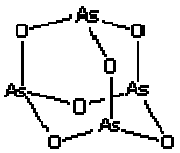
ARSENIC TRIOXIDE

(CAS Reg. No. 1327-53-3)

As_2O_3 / As_4O_6



INTERIM ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

For
NAS/COT Subcommittee for AEGLS

2009

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicological and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. Three levels X AEGL-1, AEGL-2 and AEGL-3 X are developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m;) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m;) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

TABLE OF CONTENTS

LIST OF TABLES

EXECUTIVE SUMMARY

Arsenic trioxide (As_2O_3 / As_4O_6) is a white, odorless powder of low aqueous solubility. Arsenic is the 20th most abundant element in the earth crust, and is obtained as a byproduct of the smelting of other metal ores. Arsenic trioxide is not produced in the USA, although the USA is the world's largest consumer of arsenic. The substance is mainly used in the production of pesticides and as a wood preservative. In addition, arsenic compounds have a long history of use in medicine. Fowler's solution (1% potassium arsenite solution) has been used as a medication. Arsenic trioxide has been used for the treatment of acute promyelocytic leukemia.

AEGL-1 values are not proposed, because there were no human or animal data available relating to AEGL-1 endpoints for arsenic trioxide.

No AEGL-2 effects were reported following acute inhalation exposure to arsenic trioxide. As an alternative, the AEGL-2 values are based on 1/3 of the AEGL-3 values. The proposed AEGL-2 value is supported by the absence of AEGL-2 effects in rats after repeated 6-h exposures to 25 mg/m^3 (Holson et al. 1999) and by the steep concentration-response curve for lethality.

The AEGL-3 values are based on lethality data in rats from a preliminary range-finding study of developmental toxicity. A single exposure of 6 hours resulted in a NOEL for lethality of 50 mg As_2O_3/m^3. The LOEL (with 100% lethality) was 100 mg As_2O_3/m^3 (Holson et al. 1999). A total safety factor of 10 is supported by human exposure data from workplaces (Jakubowski et al. 1998).

The calculated values are listed in the table below.

Summary of AEGL Values for Arsenic trioxide

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	No data on AEGL-1 endpoints available
AEGL–2 (Disabling)	3.7 mg/m^3	3.7 mg/m^3	3.0 mg/m^3	1.9 mg/m^3	1.2 mg/m^3	1/3 of AEGL-3
AEGL–3 (Lethal)	11 mg/m^3	11 mg/m^3	9.1 mg/m^3	5.7 mg/m^3	3.7 mg/m^3	Based on the NOEL for mortality in rats (Holson et al. 1999)

The AEGL values are expressed as arsenic trioxide (mg As_2O_3/m^3).
The cancer risk values (Appendix C) are lower than the AEGL-2 values.

References

Holson, J.F., D.G. Stump, C.E. Ulrich, and C.H. Farr. 1999. Absence of prenatal developmental toxicity from inhaled arsenic trioxide in rats. Toxicol. Sci. 51: 87-97.

1. INTRODUCTION

Arsenic trioxide (As_2O_3 / As_4O_6) is a white, odorless powder of low aqueous solubility. Arsenic is the 20th most abundant element in the earth crust (ATSDR 2000), and is obtained as a byproduct of the smelting of other metal ores. Arsenic trioxide is volatized during smelting and the flue dust (containing 20% arsenic trioxide) is roasted to obtain arsenic trioxide with a 90-95% purity, which can be further purified to 99% by successive sublimations. Arsenic trioxide is not produced in the USA, although the USA is the world's largest consumer of arsenic. Arsenic trioxide is imported mainly from China, followed by Chile (total import 30,000 metric tonnes in 1998) (ATSDR 2000). By 1990, the estimated end-use of arsenic and arsenic compounds in the USA was 70% in wood preservatives, 22% in agricultural chemicals, 4% in glass, 2% in non-ferrous alloys and 2% in other uses including semiconductors (WHO 2001). By 1998, production of wood preservatives accounted for more than 90% of the consumption of arsenic trioxide (ATSDR 2000). Arsenic compounds have a long history of use in medicine. Fowler's solution (1% potassium arsenite solution) has been used as a medication. Arsenic trioxide has been used for the treatment of acute promyelocytic leukemia (ATSDR 2000, WHO 2001).

Table 1. Chemical and Physical Properties

Parameter	Value	Reference
Synonyms	Arsenic oxide; arsenious acid; arsenious oxide; white arsenic	ATSDR 2000
Chemical formula	As_2O_3 (As_4O_6)	ATSDR 2000
Molecular weight	197.84	ATSDR 2000
CAS Reg. No.	1327-53-3	ATSDR 2000
Physical state	solid	ATSDR 2000
Color	white	ATSDR 2000
Solubility in water	37 g/L at 20 °C 115 g/L at 100 °C	ATSDR 2000
Vapor pressure	66.1 mmHg at 312 °C	
Vapor density (air = 1)	no data	
Liquid density (water = 1)	no data	
Melting point	312.3 °C	ATSDR 2000
Boiling point	613 °C sublimes	ATSDR 2000
Odor	Odorless	ATSDR 2000
Flammability	Nonflammable	ATSDR 2000
Explosive	no data	
Conversion factors	n.a.	

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

2.1.1. Case Reports

Inhalation exposure

A worker was buried under arsenic trioxide in an industrial accident. A nearby worker managed to free his head within 1-2 minutes. The victim inhaled a massive (but unknown) dose of arsenic trioxide. He also swallowed substantial (but unknown) amounts of the dust. 5-10 Minutes later he was fully released and taken to hospital. The worker showed a mixture of symptoms from both respiratory and gastrointestinal intake. The initial symptoms (cough, dyspnea, bronchitis, and conjunctivitis) were due to inhalation. Gradually, gastrointestinal symptoms such as epigastric burning, nausea and vomiting dominated the picture. These symptoms were followed by tachycardia, hypotension, and circulatory collapse. Gastric lavage, chelation therapy and other treatments could not prevent that death ensued about 6 h after the accident. Pathological changes included hemorrhages of trachea, bronchi, and alveoli, with massive lung edema. Hemorrhages were also observed in the heart, stomach and thyroid gland, the latter being congested. The myocardium showed widespread foci of necrosis. The concentration of total arsenic was 1.9 mg/L in urine, 3.4 mg/L in blood, and 550 mg/L in gastric fluid shortly after admittance to the hospital. Tissue concentrations of total arsenic at autopsy were 3.8 mg/kg in liver, 2.9 mg/kg in lung, 2.3 mg/kg in blood, 1.4 mg/kg in kidney, 1.2 mg/kg in myocardium, and 0.3 mg/kg in brain (Gerhardsson et al. 1988).

Oral exposure

A 54-year old man ingested 20 g of arsenic trioxide. He received chelation therapy and gastric lavage. However, the arsenic lump was attached to his stomach lining so firmly, that he had to undergo a total gastrectomy. He eventually died from refractory hypotension on the second day. Medical staff developed symptoms during the gastric lavage (eye pain, sore throat, and headache) and at gastrectomy (corneal erosion, laryngitis, contact dermatitis, headache and general fatigue). These symptoms were related to arsine gas produced by the reaction of arsenic with gastric acid (Kinoshita et al. 2004).

Hantson et al (2003) reported the death of a 26-year old man 26 days after being criminally intoxicated with an oral dose of probably 10 g arsenic trioxide, administered over a period of two weeks. The victim developed severe manifestations of toxic hepatitis and pancreatitis, and thereafter neurological disorders, respiratory distress, acute renal failure, and cardiovascular disturbances. Chelating agents were used to enhance arsenic elimination.

A 30-year old man and a 39-year old woman (28 weeks pregnant) developed multiple organ failure with adult respiratory distress syndrome, peaking 8-10 days after eating chocolates with a high (not specified) content of arsenic trioxide. They also developed polyneuropathy with axial degeneration, lasting for at least 26 months with only partly recovery. Both victims survived, but the fetus died on the 5^{th} day, and had extremely high arsenic tissue concentrations (8-26 mg/kg) (Bolliger et al. 1992).

A28-year old man died 3 days after the ingestion of approximately 8 g arsenic trioxide. The clinical picture was characterized by hepatonephritis, cardiomyopathy, and finally, a fatal rhabdomyalysis associated with hemolysis (Benramdane et al 1999).

