HPA Compendium of Chemical Hazards

Inorganic Arsenic

Key Points

Fire

- Non flammable under normal conditions
- Emits toxic fumes when heated to decomposition
- Use fine water spray and liquid-tight chemical protective suits with breathing apparatus

Health

- Toxic by ingestion, inhalation and skin absorption
- Corrosive
- Acute inhalation may cause cough, sore throat, breathlessness and wheezing
- Acute ingestion causes vomiting, diarrhoea and abdominal pain
- Inorganic arsenic is irritant to the eyes and skin
- Following chronic ingestion the respiratory tract, nervous system, liver, kidneys or gastrointestinal system may be affected
- Chronic inhalation may cause inflammation of the mucous membranes
- Inorganic arsenic compounds have mutagenic potential
- Inorganic arsenic is a known human carcinogen

Environment

- Dangerous for the environment
- Inform Environment Agency of substantial release incidents

Prepared by J D Pritchard
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2008
Version 3

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Inorganic Arsenic

General information

Key Points

Fire

- Non flammable under normal conditions
- Emits toxic fumes when heated to decomposition
- Use fine water spray and liquid-tight chemical protective suits with breathing apparatus

Health

- Toxic by ingestion, inhalation and skin absorption
- Corrosive
- Short-term inhalation may cause cough, sore throat, breathlessness and wheezing
- Short-term ingestion causes sickness, diarrhoea and abdominal pain
- Inorganic arsenic is irritant to the eye and skin
- Following long-term ingestion the lungs, nervous system, liver, kidneys or stomach may be affected
- Long-term inhalation may cause inflammation of the eyes and nose
- Inorganic arsenic compounds have mutagenic potential
- Inorganic arsenic is a known human carcinogen

Environment

- Dangerous for the environment
- Inform Environment Agency of substantial release incidents

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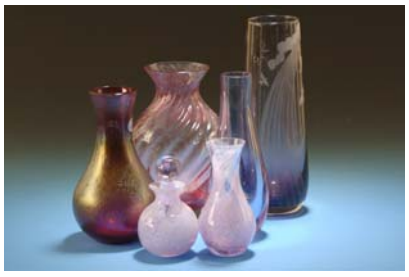
Version 2

Background

Arsenic is a metal element that occurs naturally in the earth's crust and soils. It is usually combined with other elements such as oxygen or chlorine to form compounds including arsenic trioxide or arsenic trichloride. The type of arsenic compound is important when assessing the risk to health, as some forms are much less harmful than others.

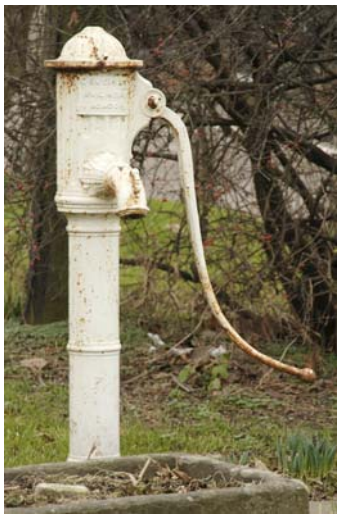
Arsenic is used in a number of industries for making electronic components, special alloys and in the manufacture of certain glass and ceramic products.



Arsenic occurs naturally in the environment so we can be exposed by breathing air and from consuming contaminated food or water. Food is the biggest source of arsenic exposure for most people in the general population, with most arsenic in the UK diet coming from fish. The form of arsenic compound found in fish, called organic arsenic, is much less harmful than most forms used industrially which are mostly inorganic. There is no evidence that eating fish poses a health risk from arsenic.

Cigarette smoke contains arsenic and smoking can double your intake of arsenic each day.

Some areas of the world have naturally high levels of arsenic in water taken from wells including in Hungary, Bangladesh, West Bengal in India and Taiwan. High levels of arsenic do not normally occur in the UK public drinking water supplies.



If exposed to arsenic, the harmful effects that may occur largely depend on the way people are exposed. Breathing air with high levels of arsenic can cause lung damage, shortness of breath, chest pain and cough, which may lead to death in severe cases. However, arsenic levels in the environment are usually not high enough to cause lung damage.

Eating food or drink contaminated with arsenic can cause stomach irritation, nausea, vomiting and diarrhoea. Large amounts can be poisonous and damage the stomach, kidneys, liver, heart and the nervous system and may cause death. Breathing or eating lower levels of air or food contaminated with arsenic over a long period of time can cause changes to the skin and damage to blood circulation.

Children exposed to arsenic will have the same symptoms of poisoning as adults. There is some evidence that exposure to high levels of arsenic can affect the unborn child. Small amounts of arsenic may also be found in breast milk.

Inorganic arsenic compounds are classified as carcinogens i.e. can cause cancer.

Production and Uses

Key Points

Production and uses

- Inorganic arsenic is produced primarily as a by-product from copper, lead and other metal smelting processes
- Uses for inorganic arsenic include glass and ceramics manufacture

Inorganic arsenic is produced primarily as a by-product from copper, lead and other metal smelting processes. Applications for inorganic arsenic include glass and ceramics manufacture. Up to 70% of global arsenic production is used in the industrial preservation of wood, as Chromated Copper Arsenate (CCA). Arsenic metal is used in electronic components (as gallium arsenide), and non-ferrous metal alloys.

