Arsenic pentoxide and arsenic acid: Human health tier II assessment

28 June 2013

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Arsenic oxide (As2O5)	1303-28-2
Arsenic acid (H3AsO4)	7778-39-4

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

This group includes arsenic pentoxide (CAS No. 1303-28-2) and arsenic acid (CAS No. 7778-39-4), collectively referred to as pentavalent arsenates. Members in this group are compounds with arsenic in an oxidation state of +5. These chemicals are chemically related as arsenic pentoxide is the anhydrous form of arsenic acid.

As arsenic acid is an analogue of phosphoric acid, this group of chemicals shows corrosive properties at low pH. The biological toxicity of this group of chemicals arises in part from the conversion of pentavalent arsenates (+5) to arsenites (+3). Furthermore, pentavalent arsenates are similar to inorganic phosphate and can replace this in biological processes of glycolysis (energy generation) and respiration (Jomova et al, 2011).

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacture information has been identified for arsenic acid (CAS No. 7778-39-4). For arsenic pentoxide (CAS No. 1303-28-2) the following Australian industrial uses were reported under previous mandatory and/or voluntary calls for information (NICNAS, 2013).

Arsenic pentoxide (CAS No. 1303-28-2) has reported site-limited use including:

- as an analytical agent in pathology laboratories.

International

Arsenic pentoxide (CAS No. 1303-28-2)

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

The chemical has reported commercial use including:

- dyeing and printing.

The chemical has reported site-limited use including:

- use in the manufacture of arsenates, insecticides, weed killer, fungicides, wood preservatives, coloured glass and metal adhesives.

Arsenic acid (CAS No. 7778-39-4)

The chemical has reported site-limited use including:

- in cotton defoliant and soil sterilisation;
- in manufacture of other arsenic compounds; and
- used in industry specific processes of glass making and wood treating.

Restrictions

Australian

This group of chemicals belong to the group entry 'arsenic' and are listed in the Poisons Standard (Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)) in Schedule 7, with the below entry for industrial uses:

"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 per cent 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:

European Union (EU) Cosmetic Directive 76/768/EEC Annex II: List of substances which must not form part of the composition of cosmetic products.

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

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):

Carc. Cat. 1; R45 (Carcinogenicity)

T; R23/25 (Acute toxicity)

Exposure Standards

Australian

The group of chemicals (arsenic and soluble compounds (as arsenic)) have an exposure standard of 0.05 mg/m³ time weighted average (TWA).

International

The following exposure standards are identified (Galleria Chemica):

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

Health Hazard Information

Toxicokinetics

Studies on experimental animals, as well as on humans, have indicated that approximately 90 % of ingested inorganic (trivalent or pentavalent) arsenic is absorbed from the gastrointestinal tract (IPCS, 1992). In the lungs, water-soluble arsenates are rapidly absorbed. As with most inorganic arsenic compounds, the chemical is considered to be poorly absorbed through the skin and dermal exposure is of less significance compared with inhalation exposure (IPCS, 1992). The chemical is reduced by glutathione (GSH) to a trivalent state and then methylated to form methylarsonic acid (MMA) and dimethylarsinic acid (DMA) which are then eliminated in urine (Jomova et al, 2011). The half-life of arsenates in humans is dependent on the dose administered, and is estimated to be 1−3 days after short-term exposure (IPCS, 1992).

Acute Toxicity

Oral

Arsenic pentoxide (CAS No. 1303-28-2) and arsenic acid (CAS No. 7778-39-4) are classified as hazardous with the risk phrase ‘Toxic if swallowed’ (T; R25) in HSIS (Safe Work Australia). The available data support this classification.

The reported median lethal dose (LD50) for arsenic pentoxide (CAS No. 1303-28-2) was 8 and 55 mg/kg bw in rats and mice, respectively (HSDB). The reported LD50 for arsenic acid (CAS No. 7778-39-4) was 50-200 mg/kg bw in CD-1 mice (REACH). Reported sublethal signs of toxicity include diarrhoea, hypoactivity, ataxia and tremors, which resolved by day four in surviving animals (REACH).

Dermal

The available data on arsenic acid (CAS No. 7778-39-4) suggest that the chemicals in this group warrant hazard classification for acute dermal toxicity (refer to **Recommendation** section).