A 17-year old woman, 7 months pregnant, inges0ted approximately 30 ml rat poison containing 1.32% arsenic trioxide. She was treated with chelators. Four days after ingestion she went into labor and

delivered a live infant that had progressive respiratory distress, and died 11 h of age. Autopsy revealed generalized petechial hemorrhages, hyaline membrane disease, and severe intra-alveolar pulmonary hemorrhage. Arsenic concentrations were very high (0.2-7.4 mg/kg) as compared to the upper levels in adult autopsy material (0.05 mg/kg) reported up to then. The mother survived (Lugo et al. 1969).

A patient died 3.5 h after the accidental ingestion of 21 g (300 mg/kg) of sodium arsenate. Postmortem study revealed brain edema, ulcerations of the whole upper gastrointestinal tract, and severe diffuse bilateral alveolar hemorrhages and lung edema (Civantos et al. 1995).

2.2. Nonlethal Toxicity

2.2.1. Case Reports

Inhalation exposure

Bolla-Wilson & Bleecker (1987) and Beckett et al. (1986) reported neuropsychological effects in a 50-year-old chemical engineer. The effects were believed to be related to subacute occupational exposure to inorganic arsenic. The exposure was not further characterized. Inorganic arsenic levels in urine and hair were elevated to 42 µg/L and 5.1 µg/g in urine and hair, respectively. Normal levels in urine are up to 20 µg/L.

Encephalopathy was described in two young male workers in a wood treatment plant following 14-18 months of occupational inhalation exposure to arsenic fumes. Exposure levels were not reported. Inorganic arsenic levels in urine were elevated to 115 and 300 µg/L (Morton & Caron 1989).

Two case reports were described by Dunlap (1921), representing 'typical histories' of nasal septum perforation, acute laryngitis, and acute dermatitis due to occupational exposure in ore smelting factories. The exposure concentrations were not estimated.

Oral exposure

A number of case reports summarized below describe suicide attempts or criminal intoxications which were not successful. The survival of the victims may be the result of effective gastric irrigation, hemodialysis, and/or immediate chelator therapy. Therefore, the doses taken by the victims may have been lethal without medical intervention.

A 34-year-old male took an oral dose of 192 mg arsenic trioxide (2 mg/kg bw) and survived following chelation therapy. The 24-hour urine arsenic concentration after initiation of chelation therapy was 2945 µg/L (Buchwald 2001).

Michaux et al. (2000) reported a case of a 41-year old woman who ingested 5 g arsenic trioxide. The initial urinary concentration of inorganic arsenic was 3663 µg/L. The victim survived after chelation therapy and gastric alkaline irrigation.

A 27-year old woman was successfully treated with chelation and gastric irrigation after an oral does of 9 g arsenic trioxide. The peak urinary concentration of inorganic arsenic was approximately 12500 µg/L (Vantroyen et al. 2004).

Przygoda et al (2001) report the existence of a group of people (Styrians) in a region of Austria in the 17th century that were 'arsenic eaters'. They consumed arsenic trioxide in amounts of 300-400 mg per dose at a regular basis (every 2-3 days) over lifetime, to improve their health. They seemed to have had no adverse health effects.

A man and a woman each took an oral dose of 2.4 g arsenic trioxide. 5 Hours after ingestion the female had a urinary concentration of arsenic of 10 mg/L. At 12 h after ingestion, the urinary concentration of arsenic in the male was 41 mg/L. Both survived after hemodialysis. Signs of intoxication (before therapy) included encephalopathic, cardiovascular, renal, and gastrointestinal toxicity (Blythe & Joyce 2001).

Isbister et al. (2004) described two arsenic overdoses in a 28- and 30-year old male. These persons took single oral doses of 10 and 25 g, respectively. Both suffered from abdominal pain. They were initially treated with whole bowel irrigation, activated charcoal and N-acetylcysteine or calcium disodium edetate. Chelation therapy was started 11-24 h after dosing. Follow-up showed no clinical evidence of peripheral neuropathy. Peak arsenic concentrations in blood of approximately 600-3800 nmol/L were observed a few hours after dosing. 24-h Urinary concentrations peaked on day one and were approximately 8500 and 1250 µmol per mol creatinine.

A 41-year-old man ingested 8-9 g of "powdered arsenic" and developed vomiting and diarrhea. He was treated for shock and anuria with hemodialysis. The urinary concentration of arsenic was initially 7.5 mg/L. Following chelation treatment this concentration increased to 9.2 mg/L in two days and then decreased to 0.2 mg/L after 14 days. Ten days after ingestion he developed a symmetric polyneuropathy. Nerve biopsy showed acute degeneration of myelinated fibers, and arsenic could be detected within the nerve fibers. The polyneuropathy slowly, but incompletely, subsided over three years, at which time another biopsy showed regenerative proliferation of myelinated and unmyelinated axons and no signs of degeneration. No arsenic was detected in this second biopsy specimen (Goebel et al. 1990).

Moore et al. (1994) reported a case of arsenic ingestion by two men, aged 19 and 21 years. The oral doses were 1 g and 4 g respectively. Both had abdominal pain, diarrhea, nausea and vomiting and one developed hypotension and acute renal failure. Peak arsenic concentrations in urine were approximately 100 and 2000 µg/L. Chelation therapy was started 36 h after ingestion. 14 Days later both patients showed normal renal and neurological functions.

A 30-year-old man tried to commit suicide by taking cocaine, rat poison (arsenic trioxide) and ethanol. The arsenic dose was approximately 2.15 mg. Following chelation and other therapies the man survived, although he was in coma from day 10 to 16, after which he developed peripheral neuropathy. The initial 24-h urine contained 21900 µg arsenic/L (Fesmire et al. 1988).

Intravenous route

Several authors (Unnikrishnan et al. 2001, Wilkinson 2001) report the occurrence of reversible cardiac arrhythmias (torsades de pointes: ventricular tachycardia) due to prolongation of cardiac repolarization (Chiang et al. 2002; Ficker et al. 2004), associated with arsenic therapy for the treatment of leukemia (i.v. dose of 0.15 mg/kg bw/day for a maximum of 50 days; CTI 2002). Westerveld et al. (2001) reported three sudden deaths among ten patients in a phase I/II study using an i.v. dose of 0.1 mg/kg bw/day during the first month of 1-4 monthly cycles of treatment. They failed to identify the cause of sudden death.

2.2.2. Experimental Studies

No human experimental studies with arsenic trioxide were located.

2.2.3. Occupational / Epidemiological Studies

Workers that had been long exposed (8-40 years) to arsenic trioxide dust showed increased vasospastic reactivity in the fingers and increased prevalence of Raynaud's phenomenon (white fingers).

10/47 Workers had a perforation of the nasal septum, acquired long ago. Forty of them reported to have occasional dermatitis of the face; one had a malignant skin tumor. Workers had slightly lower conducting velocities in peripheral motor nerves compared to controls. The authors estimated the uptake of arsenic to be not more than 0.3 mg/day. The urinary concentration of arsenic in these workers was 10-340 µg/L (Blom et al. 1985, Lagerkvist et al. 1986).

In a group of 43 smelter workers exposed to inorganic arsenic dust (particle size estimated at 5 µm) for 13-45 years, nerve conducting velocities were lower in peripheral nerves as compared to controls. The mean total absorption of arsenic was calculated to be less than 5 g over the years. The mean arsenic concentration in urine was 39 µg/L (range 5-520 µg/L) or 14.3 µg/g creatinine (Lagerkvist and Zetterlund, 1994).

Jensen and Hansen (1998) report a statistically significant increase of 23% in glycosylated hemoglobin concentrations in 46 persons working with arsenic (wood preservation) or handling arsenic-impregnated wood, as compared to a reference group (n=26). In addition, a statistically significant increase in systolic blood pressure was observed. Mean total arsenic concentrations in urine (mmol per mol creatinine) were 35.9 (range 11.5-294.5) in workers and 14.5 (range 6.0-44.0) in the reference group. Ambient exposure levels were not measured.

In a double-blind controlled study arsenic workers (employed in a copper smelting factory since approximately 15 years) showed increased incidence of subclinical (reduced nerve conducting velocity) and clinical neuropathy. The clinical and subclinical groups correlated with increased content of arsenic in urine (74-378 µg/L), hair and nails. The inhalation exposure was not estimated (Feldman et al. 1979).