Approximately 250 tons of arsenic metal were imported by the UK in 2003-2004.

Frequently Asked Questions

What is arsenic?

Arsenic is a metal that is widely distributed in the earth's crust (soil and rocks), air and water. Arsenic may be found as the metal or as a compound where it is combined with other elements, such as with oxygen to form arsenic trioxide.

What is arsenic used for?

Arsenic is used in a number of industries including the manufacture of glass and ceramics. Arsenic is also used in the industrial preservation of some wood products as well as certain specialist electronic components and alloys.

How does arsenic get into the environment?

Arsenic occurs naturally in rocks and erosion of these can cause arsenic to be released into water. Arsenic is also released into the air from human activities including smelting metals such as lead and copper. Arsenic may enter water and soil in waste from some industrial sites or waste disposal plants.

How could I be exposed to arsenic?

People are exposed to arsenic by eating foods such as fish and shellfish, and from drinking water. Cigarette smoke contains a large amount of arsenic, and smoking can double the amount taken in per day. Very low levels of arsenic are present in drinking water. Soil also may contain arsenic naturally or from contamination from some industrial processes.

If there is arsenic in the environment will I have any adverse health effects?

The presence of arsenic in the environment does not always lead to exposure. Clearly, in order for it to cause any adverse health effects you must come into contact with it. You may be exposed by breathing, eating, or drinking the substance or by skin contact. Following exposure to any chemical, the adverse health effects you may encounter depend on several factors, including the amount to which you are exposed (dose), the way you are exposed, the duration of exposure, the form of the chemical and if you were exposed to any other chemicals.

Arsenic compounds may be corrosive and cause burns to the skin or eyes on contact. Eating food or drink contaminated with high levels of arsenic can irritate the stomach, causing pain, vomiting and diarrhoea. Large amounts can damage the stomach, heart and nervous system and may cause death. Breathing high levels of arsenic dusts or vapours can damage the lungs, which may lead to death in severe cases.

Long term exposures in regions of the world with high levels of arsenic can cause skin changes, may affect blood circulation, the liver and kidneys and nervous system.

Can arsenic cause cancer?

The International Agency for Research on Cancer classified arsenic and its compounds as being carcinogenic in humans. Prolonged exposure to arsenic may produce lung, skin and bladder cancers. Because of this arsenic levels are under stringent control and exposures to arsenic in water, air and food are reduced to the lowest practical level to minimise possible

risks to health. Short term exposure to arsenic is likely to be associated at most with only a very small increase in the risk of cancer.

Does arsenic affect children or damage the unborn child?

If children breathe or ingest arsenic they may have similar effects as in adults i.e. stomach irritation and at high levels may have stomach, heart and nervous system damage.

There is some evidence, though not conclusive, that maternal inhalation exposure to arsenic may affect the unborn child. In several animal tests, high levels of arsenic caused an increased number of animals born with malformations or fewer animals born.

What should I do if I am exposed to arsenic?

It is very unlikely that the general population will be exposed to a level of arsenic high enough to cause adverse health effects.

Inorganic Arsenic

Incident management

Key Points

Fire

- Non combustible under normal conditions
- Emits toxic arsenic fumes and gaseous arsine upon decomposition
- In the event of a fire involving arsenic, use fine water spray and liquid-tight chemical protective suits with breathing apparatus

Health

- Toxic by ingestion, inhalation and skin absorption
- Corrosive
- Secondary contamination may occur
- Inhalation may cause irritation of the upper respiratory tract and cause cough, sore throat, breathlessness, wheeze, pulmonary oedema and respiratory failure
- Ingestion causes abdominal pain, vomiting, diarrhoea, hypovolaemic shock and cardiovascular collapse
- Arsenic is highly irritant and corrosive to the eye causing pain, lacrimation, conjunctivitis, photophobia and corneal damage

Environment

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Hazard Identification

Standard (UK) Dangerous Goods Emergency Action Codes[(a)]

UN		**1556**	Arsenic compound, liquid, n.o.s., inorganic, including: arsenates, n.o.s., arsenites, n.o.s., arsenic sulphides	
EAC		**2X**	Use fine water spray. Wear liquid-tight chemical protective clothing in combination with breathing apparatus*. Spillages and decontamination run-off should be prevented from entering drains and watercourses.	
APP		**B**	Gas-tight chemical protective suit with breathing apparatus**.	
Hazards	**Class**	**6.1**	Toxic substance	
	Sub risks	**-**		
HIN		**66**	Highly toxic substance	

UN		**1556**	Arsenic compound, liquid, n.o.s., inorganic, including: arsenates, n.o.s., arsenites, n.o.s., arsenic sulphides	
EAC		**2X**	Use fine water spray. Wear liquid-tight chemical protective clothing in combination with breathing apparatus*. Spillages and decontamination run-off should be prevented from entering drains and watercourses.	
APP		**-**		
Hazards	**Class**	**6.1**	Toxic substance	
	Sub risks	**-**		
HIN		**60**	Toxic or slightly toxic substance	

UN – United Nations number; EAC – Emergency Action Code; APP – Additional Personal Protection; HIN - Hazard Identification Number

* Liquid-tight chemical protective clothing (BS 8428) in combination with self-contained open circuit positive pressure compressed air breathing apparatus (BS EN 137).
** Gas-tight chemical protective clothing conforming to BS EN 943 part 2 in combination with self-contained open circuit positive pressure compressed air breathing apparatus to BS EN 137.