Dermal exposure to a 75 % aqueous solution of arsenic acid (CAS No. 7778-39-4) was reported to be acutely toxic in animal tests (OECD TG 402). The median lethal dose (LD50) in NZ White rabbits was reported as 1750 mg/kg bw (REACH). Dermal reactions noted in several animals included necrosis followed by scar formation and exfoliation (REACH). Clinical signs noted in surviving animals were decreased food consumption and occurrences of soft or mucoidal stool. Observed sub-lethal effects included hypoactivity, irregular breathing, nasal discharge and decreased food consumption (observed in animals which died within two days) (REACH). Mortality of 20 % and 100 % was observed at 1600 and 3200 mg/kg bw, respectively. Necropsy of the dead animals revealed dermal lesions and abnormalities in the lungs and gastrointestinal tract.

Inhalation

Arsenic pentoxide (CAS No. 1303-28-2) and arsenic acid (CAS No. 7778-39-4) are currently classified as hazardous with the risk phrase ‘Toxic by inhalation’ (T; R23) in HSIS (Safe Work Australia). The available data for arsenic acid (CAS No. 7778-39-4) support this classification.

Acute exposure to arsenic acid (CAS No. 7778-39-4) through inhalation was assessed in CD-1 mice according to OECD TG 403. Male and female mice exposed to 0.57, 1.01 or 2.41 mg/L resulted in mortality rates of 0, 90 and 80 % respectively. Clinical signs observed during the study included respiratory distress, increased secretory responses and diminished body weight gain. Lesions in the respiratory system were observed at necropsy (REACH).

No data are available for arsenic pentoxide (CAS No. 1303-28-2).

Corrosion / Irritation

Corrosivity

The available data suggest that the chemicals in this group warrant hazard classification for corrosivity (refer to **Recommendation** section).

In a study conducted in NZ White rabbits (according to OECD TG 404), half of the tested animals developed tissue necrosis at the application site 4.5 hours post-exposure with arsenic acid (CAS No. 7778-39-4) as a 75 % aqueous solution (REACH). The other half of animals tested had moderate to severe erythema and oedema. The study reported 100 % mortality, 24 hours after dosing. Arsenic acid was found to be corrosive in this study (REACH). Skin contact with arsenic pentoxide (CAS No. 1303-28-2) is reported to cause erythema, a burning sensation, pain, itchy rash, swelling, and eruptions. It is reported that these effects may be increased in the presence of humid environments, moisture, or perspiration on the skin (NIOSH, 2013).

Corrosive chemicals are also considered to cause irreversible effects on the eyes. This is supported by the available data on arsenic acid (CAS No. 7778-39-4) below.

In an eye irritation study in NZ White rabbits, arsenic acid (CAS No. 7778-39-4) was found to be highly irritating with severe conjunctivitis (redness, chemosis, discharge), conjunctival necrosis, iridial damage and marked corneal opacity/ulceration observed at 1, 24, 48 and 72 hours (REACH). Animals which did not have their eyes rinsed after exposure died within nine days or had to be sacrificed for humane reasons. The effects were irreversible in animals which survived up to 21 days (REACH). Arsenic pentoxide has been reported to cause eye irritation, itching, burning, conjunctivitis, watering, diplopia, photophobia, vision dimness, and eye damage or lesion formation (NIOSH, 2013).

Sensitisation

Skin Sensitisation

Arsenic acid (CAS No. 7778-39-4) was not found to induce dermal sensitisation when tested in a Buehler closed patch study. In the study, arsenic acid (CAS No. 7778-39-4) produced a 0 % sensitisation rate and was not considered to be sensitising to guinea pig skin. Two out of ten animals died during the study within 10 days (REACH). HSDB indicates that arsenic pentoxide is "capable of producing skin sensitisation", however specific details are not provided. Based on the available data, hazard classification is not warranted for skin sensitisation.

Repeated Dose Toxicity

Oral

Chemicals in this group cause serious damage to health from repeated oral exposure with a no observed adverse effect level (NOAEL) of 3.74 mg/kg bw/day for arsenic acid (CAS No. 7778-39-4). The available data warrant a hazard classification for repeated dose toxicity.