In a factory where sodium arsenite was prepared and packed, the atmospheric dust was sampled on 4 single occasions and additionally on 5 consecutive days. The dust was collected with a cascade impactor (10 minutes or more, 17.5 L/min) in four different areas. The mean values of As (mg/m^3) were 0.384 for dryers, 0.422 for sievers, 1.034 for kibblers, and 0.078 for packers. The cumulative aerodynamic size distribution was as follows: 20-38% of the particles (by mass) had an aerodynamic size smaller than 5 µm, 36-59% smaller than 10 µm, and 48-70% smaller than 15 µm, depending on the job. In the workers of that plant (1-50 working years), the mean urinary As concentrations were 243 µg/L for chemical workers, 101 µg/L for maintenance workers, 107 µg/L for packers, and 92 µg/L for controls. Clinical examinations revealed that chemical workers were grossly pigmented and approximately one-third of them had warts, usually more than one. The maintenance workers and packers "occupied an intermediate position" whilst the controls showed only in a few cases a slight pigmentation and a single wart in two instances only. One chemical worker had a perforated nasal septum. Vital capacity and exercise tolerance were comparable between the different groups examined (Perry et al. 1948).

Eleven male workers, operating a crystallizer used for refining tin ore for 6-8 years in 8-h workshifts, were seen at a skin clinic for generalized itch, dry and hyperpigmentated skin, folliculitis and superficial ulcerations. Three of them had intense itchiness of the scalp and otitis externa; two had occasional cough and difficulty in breathing; but none had other systemic symptoms. The skin effects were attributed to arsenic trioxide exposure via inhalation of dust. Analysis of the airborne dust in different areas of the factory showed arsenic trioxide contents of 0.0052 mg As_2O_3/m^3 (roaster), 0.0144 mg As_2O_3/m^3 (smelter) and 0.0082 mg As_2O_3/m^3 (refinery) (Mohamed 1998).

Two workers showed symptoms following batch mixing in a glass factory. The first worker only occasionally mixed batches. He had an urinary arsenic concentration of 13.3 mmol/mol creatinine and showed symptoms including worsening breathlessness, tremor of both hands, generalized malaise, nausea, and anorexia. The second worker regularly mixed 30 batches a week in a 1 in 3 weeks schedule.

His urinary arsenic concentration was 1845.5 mmol/mol creatinine and he developed an itchy, scaly erythematous macular rash on his forearms and face (Ide and Bullough 1988).

2.3. Neurotoxicity

Peripheral neuropathy is a common finding of arsenic trioxide exposure in workers as well in victims of oral intoxications, see previous paragraphs.

2.4. Developmental / Reproductive toxicity

Two cases of fetal death were reported in poisoned pregnant women (Bollinger et al. 1992; Lugo et al. 1969; see 2.1.1). Both mothers survived. Both authors reported very high arsenic concentrations in the fetal tissues.

2.5. Genotoxicity

Several investigations showed genotoxic effects in human cells as result of exposure to arsenic trioxide.

Workers from a smelter in Sweden, exposed to low-medium-high airborne arsenic trioxide (according to job type) showed an exposure related significant increase in chromosomal aberrations. There was a large individual variation and co-exposure to other potentially hazardous substances (Nordenson et al. 1978; Beckman et al. 1977).

Yamauchi et al. (2004) found an increase in 8-hydroxydeoxyguanine in the urine of 60% of 52 patients with acute arsenic poisoning from the accidental oral intake of arsenic trioxide, which was 2-3 fold higher than in healthy subjects.

Crossen (1983) found that in vitro exposure of human lymphocytes to sodium arsenite could either increase or decrease sister chromatid exchanges.

An increased unscheduled DNA synthesis was found in cultures of human fetal lung fibroblasts exposed to sodium arsenite (Dong and Luo 1994).

2.6. Carcinogenicity

Occupational exposure to atmospheric arsenic trioxide gives rise to increased incidences of lung cancer. This was found in studies among miners in China (Herz-Piciotto and Smith 1993), and among copper smelters in Montana (Lee-Feldstein 1986), Tacoma WA (Pinto et al. 1977; Enterline and Marsh 1982; Enterline et al. 1987; Enterline et al. 1995) and Sweden (Järup et al. 1989; Sandström et al. 1989; Sandström and Wall 1993). Occupational exposure to other arsenic compounds (lead arsenate, calcium arsenate, copper acetoarsenite, and magnesium arsenate) in a pesticides factory also led to increased incidences of respiratory cancer (Ott et al. 1974). IARC (1987) concluded that there is sufficient evidence to classify the arsenic as a human carcinogen.

2.7. Summary of human data

No quantitative human data on lethal inhalation exposure to arsenic trioxide were available. Lethal amounts of orally ingested arsenic trioxide were reported in the range of 8-20 g. Non-lethal inhalation exposure data in humans were available only from occupational settings and were mainly related to years of exposure to unspecified ambient concentrations of arsenic trioxide. Common effects reported were clinical peripheral neuropathy characterized by reduced nerve conducting velocity, perforations of nasal septa, and skin effects such as pigmentation, dermatitis and warts. In addition, encephalopathy, increased vasospastic reactivity in the fingers, increased glycosylated hemoglobin concentrations, and increased systolic blood pressure were reported. Some data on occupational airborne dust exposures were available and are presented in table 2. Here the results are expressed as arsenic and as arsenic trioxide.

Table 2. Occupational exposure measurements

Sample	mg As/m^3	mg As_2O_3/m^3	Reference	see par.
area samples	0.0039 0.0060 0.0109	0.0052 0.0082 0.0144	Mohamed 1998	2.2.3
personal breathing zone samples taken at irregular intervals during a workshift	0.259 (mean, n=10)	0.342 (mean, n=10)	Roels et al. 1982	4.1
area samples taken from 5 places at irregular intervals during a workshift	0.090 (mean, n=5)	0.119 (mean, n=5)	Roels et al. 1982	4.1
area samples taken from different areas on 4 days, sampling times between 3.5 and 8 h	0.001-0.670 (range, n=129)	0.001-0.885 (range, n=129)	Hakala and Pyy 1995	4.1
personal 8-h breathing zone samples taken on 4 days, from inside a breathing mask	0.0008-0.045 (range, n=96)	0.0011-0.059 (range, n=96)	Hakala and Pyy 1995	4.1
personal breathing zone samples worn on 5 consecutive working days	0.003-0.295 (range, n=24	0.004-0.389 (range, n=24	Pinto et al. 1976, 1977	4.1
personal 8-h breathing zone samples taken on one day	0.001-0.746 (range, n=53)	0.001-0.985 (range, n=53	Jakubowski et al. 1998	4.1
personal breathing zone samples taken on the outside of breathing masks during 8-h on a single day	0.0083 (mean, n=30) 0.046 (mean, n=23) 0.053 (mean, n=30) 0.001-1.0 (range, n=83)	0.0110 (mean, n=30) 0.061 (mean, n=23) 0.070 (mean, n=30) 0.001-1.3 (range, n=83)	Smith et al. 1977	4.1
area samples taken 1.5 m above ground at 4 places for 4 hours	0.019-0.164 (range, n=4)	0.025-0.217 (range, n=4)	Offergelt et al. 1992	4.1
personal 8-h breathing zone samples taken on 5 consecutive working days	0.006-0.502 (range, n=90)	0.008-0.663 (range, n=90)	Offergelt et al. 1992	4.1

Urinary concentrations in workers were in the range of 5 to 520 µg/L (most values within 100-200 µg/L), or 10-295 mmol per mol creatinine. For comparison, persons that (just) survived an oral intoxication had peak urinary concentrations of 100-21900 µg/L.

Arsenic trioxide induces oxidative DNA damage in exposed humans. Occupational inhalation exposure to arsenic trioxide leads to increased incidences of lung cancer. IARC (1987) concluded that there is sufficient evidence to classify arsenic as a human carcinogen.

3. ANIMAL TOXICITY DATA

3.1. Acute lethality

The acute *oral* LD_{50}'s of arsenic trioxide, given intraesophageally as an aqueous solution in different mouse strains, ranged from 26 to 48 mg/kg bw. In rats, the oral LD_{50} depended on the vehicle: given intraesophageally as an aqueous solution resulted in an LD_{50} of 145 mg/kg bw, and given as a powder in the (dry) feed resulted in an LD_{50} of 214 mg/kg bw (Harrisson et al. 1958).

3.1.1. Rats

The LD_{50} of arsenic trioxide, suspended in saline and determined after intratracheal instillation in rats, was 18.9 mg As/kg. No further details were given (Rhoads and Sanders 1985).