[a] Dangerous Goods Emergency Action Code List, HM Fire Service Inspectorate, Publications Section, The Stationery Office, 2004.

Standard (UK) Dangerous Goods Emergency Action Codes[a]

UN		**1557**	Arsenic compound, liquid, n.o.s., inorganic, including: arsenates, n.o.s., arsenites, n.o.s., arsenic sulphides	
EAC		**2X**	Use fine water spray. Wear liquid-tight chemical protective clothing in combination with breathing apparatus*. Spillages and decontamination run-off should be prevented from entering drains and watercourses.	
APP		**-**		
Hazards	**Class**	**6.1**	Toxic substance	
	Sub risks	**-**		
HIN		**66/60**	Highly toxic/toxic or slightly toxic substance	

UN		**1558**	Arsenic	
EAC		**2Z**	Use fine water spray. Wear normal fire kit in combination with breathing apparatus*. Spillages and decontamination run-off should be prevented from entering drains and watercourses.	
APP		**-**		
Hazards	**Class**	**6.1**	Toxic substance	
	Sub risks	**-**		
HIN		**60**	Toxic or slightly toxic substance	

UN – United Nations number; EAC – Emergency Action Code; APP – Additional Personal Protection; HIN - Hazard Identification Number

* Normal fire fighting clothing i.e. fire kit (BS EN 469), gloves (BS EN 659) and boots (HO specification A29 and A30) in combination with self-contained open circuit positive pressure compressed air breathing apparatus (BS EN 137).

[a] Dangerous Goods Emergency Action Code List, HM Fire Service Inspectorate, Publications Section, The Stationery Office, 2004.

Chemical Hazard Information and Packaging for Supply Classification [a]

Arsenic

Classification	**T+**	Very toxic	
	N	Dangerous for the environment	
Risk phrases	**R23/25**	Toxic by inhalation and if swallowed	
	R50/53	Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment	
Safety phrases	**S1/2**	Keep locked up and out of reach of children	
	S20/21	When using do not eat, drink or smoke	
	S28	After contact with skin, wash immediately with plenty of … (see manufacturers advice)	
	S45	In case of accident or if you feel unwell seek medical advice immediately (show the label where possible)	
	S60	This material and its container must be disposed of as hazardous waste	
	S61	Avoid release into the environment. Refer to special instructions/safety.	

[a] European Chemicals Bureau, Classification and Labelling, Annex I of Directive 67/548/EEC; http://ecb.jrc.it/classification-labelling/ (accessed 2/2007).

Chemical Hazard Information and Packaging for Supply Classification [a]

Arsenic compounds [b]

Classification	**T+**	Very toxic	
	N	Dangerous for the environment	
Risk phrases	**R23/25**	Toxic by inhalation and if swallowed	
	R50/53	Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment	
Safety phrases	**S1/2**	Keep locked up and out of reach of children	
	S20/21	When using do not eat, drink or smoke	
	S28	After contact with skin, wash immediately with plenty of … (see manufacturers advice)	
	S45	In case of accident or if you feel unwell seek medical advice immediately (show the label where possible)	
	S60	This material and its container must be disposed of as hazardous waste	
	S61	Avoid release into the environment. Refer to special instructions/safety.	

Specific concentration limits

Concentration	Classification
C ≥ 25 %	T, N; R23/25-50/53
2.5 % ≤ C < 25 %	T, N; R23/25-51/53
0.25 % ≤ C < 2.5 %	T; R23/25-52/53
0.2 % ≤ C < 0.25 %	T; R23/25
0.1 % ≤ C < 0.2 %	Xn; R20/22

[a] European Chemicals Bureau, Classification and Labelling, Annex I of Directive 67/548/EEC; http://ecb.jrc.it/classification-labelling/ (accessed 2/2007).
[b] Arsenic compounds with the exception of diarsenic trioxide, arsenic trioxide diarsenic pentaoxide, arsenic pentoxide and arsenic oxide

Physicochemical Properties [a,b,c]

CAS number	7440-38-2
Atomic weight	75
Chemical symbol	As
Common synonyms	Grey arsenic; metallic arsenic
State at room temperature	Solid
Volatility	Non-volatile at 20 °C
Specific gravity	5.7 at 14 °C (water = 1)
Flammability	Non-combustible, substance itself does not burn
Lower explosive limit	Data not available
Upper explosive limit	Data not available
Water solubility	Sparingly and extremely slowly soluble in cold water
Reactivity	Forms volatile, highly toxic arsine gas when reduced in acid solution
Reaction or degradation products	Emits toxic arsenic fumes and gaseous arsine upon decomposition
Odour	Odourless

[a] Arsenic (HAZARDTEXT® Hazard Management). In: Klasco RK (Ed): TOMES® System. Thomson Micromedex, Greenwood Village, Colorado (Edition expires [06/2007]) (accessed 02/2007).
[b] The Merck Index (14th Edition). Entry 794; Arsenic, 2006.
[c] The Dictionary of Substances and their Effects. Ed. S Gangolli. Second Edition, Volume 1, 1999.