In a 52 week oral gavage study in four adolescent rhesus monkeys, the no observed adverse effect level (NOAEL) was 3.74 mg/kg bw/day for arsenate. Effects observed at higher concentrations (7.5 mg/kg bw/day) included vomiting and unformed faecal stools within five days of being given the compound (REACH). The male animals showed marked salivation and uncontrolled head shaking. Histopathological changes included: vacuolation of the hepatocytes, decrease of glycogen and dilatation of the proximal kidney tubules. Both animals receiving 7.5 mg/kg bw/day were killed on day 13 for humane reasons (REACH).

There are no data available for arsenic pentoxide (CAS No. 1303-28-2).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

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

A number of studies have investigated the genotoxic potential of chemicals in this group. In vitro gene mutation studies were equivocal (ATSDR, 2007). In a range of studies the chemicals induced in vitro (chromosomal aberrations, sister chromatid exchanges and morphological transformations (without activation)) and in vivo (somatic mutations and mitotic recombinations, and chromosomal aberrations) genotoxicity. (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 pentavalent arsenates, as ‘carcinogenic to humans’ (Group 1) (IARC, 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 (IARC, 2012).

Reproductive and Developmental Toxicity

The hazardous substances databank reports that arsenic pentoxide (CAS No. 1303-28-2) can cause adverse parental effects when injected subcutaneously in mice and affect spermatogenesis when injected into the testes in rats (HSDB). These studies do not follow OECD testing guidelines for the assessment of reproductive and/or developmental toxicity.

While no specific information is available for arsenic acid (CAS No. 7778-39-4), data for inorganic arsenics indicate a potential for the compound to cross the placenta and cause spontaneous abortion or stillbirth (HSDB).

As this group of compounds transforms to arsenites, the NICNAS assessment of trivalent arsenites was considered. The trivalent assessment concluded that there was insufficient evidence, or evidence secondary to maternal toxicity, to classify the compounds under reproductive or developmental toxicity (NICNASa). In the absence of more comprehensive information, the available data are not sufficient to recommend a hazard classification for this group of chemcials.

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, dermal and inhalation routes of exposure) and local effects (corrosivity). The chemicals also cause harmful effects following repeated exposure.

Public Risk Characterisation

In Australia, chemicals in this group have site-limited uses.

Given the uses identified for the chemicals in this group, it is unlikely that the public will be exposed. Hence, the public risk from these 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, the pentavalent arsenates may pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposure are implemented. The group of chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) 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

Work Health and Safety

The chemicals 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.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Toxic if swallowed (T; R25)* Harmful in contact with skin (Xn; R21) Toxic by inhalation (T; R23)*	Toxic if swallowed - Cat. 3 (H301) Harmful in contact with skin - Cat. 4 (H312) Toxic if inhaled - Cat. 3 (H331)
Irritation / Corrosivity	Causes burns (C; R34)	Causes severe skin burns and eye damage - Cat. 1 (H314)
Repeat Dose Toxicity	Danger of serious damage to health by prolonged exposure (Xn; R48)	May cause damage to organs through prolonged or repeated exposure - Cat. 2 (H373)
Genotoxicity	Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68)	Suspected of causing genetic defects - Cat. 2 (H341)