In a preliminary range-finding study of developmental toxicity (Holson et al. 1999, see also paragraphs 3.2.2 and 3.4), groups of 10 female Crl:CD(SD)BR rats were whole-body exposed for 6 hours to arsenic trioxide dust (MMAD approximately 2.0 µm) at concentrations of 25, 50, 100, 150, and 200 mg/m^3 (expressed as arsenic trioxide). After one day of exposure (6-h) all rats at 100, 150 and 200 mg/m^3 died or were sacrificed *in extremis*. No deaths occurred in the 25 and 50 mg/m^3 groups. After a 3-day recovery period the range-finding study continued with target concentrations of 0.1, 1, 10, and 25 mg/m^3. The 10 females formerly exposed to 50 mg/m^3 were now assigned to the 25 mg/m^3 group, and the 10 females formerly exposed to 25 mg/m^3 were now assigned to the 10 mg/m^3 group. Twenty additional untreated rats were assigned to the 0.1 and 1 mg/m^3 groups. The measured concentrations were 0.11, 1.2, 10, and 26 mg As_2O_3/m^3. Exposure continued from 14 days prior to mating until gestational day 19. The number of deaths in these groups was 0, 0, 0, and 5, respectively, at the end of the study. One female died on exposure day 12 (pre-mating period) and four females died during gestation days 14 and 19.

TABLE 3. Summary of Acute Lethal Inhalation Data in Laboratory Animals

Species	Concentration (mg As_2O_3/m^3)	Exposure Time	Death[a]	Reference
Rat	25[b]	6-h	0/10	Holson et al. 1999
	50[b]		0/10	
	100		10/10	
	150		10/10	
	200		10/10	
Rat	0.11	6-h/d, 33 days	0/10	Holson et al. 1999
	1.2		0/10	
	1*25 + 33*10		0/10	
	1*50 + 33*26		5/10	

[a] number of deaths per number of animals tested

[b] after 3 observation days these animals were used in the subsequent study, presented in the next table-row.

3.2. Nonlethal toxicity

3.2.1. Rabbits / Guinea Pigs / Hamsters

Six Syrian Golden Hamsters were given intratracheal instillations with arsenic trioxide, suspended in phosphate buffer, twice a week for eight weeks, at a dose of 1.3 mg/kg bw. All animals were sacrificed after the last instillation. Lung, spleen, liver and kidney were subjected to histopathological examination. Bodyweight did not change as compared to control animals. Relative lung weight was 20% greater than that of controls, whereas liver weight was 11% lower. Microscopic evaluation of the lungs showed foci of mild to severe inflammatory response, consisting mainly of neutrophils. In addition mild

hyperplasia of alveolar or bronchiolar cells was observed. The other organs examined showed no histopathological changes (Tanaka et al. 2000).

In a kinetic study (see also paragraph 4.1), groups of 6 male and 6 female New Zealand white rabbits were whole body exposed to arsenic trioxide at measured concentrations of 0, 0.05, or 1.1 mg/m^3 (phase I), and 0, 0.1, or 0.22 mg/m^3 (phase II) for 8-h per day, 7 days per week, for 8 weeks. It is not entirely clear whether the exposure concentrations were expressed as arsenic (mg As/m^3) or as arsenic trioxide (mg As_2O_3/m^3). The arsenic trioxide aerosols were generated by means of a dust-feeder system. The measured MMAD ranged from 3.2 to 4.1 µm (GSD 1.64-2.20). The animals were observed daily for clinical signs. No clinical signs were noted at any dose level and weekly measurements showed no effect on bodyweight (Beck et al. 2002).

3.2.2. Rats

In a preliminary range-finding study of developmental toxicity published by Holson et al. (1999; see also paragraphs 3.1.1 and 3.4), groups of 10 female Crl:CD(SD)BR rats were whole-body exposed to arsenic trioxide dust (MMAD approximately 2.0 µm) at measured concentrations of 0, 0.11, 1.2, 10, and 26 mg As_2O_3/m^3 for 6-h per day from 14 days prior to mating until gestation day 19. Decreased food consumption and decreased bodyweight gain or body weight loss were observed during gestation in the 26 mg As_2O_3/m^3 group. Rales were reported in rats exposed to 10 and 26 mg As_2O_3/m^3. In addition, gasping and labored breathing were sporadically noted in animals exposed to the highest concentration of 26 mg As_2O_3/m^3. Other effects at the highest concentration included the presence of red material around the urogenital area, nose, and eyes, and yellow staining of the urogenital area. Gross necropsy of all animals at the end of the study revealed distension of the gastrointestinal tract and dark red contents (hyperemia and discharge of plasma into the intestinal lumen, where it coagulates). The lungs of all animals appeared normal, indicating absence of pulmonary irritation.

In the definitive study of developmental toxicity (Holson et al. 1999) groups of 24 female Crl:CD(SD)BR rats were whole-body exposed to arsenic trioxide dust (MMAD approximately 2.0 µm) at mean measured concentrations of 0, 0.32, 3.4, and 11 mg As_2O_3/m^3 for 6-h per day from 14 days prior to mating until gestational day 19. There was no treatment-related mortality. Maternal toxicity was observed at the highest concentration only as evidenced by rales and a decreased food consumption and body weight gain. The NOAEL for maternal toxicity was 3.4 mg As_2O_3/m^3.

Eight male Fisher-344 rats were given a single intratracheal instillation of arsenic trioxide at a dose of 17 mg/kg bw. The substance was given as a microsieved powder (mean count diameter 9.17 µm, mean volume diameter 18.58 µm) suspended in 0.7 ml saline. After 14 days, 5 of the rats were used for the determination of lung retention and blood analysis, the remaining 3 rats were submitted for histological examination. There was no lung retention of arsenic trioxide and the blood concentration was 36 ± 3 ppm, representing 20% of the dose administered. The lung dry weight, lung protein content, lung DNA content, and the DNA:lung wet weight ratio were significantly increased, as was the 4-HP content, indicating a fibriogenic response. Histopathologically, the lungs showed multifocal interstitial pneumonia which was focally severe and compounded with focal proliferative bronchiolitis and alveolitis. Alveolar walls were thickened with hyperplastic pneumocytes while foamy macrophages were observed in the alveolar lumina. It was noted that no histopathological evidence was found for fibriogenic changes (Webb et al. 1986).

Eight male Wistar rats Hamsters were given intratracheal instillations with arsenic trioxide, suspended in phosphate buffer, twice a week for eight weeks, at a dose of 1.3 mg/kg bw. The study focused on testicular changes. At sacrifice after the last instillation, none of these rats showed any histopathological changes of the testis or sperm (Omura et al. 1996). It is noted that oral administration of

0.5 mg arsenic trioxide/kg bw/day to mice for 30 days did result in structural changes of the testis (Chinoy et al. 2004).

3.2.3. Mice

A single 3-h inhalation exposure to aerosols of arsenic trioxide (0, 0.125, 0.270, 0.500, and 0.940 mg As/m^3, corresponding to 0, 0.165, 0.356, 0.660, and 1.24 mg As_2O_3/m^3; MMAD 0.4 µm, GSD 2.6) in female CD-1 mice was followed by infectious aerosol challenges to measure the changes in susceptibility to Streptococcus and the changes in bactericidal activity to Klebsiella pneumonia. Exposures to arsenic trioxide resulted in a higher susceptibility to a Streptococcus infection as evidenced by a dose-related increase in excess mortality (6.4-50.5%) at all exposure concentrations which was statistically significant from 0.356 mg As_2O_3/m^3 and higher. Multiple 3-h exposures (5 or 20) did not enhance the effects on mortality. It is noted that the investigators did not expose mice to arsenic trioxide without bacterial challenges. The bactericidal activity against K. pneumonia measured 3-h after the infection was not changed at 0.165 mg As_2O_3/m^3. At 0.356 mg As_2O_3/m^3 the activity was significantly decreased after 1 and 20 3-h exposures, but not after 5 3-h exposures. Significant decreases in activity were observed after single and multiple exposures to 0.660 and 1.24 mg As_2O_3/m^3 (Aranyi et al. 1985).

TABLE 4. Summary of Nonlethal Inhalation Data in Laboratory Animals

Species	Concentration (mg/m^3)	Exposure Time	Effect	Reference
rabbits	0.05-1.1 mg/m^3 it is not clear whether this is expressed as As or as As_2O_3	8-h/day for 8 weeks	no clinical signs and no effects on bodyweight at any exposure level	Beck et al. 2002
mice	0.356-1.24 mg As_2O_3/m^3	3-h	increased susceptibility to bacterial infections	Aranyi et al. 1985
rats	0, 0.11, 1.2, 10, and 26 mg As_2O_3/m^3	6-h/day, for 33 days	Rales at 10 and 26 mg/m^3, sporadical gasping and labored breathing at 26 mg/m^3	Holson et al. 1999

3.3. Neurotoxicity

No data.