Threshold Toxicity Values

THRESHOLD LEVELS		
EXPOSURE BY INHALATION		SYMPTOMS
ppm	mg m^{-3}	
-	-	Data not available

Published Emergency Response Guidelines

Emergency Response Planning Guideline (ERPG) Values

	Listed value (ppm)	Calculated value (mg m^{-3})
ERPG-1*	Data not available	
ERPG-2**		
ERPG-3***		

* Maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hr without experiencing other than mild transient adverse health effects or perceiving a clearly defined, objectionable odour.
** Maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hr without experiencing or developing irreversible or other serious health effects or symptoms which could impair an individual's ability to take protective action.
*** Maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hr without experiencing or developing life-threatening health effects.

Acute Exposure Guideline Levels (AEGLs) [(a)]

	mg m^{-3}				
	10 min	**30 min**	**60 min**	**4 hr**	**8 hr**
AEGL-1†	-	-	-	-	-
AEGL-2††	3.7	3.7	3.0	1.9	1.2
AEGL-3†††	11	11	9.1	5.7	3.7

† The level of the chemical in air at or above which the general population could experience notable discomfort.
†† The level of the chemical in air at or above which there may be irreversible or other serious long-lasting effects or impaired ability to escape.
††† The level of the chemical in air at or above which the general population could experience life-threatening health effects or death.

[a] U.S. Environmental Protection Agency. Acute Exposure Guideline Levels, http://www.epa.gov/oppt/aegl/pubs/chemlist.htm (accessed 02/2007)

Exposure Standards, Guidelines or Regulations

Occupational standards

WEL[a]	LTEL(8 hour reference period): 0.03 ppm (0.1 mg m^{-3})
	STEL (15 min reference period): No guideline value specified

Public health guidelines

DRINKING WATER QUALITY GUIDELINE[b]	10 µg L^{-1} as As (provisional value)
AIR QUALITY GUIDELINE [c]	1 µg m^{-3} equates to an estimate of lifetime risk 1.5 × 10^{-3}
SOIL GUIDELINE VALUE AND HEALTH CRITERIA VALUES [d,e]	**Residential with plant uptake:** 20 mg kg^{-1} dry weight soil
	Residential without plant uptake: 20 mg kg^{-1} dry weight soil
	Allotments: 20 mg kg^{-1} dry weight soil
	Commercial/industrial: 500 mg kg^{-1} dry weight soil
	Index dose $_{oral}$ 0.3 µg kg^{-1} bw day^{-1}
	Index dose $_{inhalation}$ 0.002 µg kg^{-1} bw day^{-1}

WEL – Workplace exposure limit; LTEL - Long-term exposure limit; STEL – Short-term exposure limit

[a] Health & Safety Executive. EH40/2005 Workplace Exposure Limits 2005. The Stationery Office, London, 2005

[b] Interim Guidance on the Water Supply (Water Quality) Regulations 2000 (England) and the Water Supply (Water Quality) Regulations 2001 (Wales). Drinking Water Inspectorate, September 2003.

[c] Air Quality Guidelines for Europe. World Health Organization Regional Office for Europe, Copenhagen WHO Regional Publications, European Series, No. 91, Second Edition, 2000.

[d] Department for Environment Food and Rural Affairs (DEFRA). Soil Guideline Values for Arsenic Contamination, 2002.

[e] Department for Environment Food and Rural Affairs (DEFRA). Contaminants in Soil: Collation of Toxicological Data and Intake Values for Humans. Arsenic. 2002.

Health Effects[a]

Major routes of exposure

- Toxic by ingestion, inhalation and dermal absorption.

Immediate Signs or Symptoms of Acute Exposure [b-e]

- Ingestion: features usually start within 30 minutes to 2 hours. Common features include abdominal pain, vomiting, diarrhoea leading to hypovolaemic shock myocardial depression and cardiovascular collapse. Trivalent arsenic is corrosive to the mouth and mucous membranes causing oral burns, dysphagia and haemorrhagic gastroenteritis.
- Other features of ingestion that may occur include ECG changes, CNS depression, convulsions, encephalopathy and coma, pulmonary oedema, adult respiratory distress syndrome and acute respiratory failure.
- Inhalation: Arsenic compounds are irritant to the upper airways. Features include cough, sore throat, breathlessness, wheeze, pulmonary oedema and respiratory failure. Features of systemic toxicity may also occur.
- Dermal exposure: Arsenic compounds are irritant and corrosive. Trivalent arsenic compounds are well absorbed through the skin and may lead to features of systemic toxicity.
- Ocular exposure: Highly irritant and corrosive to the eye causing pain, lacrimation, blepharospasm, conjunctivitis, photophobia, visual disturbance and corneal damage.

