant effects are described in an observational study, which suggested that the degree of anaemia in occupationally exposed workers at facilities (involving the cyanide extraction of gold) to be proportional to the duration of exposure to arsine (CICAD, 2002).

A further study identified reduced haemoglobin levels in zinc ore smelting workers who were occupationally exposed to arsine and who had urinary arsenic concentrations below 0.2 mg/L. However, once a special ventilation system had been installed, the haemoglobin levels in the workers gradually returned to their normal values (CICAD, 2002).

Intravascular haemolysis developing within a few hours is characteristic of arsine poisoning. The haematological changes in humans are consistent with those observed in laboratory animals and include anaemia, damage to red blood cells and leucocytosis, accompanied by increased plasma-free haemoglobin, iron, and potassium concentrations (CICAD, 2002).

Renal effects noted after arsine poisoning are a downstream result of the haematological effects mentioned. Haemoglobinuria resulting from arsine poisoning has been reported to result in renal tubule blockage, oliguria, or anuria. Anuria can develop within two days after exposure. Untreated renal failure (treatment through dialysis) resulting from severe arsine intoxication is reported to cause death (CICAD, 2002).

Genotoxicity

No data are available on the chemical. Inorganic arsenic compounds do not induce point mutations, but have been reported to induce chromosomal abnormalities in vitro (including changes in the structure and number of chromosomes, endoreduplication, sister chromatid exchange, and effects on methylation and repair of DNA) (CICAD, 2002). However, the data are too limited to draw a firm conclusion (ATSDR, 2007; NICNAS).

Carcinogenicity

The chemical is carcinogenic and warrants classification.

No data are available for the chemical. However, the International Agency for Research on Cancer (IARC) determined that 'Arsenic and inorganic arsenic compounds are *carcinogenic to humans (Group 1)*', based on human and animal data, information on metabolites, chemical characteristics and mode of action of carcinogenicity (IARC, 2012). IARC considered that arsenic species share the same metabolic pathway, being arsenate to arsenite to methylarsonate to dimethylarsenite. Therefore, IARC concluded that 'independent of the mechanisms of the carcinogenic action, and independent of which of the metabolites is the actual ultimate carcinogen, different inorganic arsenic species should be considered as carcinogenic'.

Arsine metabolises to arsenite and monomethylarsonic and dimethylarsinic acids (IPCS, 1997). Considering that the metabolites of the chemical are reported to cause carcinogenicity and that arsenite is already classified on HSIS as a Category 1 carcinogen, arsine should also be considered carcinogenic to humans.

Reproductive and Developmental Toxicity

Based on the available animal studies, the chemical is not toxic to development. Overall, the available data are inconclusive in regards to reproductive and developmental toxicity for inorganic arsenic compounds (NICNAS a).

In an animal study, CD-1 mice and Fischer 344 rats were exposed to the chemical by inhalation (0.08, 1.6, or 8.1 mg/m³) from gestation days 6–15. In rat dams, splenomegaly (increase in spleen size) and decreased packed red cell volume were observed at the highest dose. In mice, dams exposed to 8.1 mg/m³ developed significant splenomegaly. However, no developmental toxicity was observed in either species (CICAD, 2002).

Other Health Effects

Neurotoxicity

Cases of accidental poisoning in humans have indicated that the chemical can induce the following acute symptoms indicative of neurotoxicity—disorientation, chills, convulsions, and paraesthesia. Other symptoms, such as peripheral neuropathy, are

reported to occur up to 10 days after acute exposure, and in one case, symptoms of regressive polyneuritis in the lower and upper extremities were observed three months after exposure (CICAD, 2002).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effect (cumulative toxicity and carcinogenicity), and a systemic acute effect (acute toxicity by inhalation route of exposure). The chemical may also cause toxic effects following repeated exposure through inhalation.

Public Risk Characterisation

The chemical is used in semiconductor manufacturing in the microelectric industry and is completely consumed in this application.

Given the uses identified for the chemical, it is unlikely that the public will be exposed. Therefore the risk to the public is not considered to be unreasonable.

The chemical is currently listed on Schedule 7 of the SUSMP with the exemptions not being relevant to the uses of the chemical. 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, inhalation exposure of workers to the chemical may occur if adequate precautions are not taken.

Given the critical systemic long-term and acute health effects, the chemical may pose an unreasonable risk to workers unless adequate control measures to minimise inhalation exposure to the chemical are implemented. The chemical 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 the chemical 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

Public Health

No regulatory controls are required, as apart from the industrial use of the chemical in the manufacture of semiconductors, the chemical is not available to the public due to scheduling restrictions.

Work Health and Safety

The chemical is 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.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Very toxic by inhalation (T+; R26)*	Fatal if inhaled - Cat. 1 (H330)
Repeat Dose Toxicity	Toxic: danger of serious damage to health by prolonged exposure through inhalation (T; R48/23)	Causes damage to organs through prolonged or repeated exposure - Cat. 1 (H372)
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 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.

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Last update 28 June 2013

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