3.4. Developmental / Reproductive toxicity

In a brief article, Nagymajtényi et al. (1985) report a developmental study in which mice (strain not given) were exposed to atmospheric arsenic trioxide concentrations of 0, 0.26, 2.9, and 28.5 mg/m^3 in inhalation chambers for 4-h per day during gestation days 9 through 12. It is unclear whether the exposure concentrations were expressed as arsenic (mg As/m^3) or arsenic trioxide (mg As_2O_3/m^3). Aerosols were generated from an aqueous solution, but no further details were given on generation, characterization, monitoring or analytical methods. The authors report a significant decreased fetal weight at the two highest doses. They also report significantly increased skeletal malformations (sternal, vertebral, skull; not further specified) at the highest dose, but failed to quantify malformations on a litter basis, and did not discuss the nature and severity of the observed malformations. The authors categorized skeletal variations

(including retarded ossification) as malformations, which is not in line with standardized terminology. In addition, the authors did not report on the occurrence of maternal effects. In the liver of fetuses from high dose animals, increased chromosomal aberrations were found.

Groups of 24 female Crl:CD(SD)BR rats were whole-body exposed to arsenic trioxide dust (MMAD approximately 2.0 µm) at mean measured concentrations of 0, 0.32, 3.4, and 11 mg As_2O_3/m^3 for 6-h per day from 14 days prior to mating until gestational day 19. There was no treatment-related mortality. Maternal toxicity was observed at the highest concentration only as evidenced by rales and a decreased food consumption and body weight gain. Intrauterine parameters were unaffected by treatment. No treatment related malformations or developmental variations were noted at any exposure level. The NOAEL for maternal toxicity was 3.4 mg As_2O_3/m^3 (Holson et al. 1999).

3.5. Genotoxicity

Honma et al. (1999) evaluated a number of chemicals, including arsenic trioxide, for their ability to induce gene mutations *in vitro* in the mouse lymphoma TK system. Arsenic trioxide was tested with and without metabolic activation (rat S9) at a concentration of (probably) 1%, and showed positive results under both conditions.

The same mouse lymphoma test was used by Moore et al. (1997) to test sodium arsenite, sodium arsenate, and the mono- and di-methylated metabolites (MMA and DMA, these are also metabolites of arsenic trioxide). A genotoxic response was observed for all four compounds, but for sodium arsenite and arsenate at much lower concentrations (1-2 and 10-14 µg/ml, respectively) than for MMA and DMA (2500-5000 and almost 10000 µg/ml, respectively). The researches also analyzed the induction of microscopically visible gross chromosomal aberrations. Sodium arsenite, sodium arsenate and MMA were considered clastogenic, whereas DMA, despite a slight response, could not be classified as such. Sodium arsenite and DMA induced micronuclei, and sodium arsenite and sodium arsenate induced polyploidy.

Hei et al. (1998) tested arsenite *in vitro* for gene mutations in A_L hybrid cells that contain a standard set of CHO-K1 chromosomes and a single copy of human chromosome 11. A dose-dependent response was seen in mutants at both the $HPRT^-$ and $S1^-$ locus. Co treatment with the oxygen radical scavenger dimethyl sulfoxide (DMSO) significantly reduced the mutagenic response.

Sodium arsenite was tested *in vitro* for chromosomal aberrations and sister chromatid exchanges in Chinese hamster ovary cells. The most profound effect was a marked increase in endoreduplication. Also chromosomal aberrations were significantly increased, as were SCE's but to a lesser extent (Kochhar et al. 1996).

Banu et al. (2001) performed an *in vivo* Comet assay where DNA strand breaks were analyzed in blood leukocytes of mice given single oral doses of 0, 0.13, 0.27, 0.54, 1.08, 2.15, 4.30, and 6.45 mg arsenic trioxide/kg bw. All doses induced a significant increase in tail length at 24, 48, and 72 after dosing. The response at 48 h was higher than at 24 h, but gradually decreased after 72 h, indicating DNA repair activity.

The *in vivo* clastogenicity of sodium arsenite was investigated in BALB/c mice. A dose-related increase in micronucleated polychromatic bone marrow cells was observed in mice given i.p. doses of 0.5, 2.5, 5.0, and 10.0 mg/kg bw. A dominant lethal test in mice given an i.p. dose of 5.0 mg/kg bw and a sperm abnormality test in mice given i.p. doses of 2.5, 5.0, and 7.5 mg/kg bw showed negative results (Deknudt et al. 1986).

Arsenic trioxide and dimethylarsinic acid (DMA), a main metabolite of arsenic trioxide, were tested for gene mutations in several organs of transgenic mice ("Muta Mouse") given i.p. doses of 7.6 mg/kg bw for 5 days (arsenic trioxide) and 10.6 mg/kg bw for 5 days (DMA). Treatment with arsenic trioxide did not result in increases of mutant frequencies, whereas treatment with DMA resulted only in a weak increase in the lung but not in other organs. Analysis of micronucleated peripheral blood reticulocytes showed marginally positive results with arsenic trioxide but negative results with DMA (Noda et al. 2002).

3.6. Carcinogenicity

Ishinishi et al. (1976) did not find any malignant tumors following installation of 2 or 10 mg arsenic trioxide/kg bw per day for 40 days in the stomach of Wistar-King rats (observation for 30 weeks), or following installation of 3 mg arsenic trioxide (aqueous suspension) in the lungs of Wistar-King rats once a week for 4 months (lifetime observation).

Pershagen et al. (1984) examined the pulmonary carcinogenicity of arsenic trioxide (As) and benzo[a]pyrene (BaP), alone or in combination, in male Syrian golden hamsters. The substances were given by intratracheal instillation, once a week, for 15 weeks. At each instillation about 3 mg/kg bw as arsenic and/or 6 mg/kg bw of BaP was administered. Carcinomas of the larynx, trachea, bronchi or lungs were found in 3/25, 17/40, and 25/54 animals of the As, BaP, and As+BaP groups.

Another pulmonary carcinogenicity study in male Syrian golden hamsters was published by Yamamoto et al. (1987). They administered the hamsters arsenic trioxide by intratracheal instillation at a dose of 3.75 mg/kg bw, once a week for 15 weeks. One lung adenocarcinoma was found in the 17 hamsters given arsenic trioxide, and one lung adenosquamous carcinoma in the 21 hamsters of the control group.

Ishinishi et al. (1983) studied the carcinogenicity of arsenic trioxide in female Syrian golden hamsters in two experiments. In both experiments, the hamsters received the substance by intratracheal instillation, once a week for 15 weeks. In the first experiment, the first dose was 1.0 mg As, the following 3 doses were 0.5 mg As, and the last 11 doses were 0.25 mg As, so these hamsters received a total dose of 5.25 mg As. In the second experiment, the hamsters received 15 doses of 0.25 mg, adding up to a total dose of 3.75 mg. All hamsters were observed during their entire life span. In the arsenic treated groups, 3/10 hamsters with lung adenomas were found in the first experiment, and 2/20 hamsters with lung adenomas in the second experiment. No tumors were found in either control group.

3.7. Summary of animal data

No acute LC_{50} studies following inhalation of arsenic trioxide were available. The only inhalation lethality data in animals were produced by a preliminary developmental study in mice where all animals died after a 6-h exposure to arsenic trioxide at concentrations of 100 mg As_2O_3/m^3 and higher. No animals died at concentrations up to 50 mg As_2O_3/m^3 (see table 2).

Mice exposed to air concentrations of 0.356-1.24 mg As_2O_3/m^3 showed increased susceptibility to bacterial infections.

Effects on fetuses were reported by Nagymajtényi et al. (1985) at inhalation exposures of 2.9 and 28.5 mg/m^3, but the study was incomplete and deficient in study design and reporting. Moreover, it was unclear whether the exposure concentration were expressed as arsenic or arsenic trioxide. A well performed developmental study in rats (Holson et al. 1999) showed no evidence of reproductive or fetal toxicity up to the highest exposure concentration of 11 mg As_2O_3/m^3; the highest concentration produced maternal toxicity (rales and reduced bodyweight gain) and the NOAEL was 3.4 mg As_2O_3/m^3. In the connected range finding study, a concentration of 26 mg As_2O_3/m^3 for 6-h per day during 33 days caused rales and sporadically gasping and labored breathing.

Arsenic trioxide and its methylated metabolites induced gene mutation *in vitro*. A mutagenic response of arsenic trioxide was not found *in vivo* using transgenic mice, but dimethylarsinic acid gave a weak increase in mutants in the lung. Arsenic trioxide induced chromosomal aberrations, i.e. DNA strand breaks, in an *in vivo* Comet assay in mice.