TOXBASE - http://www.toxbase.org
[a] TOXBASE: Arsenic and arsenic compounds, 2003.
[b] TOXBASE: Arsenic – features and management, 2003.
[c] TOXBASE: Arsenic – inhalation, 2003.
[d] TOXBASE: Arsenic – skin contact, 2003.
[e] TOXBASE: Arsenic – eye contact, 2003.

Decontamination and First Aid[(a)]

Important Notes

- Secondary contamination may occur.
- Ambulance staff, paramedics and emergency department staff treating chemically-contaminated casualties should be equipped with Department of Health approved, gas-tight (Respirex) decontamination suits based on EN466:1995, EN12941:1998 and prEN943-1:2001, where appropriate.

Dermal exposure[(b)]

- Remove patient from exposure.
- Remove contaminated clothing, place in double, sealed, labelled clear bags and ensure they are stored away from other patients and staff.
- Wash any affected areas with copious amounts of water.
- Treat skin burns conventionally.

Ocular exposure[(c)]

- Remove patient from exposure.
- Remove contact lenses if necessary and immediately irrigate the affected eye thoroughly with water or 0.9% saline for at least 10-15 minutes. Continue until the conjunctival sac is normal (7.5 – 8.0).
- Any particles lodged in the conjunctival recesses should be removed.
- Patients with corneal damage and those whose symptoms do not resolve rapidly should be referred for ophthalmological assessment.

Inhalation[(d)]

- Remove patient from exposure.
- Maintain a clear airway and adequate ventilation.
- Give humidified oxygen.
- Apply other measures as indicated by the patient's clinical condition.

Ingestion[(e)]

- Ensure clear airway and adequate ventilation.
- Consider gastric lavage if a significant amount has been ingested within 1 hour and vomiting has not already occurred. Activated charcoal is unlikely to be of benefit.
- Commence intravenous fluids in patients with diarrhoea and vomiting.
- Apply other measures as indicated by the patient's clinical condition.

TOXBASE - - http://www.toxbase.org
[a] TOXBASE: Arsenic and arsenic compounds, 2003.
[b] TOXBASE: Arsenic – skin contact, 2003.
[c] TOXBASE: Arsenic – eye contact, 2003.
[d] TOXBASE: Arsenic - inhalation, 2003.
[e] TOXBASE: Arsenic – features and management, 2003.

Inorganic Arsenic

Toxicological overview

Key Points

Kinetics and metabolism

- Absorption of arsenic is largely dependent on the solubility and particle size
- Concentrations of arsenic or its metabolites in blood, hair, nails and urine may be used as biomarkers of arsenic exposure
- Blood arsenic is a useful biomarker only in the case of acute arsenic poisoning or stable chronic high-level exposure
- 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

Health effects of acute exposure

- Single doses of inorganic arsenic may be highly toxic by ingestion and inhalation
- Both ingestion and inhalation may cause gastrointestinal effects such as nausea, diarrhoea and abdominal pain
- Multi-organ failure may occur in severe cases following ingestion
- Inorganic arsenic is irritant to the eye and skin

Health effects of chronic exposure

- Following chronic ingestion a range of non-specific symptoms of the respiratory tract, CNS, endocrine system, liver, kidneys or gastrointestinal system may occur
- Chronic inhalation of arsenic may cause irritation of the mucous membranes leading to conjunctivitis, pharyngitis and rhinitis
- Inorganic arsenic compounds have mutagenic potential
- Inorganic arsenic is a known human carcinogen which acts via a genotoxic mechanism

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Toxicological Overview

Summary of Health Effects

Single doses of inorganic arsenic may be highly toxic by ingestion and inhalation (70-180 mg orally has been fatal). Trivalent arsenic is, in general, more toxic than pentavalent arsenic [1].

Inorganic arsenic is a known human carcinogen which acts via a genotoxic mechanism [2]. It is assumed, therefore, that there is no threshold for such effects and that risk management measures should ensure that exposures are as low as reasonably practical. There is sufficient evidence that chronic exposure to inorganic arsenic in drinking water causes non-melanoma skin cancers and an increased risk of bladder and lung cancers in humans.

The effects of inorganic arsenic on the vascular periphery are well documented. Long-term ingestion of contaminated drinking water may lead to, Raynaud's phenomenon and acrocyanosis and progression to endarteritis obliterans and gangrene of the lower extremities ("Black foot disease"). An increased incidence of cardiovascular disease has also been noted. Haematologically, anaemia and leucopenia may occur together with disturbances in haem synthesis.

Chronic exposure to inorganic arsenic compounds may lead to peripheral and central neurotoxicity [1]. Early events may include paresthesiae followed by muscle weakness. In the periphery, both motor and sensory neurones are affected.

Characteristic dermal lesions after chronic oral or inhalation exposure may include hyperpigmentation and hyperkeratosis.

Other toxic effects associated with chronic exposure to inorganic arsenic include liver injury, cardiovascular disease and diabetes mellitus.