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
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 and inhalation exposure to the chemicals in this group 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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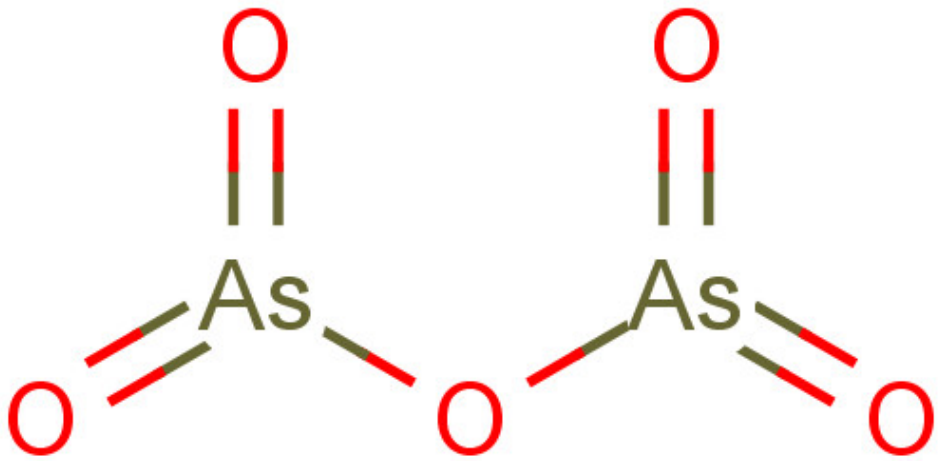
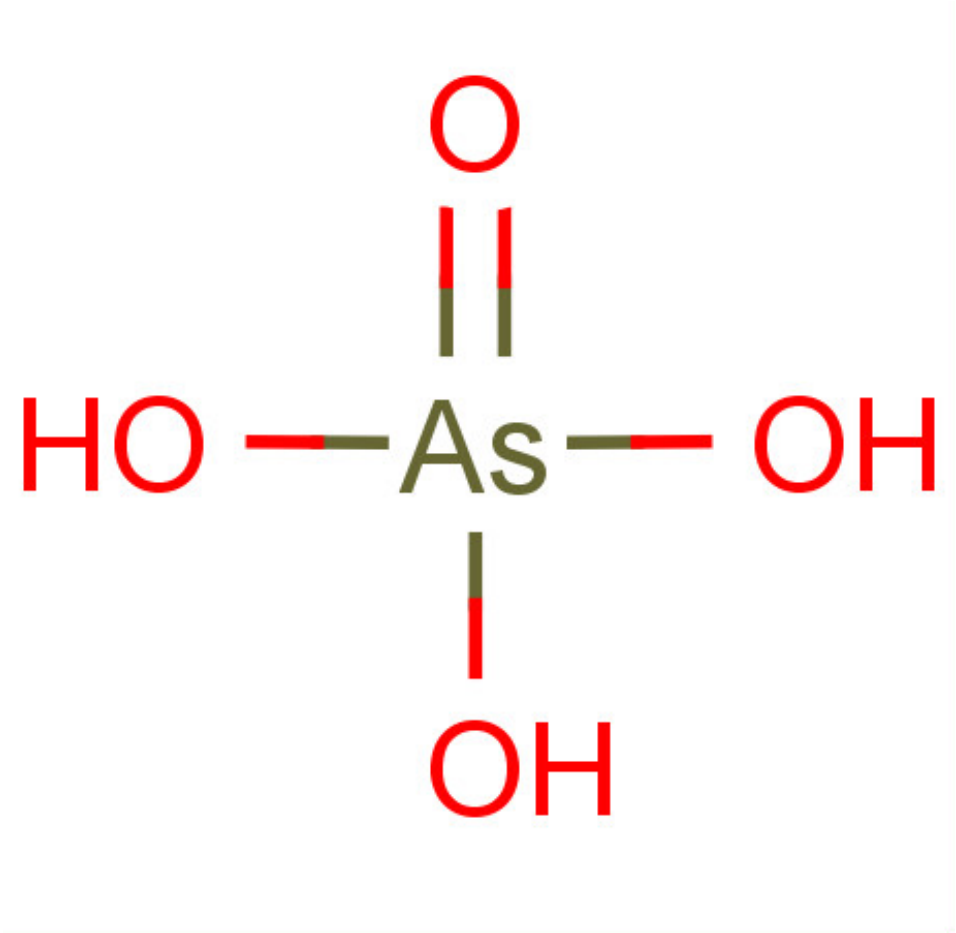
Last Update 28 June 2013

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Arsenic oxide (As2O5)** Arsenic pentoxide Arsenic acid anhydride Diarsenic pentoxide 2,4,6,8,9,10-Hexaoxa-1,3,5,7-tetraarsatricyclo[3.3.1.1<3,7>]decane-1,3,5,7-tetraone

CAS Number	1303-28-2
Structural Formula	
Molecular Formula	As2O5
Molecular Weight	229.84

Chemical Name in the Inventory and Synonyms	**Arsenic acid (H3AsO4)** Arsenate Arsenic acid Orthoarsenic acid
CAS Number	7778-39-4
Structural Formula	

	
Molecular Formula	AsH3O4
Molecular Weight	141.94

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