No studies were located regarding cancer in animals after inhalation exposure to arsenic trioxide. Several studies with intratracheal exposure showed weak increases in lung adenomas and/or carcinomas. IARC (1987) concluded that there is limited evidence that arsenic is carcinogenic to animals.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Absorption

Six healthy male human volunteers (28-60 years of age, 64-84 kg bodyweight) were given 0.06 ng ^{74}As (as arsenic acid) in a gelatin capsule after fasting. Whole body radioactivity counts were performed daily for two weeks. Complete 24-h urine and feces samples were collected for 7 days. There was only little variation in the results of the subjects. Essentially all arsenic was absorbed from the gastrointestinal tract; 62% was recovered in the urine and 6% in the feces. Whether the arsenic in feces was non-absorbed or excreted via bile could not be determined from this study. Blood analysis showed a peak concentration at 4 h after administration (Pomroy et al. 1980).

Roels et al. (1982) postulate that ingestion is an important route of exposure for workers exposed to arsenic trioxide dust in a glassware factory. Although the mean airborne levels of arsenic were 0.259 mg As/m^3 (corresponding to 0.342 mg As_2O_3/m^3) as measured by personal samplers, and 0.090 mg As/m^3 (corresponding to 0.119 mg As_2O_3/m^3) as measured by static area samplers, the level of the respirable fraction measured on two occasions was very low (0.0009 and 0.0030 mg As/m^3, corresponding to 0.001 and 0.0040 mg As_2O_3/m^3). Despite the low respirable levels, the mean urinary arsenic content was as high as 300 µg/g creatinine. The hand contamination increased a ten-fold during the workshift, and the mouth contamination increased a two-fold.

Groups of 6 male and 6 female New Zealand white rabbits were whole body exposed to arsenic trioxide at measured concentrations of 0, 0.05, or 1.1 mg/m^3 (phase I), and 0, 0.1, or 0.22 mg/m^3 (phase II) for 8-h per day, 7 days per week, for 8 weeks. It is not entirely clear whether the exposure concentrations were expressed as arsenic (mg As/m^3) or as arsenic trioxide (mg As_2O_3/m^3). The arsenic trioxide aerosols were generated by means of a dust-feeder system. The measured MMAD ranged from 3.2 to 4.1 µm (GSD 1.64-2.20). The animals were observed daily for clinical signs. Blood samples were taken after the last exposure, and analyzed for the concentrations of total inorganic arsenic (III + V), monomethylarsenic acid (MMA), and dimethylarsinic acid (DMA). No clinical signs were noted at any dose level and weekly measurements showed no effect on bodyweight. Mean levels of total inorganic arsenic in blood were (M-F) 2.25-0.58 µg/L in the first control group and 1.06-1.09 µg/L in the second control group, 2.11-0.64 in the 0.05 mg/m^3 group, 1.25-1.12 in the 0.1 mg/m^3 group, 1.65-2.28 in the 0.22 mg/m^3 group, and 4.15-8.30 µg/L in the 1.1 mg/m^3 group. Only in the highest exposure group the levels were significantly elevated. MMA and DMA levels were below the detection limit (0.13 µg/L) in controls, and dose-dependently increased in exposed rabbits from 0.1 mg/m^3 (MMA) and 0.05 mg/m^3 onwards to final levels of 4.12-9.46 µg MMA/L and 30.33-41.50 µg DMA/L at 1.1 mg/m^3 (Beck et al. 2002).

Distribution

Several organs taken from a suicide victim who died 3 days after ingestion of approximately 8 g arsenic trioxide were analyzed for total arsenic and different arsenic species. The total arsenic concentration was highest in liver (147 µg/g dry weight), followed by kidney (26.6 µg/g). Muscle, heart, spleen, pancreas, lungs, cerebellum and brain contained 8.3-12.3 µg/g, skin 2.9 µg/g, and hemolyzed blood 0.4 µg/g. In all tissues, As(III) was the main species found, comprising 75-85% of the total arsenic in most organs except cerebellum, brain and skin (47-56%). The proportions of the metabolites dimethylarsinic acid (DMA) and monomethylarsonic acid (MMA) were relatively small, and As(V) concentrations were lower than the limit of quantification except in liver and kidney (Benramdane et al. 1999).

Tissue samples from subjects who died in accidents in Bombay were analyzed for total arsenic content. Geometric mean concentrations were 355 µg/kg in hair, 13 µg/kg in liver and lungs, 9.5 µg/kg in spleen, 5.8 in kidney, 4.6 in blood, 3.8 in brain, and 0.6 µg/kg in milk (Dang et al. 1982).

Radiolabelled arsenic trioxide in saline was instilled intratracheally in groups of five young female Fischer rats. Serial necropsies were performed up to 30 days after administration. The time to clear 50% of the lung burden was 31 minutes. Arsenic was mainly distributed to the carcass, presumably located in the pelt, since muscle contained no activity at 7 days. One month after exposure, the skeleton contained 21%, the liver 16% and the gut 7% of the initial dose, and all were increasing at this time. About 25% of the amount given was excreted by 30 days, with urine accounting for two thirds of the total (Rhoads and Sanders 1983).

Twenty male Syrian golden hamsters were given weekly intratracheal instillations of arsenic trioxide (MMD 8 µm) at a dose of 0.3 mg (as As). Immediately after the first instillation, 5/20 animals were sacrificed for tissue analysis. 14/15 Animals survived the second instillation; four of them were sacrificed and the rest of them received a third instillation, after which 4 of them were sacrificed. 2/10 Animals survived this third instillation and received the fourth instillation, and were finally sacrificed a week later. The average arsenic content in the lungs was 386 mg/kg wet weight after the first instillation and declined to 0.81 mg/kg one week after the second instillation. Similar differences were seen in animals killed 0 and 1 week after the fourth instillation. The arsenic concentration in the liver was 0.24 mg/kg one week after the second instillation and 1.2 mg/kg one week after the fourth instillation. At these time points, arsenic also accumulated in hair; samples contained 4.4 and 17.3 mg/kg, respectively (Pershagen et al. 1982).

Metabolism

Farmer and Johnson (1990) analyzed urine samples of workers from different occupational groups. The mean urinary arsenic concentrations (trivalent and pentavalent, including the mono- and dimethyl metabolites) were (µg/g creatinine) 4.4 in controls, <10 for those in the electronics industry, 47.9 for timber treatment workers, 79.4 for glass workers, and 245 for chemical workers. The average urinary speciation pattern was 1-6% As (V), 11-14% As (III), 14-18% monomethylarsonic acid, and 63-70% dimethylarsinic acid.

The presence of arsenic species was studied in the urine of a young man who had ingested 0.6 g arsenic trioxide and who was treated with the chelator DMPS. The predominant amount of excreted arsenic was unchanged As(III) (37.4%), followed by As(V) (2.6%), pentavalent monomethylarsonic acid (2.1%) and pentavalent dimethylarsinic acid (0.2%). The substantial part that was not recovered could be, according to the authors, arsenite-DMPS complexes (Heinrich-Ramm et al. 2003).

Excretion

Excretion via the kidneys is the major route of elimination of inorganic arsenic and its metabolites, regardless of the route of exposure (WHO 1981, 2001; ATSDR 2000).

Hakala and Pyy (1995) reported half-lives in urine of 8, 12, 20, and 40 h for As (V), As (III), monomethylarsonic acid, and dimethylarsinic acid, respectively.

Relation between inhalation exposure and urinary excretion

Pinto et al. (1976, 1977) found a linear relationship between airborne arsenic exposure, as measured by breathing zone personal sampling on 24 workers during 5 consecutive working days, and urinary excretion of arsenic: *airborne arsenic (µg/m^3) = 0.304 * urinary arsenic (µg/L)* (see figure 1.). Overall, the mean airborne concentration was 0.053 mg As/m^3 (range 0.003-0.295 mg As/m^3, corresponding to 0.004-0.389 mg As_2O_3/m^3) and the mean urinary concentration was 174 µg/L. The mean urinary level increased from 152 µg/L at the first day to 200 µg/L at the last day of a 5-days exposure period.