There is limited data from epidemiology to suggest that inorganic arsenic may be a human developmental toxicant, but it is not possible to draw any definitive conclusions. Administration of high doses of inorganic arsenic by oral, intraperitoneal or intravenous routes may cause embryolethality or foetal malformations in laboratory animals.

Inorganic arsenic may cause irritation of the mucous membranes leading to conjunctivitis and pharyngitis and rhinitis after inhalation. Skin irritation and allergic contact dermatitis may occur after exposure to inorganic arsenic compounds.

Kinetics and metabolism

Absorption of arsenic in inhaled airborne particles is highly dependent on the solubility and the size of particles; material that reaches the lungs will be well absorbed. Studies in experimental animals and humans have shown that both soluble pentavalent and trivalent arsenic compounds are rapidly and extensively absorbed from the gastrointestinal tract (over 90%); these include arsenious acid and sodium arsenite [1, 3]. Insoluble compounds such as arsenic disulphide are poorly absorbed.

Inorganic arsenic compounds react with sulphhydryl (-SH) groups of cellular proteins, thereby inhibiting enzymes and therefore oxidative processes including pyruvate and succinate pathways [4].

Arsenic metabolism is characterized by two main types of reactions: (a) reduction reactions of pentavalent to trivalent arsenic, and (b) oxidative methylation reactions in which trivalent forms of arsenic are sequentially methylated to form mono-, di- and trimethylated products using *S*-adenosyl methionine (SAM) as the methyl donor and glutathione (GSH) as an essential co-factor [5].

Methylated products (MMA and DMA) are readily excreted in urine. Animal and human studies suggest that arsenic methylation may be inhibited at high acute exposures.

The metabolism and disposition of inorganic arsenic may be influenced by its valence state, particularly at high dose levels. Studies in laboratory animals indicate that administration of trivalent arsenic, such as arsenic trioxide, results initially in higher concentrations in most tissues than does the administration of pentavalent arsenic. However, the trivalent form is more extensively methylated, leading to similar long-term excretion.

Concentrations of arsenic or its metabolites in blood, hair, nails and urine may be used as biomarkers of arsenic exposure. Blood arsenic is a useful biomarker only in the case of acute arsenic poisoning or stable chronic high-level exposure [1]. 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 [3].

Sources and route of human exposure

Dietary arsenic is the key source of intake for most of the population. Arsenic in the diet is predominantly organic, which is much less toxic than inorganic arsenic. Total arsenic (organic and inorganic species) in fish and shellfish may be higher than most foods; however, inorganic arsenic constitutes less than 1% of this total [6].

High levels of arsenic may be found in water from wells, notably in Bangladesh, West Bengal in India, Taiwan and Hungary.

Workers at smelting plants or residents nearby may be exposed to higher than normal levels of arsenic. Individuals sanding or burning wood preserved with inorganic arsenic may come into contact with vapours or dusts containing inorganic arsenic.

Systemic toxicity may occur after inhalation, ingestion or topical exposure to inorganic arsenic.

Health Effects of Acute / Single Exposure

Human Data

Inhalation

Due to the irritant nature of a number of inorganic arsenic compounds, rhinitis, pharyngitis, laryngitis, and tracheobronchitis may occur. Tracheal and bronchial haemorrhage may complicate severe cases [4]. Gastrointestinal effects including nausea, diarrhoea and abdominal pain have been associated with inhalation of arsenical dusts.

Ingestion

Ingestion of large doses of arsenic may lead to acute symptoms within 30-60 min; effects may be delayed when the arsenic is taken with food. An acute gastrointestinal syndrome is the most common presentation of acute arsenic poisoning characterised by a metallic or garlic-like taste associated with dry mouth, burning lips and dysphagia [1, 7]. Violent vomiting may ensue and may eventually lead to haematemesis. CNS findings may include headaches, weakness and delirium. Gastrointestinal symptoms caused by paralysis of the capillary control in the intestinal tract may include profuse watery diarrhoea and may lead to a decrease in blood volume, lowered blood pressure and electrolyte imbalance. Thus, after the initial gastrointestinal problems, rhabdomyolysis and multi-organ failure may occur, including renal failure, respiratory failure, failure of vital cardiovascular and brain functions, and death [1].

In humans, the smallest recorded fatal oral dose is approximately 70-180 mg [3]. Inorganic arsenic crosses the placental barrier and foetal death has been reported following acute maternal intoxication [4]. 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 [8].

Dermal / ocular exposure

Arsenic trioxide is irritant to the skin and mucous membranes. Pain, lacrimation, blepharospasm, conjunctivitis and corneal damage may occur after exposure to dusts or vapours containing inorganic arsenic. Corrosive compounds such as arsenic trichloride may pose a risk for systemic toxicity due to enhanced absorption through damaged skin.

Delayed effects following an acute exposure

Survivors of acute toxicity often develop bone marrow suppression (anaemia and leucopenia), haemolysis, hepatomegaly, melanosis and polyneuropathy resulting from damage to the peripheral nervous system.

Central and peripheral polyneuropathy is usually more severe in the sensory nerves, but may also affect the motor neurones [9, 10]. In common with other heavy metals, cognitive impairment and behavioural changes may occur. 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 [4].