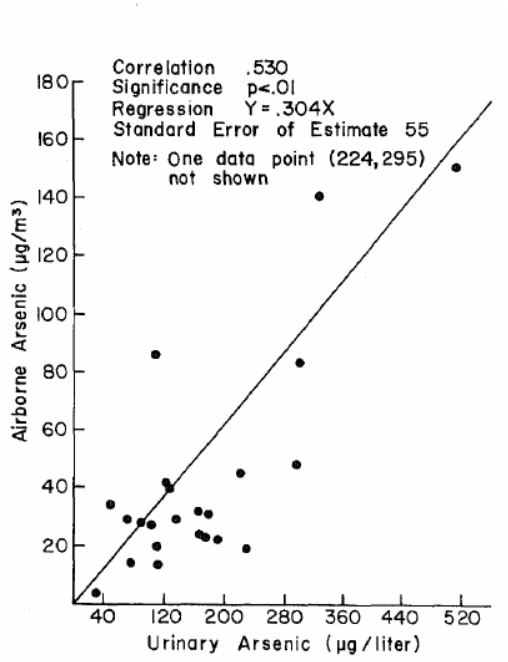


Figure 1. Relationship between urinary arsenic excretion and concentration of inhaled arsenic as published by Pinto et al. 1976. Note: one data point (224, 295) not shown.

Likewise, Hakala and Pyy (1995) found a similar correlation between airborne arsenic (breathing zone and area sampling) and urinary excretion of the sum of trivalent and pentavalent arsenic for 24 male workers exposed to arsenic trioxide dust. They calculated that an 8-h TWA of 10 µg As/m^3 will lead to a mean inorganic arsenic concentration of 5 µg/L in 0-8-h urine (*airborne arsenic (µg/m^3) = 0.446 * urinary inorganic arsenic (µg/L) + 0.4)* (see figure 2.) A good correlation was also found when monomethylarsonic acid was included. The concentration of dimethylarsinic acid was however not included in the formula because it peaks only 20 h after exposure. The range of personal breathing zone 8-TWA exposures measured over 4 working days was 0.0008-0.045 mg As/m^3, corresponding to 0.0011-0.059 mg As_2O_3/m^3. Area samples (n=129) taken on the same days varied between 0.001 and 0.670 mg As/m^3 (corresponding to 0.001-0.885 mg As_2O_3/m^3). It was noted that workers wore half face-piece respirators in high exposure areas. Breathing zone samples were taken from the inside of the face-piece.

Jakubowski et al. (1998) performed an analysis of 8-h breathing zone air samples from 53 workers exposed to arsenic trioxide, and corresponding urine samples taken after the work shift on a single day. The breathing zone TWA concentrations ranged from 0.001 to 0.746 mg As/m^3

(corresponding to 0.001-0.985 mg As_2O_3/m^3) and the urinary concentration of total inorganic arsenic and the mono- and dimethyl metabolites ranged from 3 to 850 µg/L. It was noted that the level of urinary arsenic in subjects exposed to less than 50 µg/L was still highly variable (7-607 µg/L), which was attributed to the fact that dimethylarsinic acid was included in the measurements. This metabolite has a long half-life (40 h; Hakala and Pyy 1995) and its measured concentration reflects mainly the exposure on the days before. As the exposure levels varied from day to day, the linear relationship (*log urinary arsenic+metabolites (µg/L) = 0.616 log airborne arsenic (µg/m^3) + 0.799*) presented below (figure 3) may not be entirely reliable.

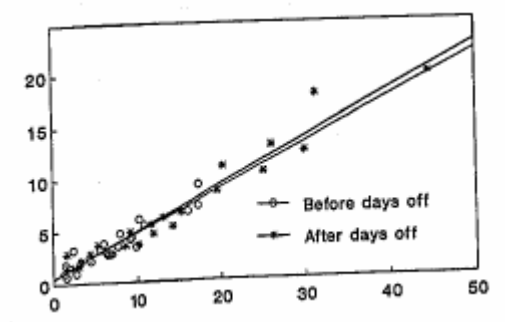


Figure 2. Relationship between TWA arsenic concentrations in air (µg As/m^3; x-axis) and inorganic arsenic in urine (µg As/L; y-axis) (Hakala and Pyy 1995).

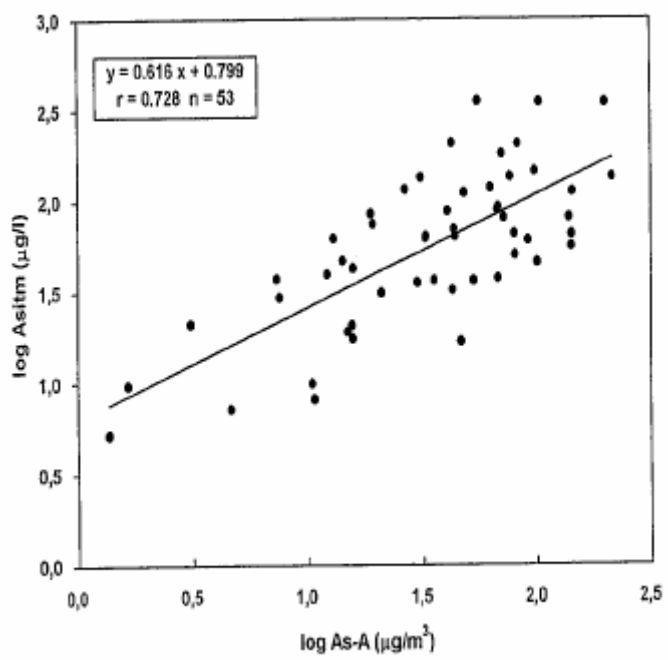


Figure 3. Correlation between urinary inorganic arsenic plus methylated metabolites and the airborne urinary concentration. Urinary samples with specific gravity lower than 1.01 and higher than 1.03 (n=14) were not considered in the data analysis (Jakubowski et al. 1998).

Yager et al. (1997) also included inorganic arsenic and both monomethylarsenic and dimethylarsinic in their analysis of urine samples from workers of a coal-fired power plant exposed to arsenic containing coal fly ash, but they sampled over 5 consecutive workdays. Also 8-h personal breathing zone samples were taken over this period. Boiler cleaners, boilermaker, and technicians were exposed to a mean 8-h TWA arsenic concentration of 0.0595, 0.0172, and 0.0021 mg As/m^3 respectively,

and had mean urinary concentrations of inorganic arsenic plus the mono- and dimethyl metabolites of 22.1, 13.4, and 11.4 µg/g creatinine. The authors found a relationship of *log urinary As (µg/g creatinine) = 0.43 + 0.101 log airborne arsenic (µg/m^3)*. They calculated that a 8-h TWA concentration of 10 µg/m^3 would result in a urinary concentration of 13.2 µg/g creatinine, and they concluded that bioavailability of arsenic from coal fly ash is one-third of that for a similar airborne concentration of arsenic trioxide dust.

The relationship between excreted arsenic species (As(III,V), monomethylarsenic acid (MMA), dimethylarsinic acid (DMA) and 8-h single day breathing-zone exposure measurements in copper smelter workers (n=83 plus 41 controls) exposed to arsenic trioxide was investigated by Smith et al. (1977). The subjects excreted arsenic primarily as methylated species (50% DMA and 20% MMA). The authors established a linear relation between DMA in urine and arsenic exposure: *DMA = 9.66* (airborne As)$^{0.367}$*. As the distribution of arsenic species it can be calculated that an exposure to 50 µg/m^3 corresponds with a urinary level of 62 µg/L (As+MMA+DMA). For a subset of workers (n=38) the particle size distribution was determined, showing that more than half of the arsenic was present in irrespirable particulates in the 'high exposure group' (n=30; mean 8-h TWA of 0.053 mg As/m^3, equal to 0.070 mg As_2O_3/m^3) and the 'low exposure group' (n=30; mean 8-h TWA of 0.0083 mg As/m^3, equal to 0.0110 mg As_2O_3/m^3), but in the 'medium exposure group' (n=23; mean 8-h TWA of 0.046 mg As/m^3, equal to 0.061 mg As_2O_3/m^3) the majority was respirable. It was found that urinary excretion of As (III), MMA and DMA were more closely related to irrespirable particulate exposure than the respirable. The range of 8-h TWA's was not given, but the figure presented below (figure 4) indicates that the TWA's were log-normally distributed with highest values of approximately 1.0 mg As/m^3 (1.3 mg As_2O_3/m^3). However, it was noted that smelter workers wore breathing masks to reduce the exposure, so the real exposure of the workers must have been lower.