Animal and In-Vitro Data

General toxicity

The toxic action of inorganic arsenic in experimental animals resembles that seen in man.

Inhalation

In one study, rats were dosed with gallium arsenide and arsenic trioxide (100 and 17 mg kg^{-1}, 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 [1].

Ingestion

The oral LD_{50} of arsenic ranges from 15 to 293 mg kg^{-1} in rats, and from 11 to 150 mg kg^{-1} in other experimental animals [3]. Symptoms observed from arsenic trioxide intoxication in the rat include convulsions, retching and haemorrhaging in the intestinal tract [1].

Dermal / ocular exposure

Inorganic arsenic compounds may be highly irritating to both skin and eye, and lethality has been noted after administration using standard regulatory tests. Studies in guinea pigs did not yield evidence of a sensitization reaction to inorganic arsenic [10].

Health Effects of Chronic / Repeated Exposure

Human Data

It is pertinent to note that many of the chronic toxicities reported in humans are derived from studies that consider areas of the world where arsenic occurs at high concentrations in well water (tens, hundreds or even thousands of micrograms per litre) [2].

In the UK, arsenic in drinking water is not to exceed 10 µg L^{-1} [11], and so this finding is unlikely to present clinically, but may be seen in immigrants from affected areas such as parts of Taiwan, South America, West Bengal in India or Bangladesh.

General toxicity

Signs of chronic toxicity may be difficult to diagnose: a number of body systems may be affected and to different extents. The onset after chronic exposure is insidious with a range of non-specific symptoms reported such as abdominal pain, diarrhoea, vomiting, weight loss and sore throat.

Table 1: Summary of key effects observed in humans after chronic arsenic exposure.

System or Organ	Effect
Respiratory Tract	Inflammation and tracheobronchitis
Dermal	Hyperkeratosis and changes to pigmentation (melanosis)
Vascular	Peripheral vascular disease; ("Blackfoot disease"), myocardial injury
Haematological	Bone marrow depression (resulting in leucopenia and anaemia)
Neurological	Peripheral neuropathy, encephalopathy
Endocrine	Diabetes mellitus
Liver	Hepatomegaly, cirrhosis, altered haem metabolism
Kidneys	Proximal tubule degeneration, papillary and cortical nephrosis
Gastrointestinal	Diarrhoea, vomiting

Inhalation

Inorganic arsenic may cause irritation of the mucous membranes leading to conjunctivitis, pharyngitis and rhinitis and perforation of the septum [5]. Another syndrome noted in smelter workers includes symptoms of tracheobronchitis and signs of pulmonary insufficiency, often due to emphysematous lesions. This picture was found especially among those who had received mixed exposure to arsenic and sulphur dioxide [12].

Dermal changes are major indicators of chronic arsenic toxicity following inhalation or oral exposure (see below).

Although there is good evidence that acute arsenic poisoning causes neurological effects, especially in the peripheral nervous system, there is little evidence of neurological effects from long-term lower-level environmental or occupational exposure. The few published

studies have suggested changes in peripheral nerve function after arsenic exposure, but the studies have been limited by small numbers, different methods used to assess the end-points and co-exposure to other known neurotoxins [1].

Ingestion

Symmetrical hyperkeratoses of the palms and soles, as well as melanosis and exfoliative dermatitis are major indicators of chronic arsenic toxicity following oral or inhalation exposure, but may take years to develop. The skin changes may progress and cover the entire body in multiple forms, and eventually develop into skin cancer [10]. The LOAEL (lowest observed adverse effect level) that results in dermal lesions following oral exposure has been estimated at between 10-100 µg kg day^{-1} [13].

Perivascular effects of inorganic arsenic in humans are well documented [1]. Long-term ingestion of contaminated drinking water may lead to acrocyanosis, Raynaud's phenomenon (a peripheral vascular disease characterized by spasm of the digital arteries and numbness of the fingers). In extreme cases, this may progress to endarteritis obliterans and gangere of the lower extremities ("Black foot disease"). Anaemia and leucopenia may occur together with disturbances in haem synthesis. An increased incidence of myocardial injury, cardiac arrhythmias and cardiomyopathy and cerebrovascular disease (especially cerebral infarction) has been associated with exposure to inorganic arsenic [1].

There is evidence that chronic arsenic ingestion may cause neurological effects, especially in the peripheral nervous system [2]. Signs and symptoms may include motor paralysis, tingling of the skin of extremities, foot and wrist drop, tremors, severe pain and ataxia [3]. In common with other heavy metals, cognitive impairment and behavioural changes may occur. A NOAEL (No observed adverse effect level) of 0.7 µg kg day^{-1} inorganic arsenic in drinking water has been derived using neurological effects as the reported adverse effect [13].

There is suggestive evidence of an increase in the incidence of diabetes mellitus [1] in response to chronic arsenic exposure and hepatic and renal injury. Non-specific gastrointestinal effects including diarrhoea and vomiting have been seen in chronic arsenic poisoning.

Dermal / ocular exposure

Allergic contact dermatitis may occur from repeated dermal exposure and is frequently seen among workers who are exposed to arsenic trioxide [3]. A study of 11 workers at a tin smelting factory where arsenic trioxide levels ranged from 5.2 to 14.4 mg m^{3} showed generalized itch, dry and hyper-pigmented skin, folliculitis, and superficial ulcerations [10]. Conjunctivitis may also occur after exposure to vapours or dusts containing inorganic arsenic [10].

Genotoxicity

Inorganic arsenic compounds clearly have mutagenic potential [13]. In humans, arsenic is a chromosomal mutagen (an agent that induces mutations involving more than one gene, typically large deletions or rearrangements). Arsenic appears to have limited ability to induce point mutations. However, elevated frequencies of micronuclei, chromosomal aberrations and aneuploidy have been detected in the peripheral lymphocytes or urothelial cells, or both, of people exposed to elevated levels of arsenic [2].

Carcinogenicity

IARC have classified inorganic arsenic as a known human carcinogen [2].

Chronic inhalation of inorganic arsenic can cause cancer in humans. A number of studies have shown good correlations between occupational exposure to arsenic and cancer in workers in such environments as copper smelting plants [1]. In one study, an almost ten-fold increase in the incidence of lung cancer was found in workers most heavily exposed to arsenic [14]. Smelter workers are however, exposed to other factors in the working environment, some of which may be carcinogenic. An attempt was made to control for exposure to sulphur dioxide, copper, lead, nickel, selenium, antimony and bismuth in one case-control study, and the excess lung cancer remained. Smoking habits have also been considered in two studies and could not account for the excess of lung cancer noted [15]. With regard to histological type of lung cancer, a significant, relative excess of adenocarcinomas and a slight excess of oat-cell cancers were seen among smelter workers [14].

Long-term ingestion of drinking water contaminated with inorganic arsenic has been causally linked to an increased risk of a number of other cancers [1]. However, in the most recent IARC review in 2004 there was considered to be sufficient evidence in humans that arsenic in drinking-water causes cancers of the urinary bladder, lung and skin only [2].

The skin cancers induced by arsenic are of the non-melanoma type such as Bowen's disease, a squamous cell epithelioma *in situ* [2].

Reproductive and developmental toxicity

The effects of chronic inorganic arsenic on human reproduction are unclear. An association between inhalation exposure to arsenic and an increased risk of adverse developmental effects (foetal, 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 was also exposure 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 [1, 13].

Animal and In-Vitro Data

General toxicity

Long-term administration has produced liver lesions, anaemia, and pathological skin changes in animal models [3].

Genotoxicity

In-vitro studies to investigate the ability to induce point mutations are largely negative [1]. However, positive results were obtained in a number of studies to investigate clastogenicity *in-vitro* in mammalian cells. Inorganic arsenic compounds clearly have mutagenic potential [13].

Inorganic arsenic induces sister chromatid exchanges, chromosomal aberrations and DNA–protein cross-links in human lymphocytes and fibroblasts. These effects are dose-dependent, and sodium arsenite is more potent than sodium arsenate [1].

Clastogenic activity has also been consistently demonstrated *in-vivo* when inorganic arsenic compounds have been investigated in the bone marrow of mice [1].

Carcinogenicity

There is limited evidence for the carcinogenicity of sodium arsenite, calcium arsenate and arsenic trioxide and inadequate evidence for the carcinogenicity of sodium arsenate and arsenic trisulphide [2]. There is limited evidence that supports the carcinogenicity of inorganic arsenic from ingestion, which may in part be due its metabolism [14].

Arsenic trioxide has induced low incidences of carcinomas, adenomas, papillomas and adenomatoid lesions of the respiratory tract in hamsters after intratracheal instillation. A high incidence of lung carcinomas was induced in rats following a single intratracheal instillation of a pesticide mixture containing calcium arsenate. Intratracheal instillations of calcium arsenate into hamsters resulted in a borderline increase in the incidence of lung adenomas, while no such effect was observed with arsenic trisulphide. Sodium arsenite enhanced the incidence of renal tumours induced in rats by intraperitoneal injection of *N*-nitrosodiethylamine [14].

Reproductive and developmental toxicity

Administration of high doses of inorganic arsenic by oral, intraperitoneal or intravenous routes may cause embryolethality, increased resorptions or foetal malformations in laboratory animals [1].

The major teratogenic effects induced by inorganic arsenic in laboratory animals are neural tube defects. The malformations seen are dependent on the dose of arsenic administered as well as the gestational age. Sodium arsenite is a more potent teratogen than sodium arsenate, and parenteral administration of inorganic arsenic is more effective than oral administration. Administration of an acute oral dose of arsenite that is toxic to or near the lethal dose of pregnant mice (40–45 mg kg^{-1}) or hamsters (20–25 mg kg^{-1}) induces a low incidence of teratogenic malformations [1].

An oral study in mice found no significant impact on reproductive success. However, a slightly altered male: female ratio and a slight trend towards a smaller number of pups per litter were noted [13].

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This document will be reviewed not later than 3 years or sooner if substantive evidence becomes available.