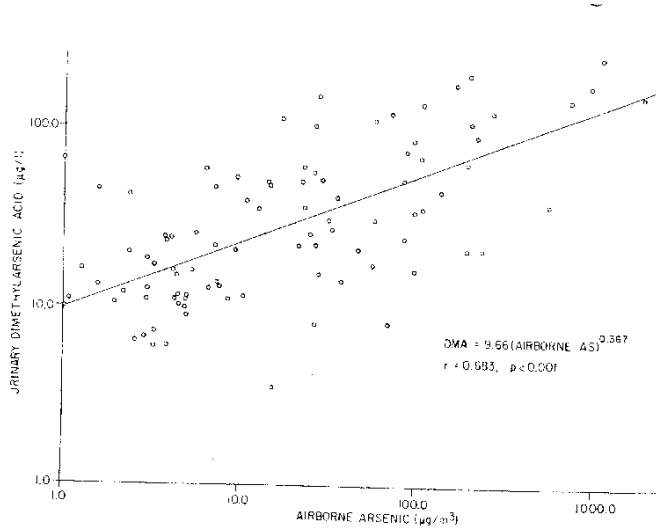


Figure 4. Relationship between airborne arsenic (µg As/m^3; x-axis) and urinary excretion of DMA (µg/L; y-axis) (Smith et al. 1977)

Offergelt et al. (1992) examined the relation between exposure to arsenic trioxide dust and fumes in a sulfuric acid production plant and the urinary excretion of inorganic arsenic and the methylated metabolites. Eighteen healthy workers wore personal samples on their shoulders on five consecutive working days. The 8-h TWA concentrations of arsenic ranged from 0.006 to 0.502 mg As/m^3, corresponding to 0.008-0.663 mg As_2O_3/m^3. Area samplers at 1.5 m above ground in four workplaces for four hours revealed arsenic concentrations of 0.019-0.164 mg As/m^3, corresponding to 0.025-0.217 mg As_2O_3/m^3. Urine samples from just before and immediately after the shift were collected and analyzed for arsenic species. The authors produced significant correlations for inorganic arsenic in urine (*log(inorganic arsenic [µg/g creatinine]) = 0.443 + 0.401*log(As_air [µg/m^3])*) (see figure 5) and for inorganic arsenic in urine including the methylated metabolites (*log(inorg As+MMA+DMA [µg/g*

*creatinine]) = 1.13 + 0.353*log(As_air [µg/m^3]))*. They calculated that an 8-h exposure to 50 µg/m^3 arsenic in air would lead to a urinary concentration of 54 µg (inorganic arsenic plus metabolites)/g creatinine.

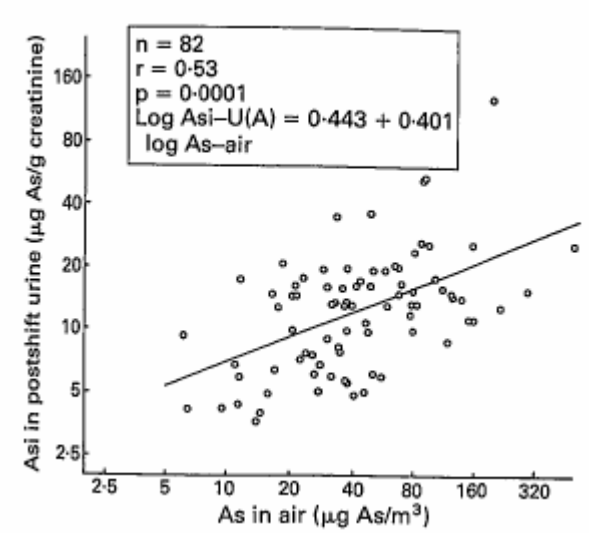


Figure 5. Relation between airborne arsenic and urinary excretion of inorganic arsenic (Offergelt et al. 1992)

4.2. Mechanism of Toxicity

Arsenic reacts with sulfhydryl groups in tissue proteins and thus interferes with a number of enzyme systems essential to cellular metabolism (WHO 1981, 2001; Gerhardsson et al 1988, Hughes 2002). Arsenic trioxide can act at several points in mitochondrially induced apoptosis, including degradation of peroxides and interaction with glutathione-related enzymes (Davison et al. 2002; Jimi et al. 2004).

Barchowsky et al. (1999) found that arsenic trioxide induced cell proliferation with oxidant accumulation, and cell death in primary porcine aortic endothelial cells. Oxidative stress leads to changed patterns of gene expression (Burchinon et al. 2003). DNA oxidation, as indicated by the production of 8-oxo-2'-deoxyguanosine, was induced in tissues of mice given dimethylarsinic acid, a main metabolite of arsenic trioxide (Yamanaka et al. 2001).

4.3. Structure Activity Relationships

No data.

4.4. Other relevant information

4.4.1. Species variability

Methylation is the main route of detoxification and excretion in humans. Dimethylarsinic acid (DMA) was the main metabolite (63-70%) found in the urine of workers exposed to normal ambient workplace concentrations in five different industries (Farmer and Johnson 1990). Substantial differences in methylation among laboratory species have been reported. Urine from rats contained 5% of the radioactivity as DMA following i.v. administration of arsenic acid, and from mice 43% (Odanaka et al. 1980). Hence mice and in particular rats seem to metabolize arsenic compounds less than humans do. However, it should be noted the i.v. dose of 1 mg/kg bw given to the animals was much higher than the dose received by humans in an occupational situation (maximum of approximately 0.1 mg/kg bw on a

whole working day). The results in humans and laboratory species are therefore difficult to compare in a quantitative way. It was also noted that the radioactivity in blood of the same rats consisted of 94% DMA. Qualitatively, the metabolism is similar in all species studied. In conclusion, there is insufficient evidence that the metabolism in humans and laboratory animals is substantially different.

Rats seem to be slightly less sensitive to arsenic toxicity than mice, as judged by comparison of oral LD_{50}'s (Harrisson et al. 1958). Furthermore, oral data presented by ATSDR (2000) indicate that humans are more sensitive than laboratory animals including rats with respect to long term effects.

4.4.2. Intraspecies variability / Susceptible populations

No data.

4.4.3. Irritation and Sensibilisation

No data.

4.4.4. Concentration-Exposure Duration Relationship

No data.

4.4.5. Concurrent Exposure Issues

Organoarsenicals are natural components of food, in particular seafood. Consumption of a meal of fish or shellfish can raise urinary arsenic to concentrations in excess of 500 µg/L, more than 50 times the typical background level (Farmer and Johnson 1990). Hence the dietary arsenic exposure may interfere with the estimation of exposure to inorganic arsenic when the analytical method for the determination of arsenic in e.g. urine can not distinguish between inorganic (and simple methylated forms) and organic forms of arsenic.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of human data relevant to AEGL-1

No quantitative acute inhalation data with arsenic trioxide in humans are available.

5.2. Summary of animal data relevant to AEGL-1

No studies were available in which endpoints relevant to AEGL-1 were investigated in animals following acute inhalation exposure to arsenic trioxide.

5.3. Derivation of AEGL-1

Due to the lack of human and animal data on AEGL-1 endpoints for arsenic trioxide, no AEGL-1 values is recommended.

TABLE 5. AEGL-1 Values for Arsenic trioxide

10-minute	30-minute	1-hour	4-hour	8-hour
NR	NR	NR	NR	NR

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of human data relevant to AEGL-2

No quantitative acute inhalation data with arsenic trioxide in humans are available. The highest mean occupational concentration was 0.670 mg As/m^3, equal to 0.885 mg arsenic trioxide/m^3 (Hakala and Pyy 1995) for area samples, and the highest mean 8-h TWA was 0.746 mg As/m^3, equal to 0.985 mg arsenic trioxide/m^3 for breathing zone samples (Jakubowski et al. 1998). Although these concentrations are normal workplace exposures, it remains unknown if these exposures may cause AEGL-2 effects in unprotected workers at short exposure durations.

6.2. Summary of animal data relevant to AEGL-2

No studies were available in which endpoints relevant to AEGL-2 were investigated in animals following acute inhalation exposure to arsenic trioxide. In the range-finding study of Holson et al. (1999) only rales and sporadically gasping and labored breathing was observed following 33 days of exposure to arsenic trioxide at the highest concentration of 26 mg As_2O_3/m^3.

6.3. Derivation of AEGL-2

Due to the lack of human and animal data on AEGL-2 endpoints for arsenic trioxide, the AEGL-2 values will be based on 1/3 of the AEGL-3 values. The proposed AEGL-2 values are supported by the absence of AEGL-2 effects in rats after repeated exposure to 25 mg/m^3 and the steep concentration-response curve for lethality.

The following AEGL-2 values were derived:

TABLE 6. AEGL-2 Values for Arsenic trioxide

10-minute	30-minute	1-hour	4-hour	8-hour
3.7 mg/m^3	3.7 mg/m^3	3.0 mg/m^3	1.9 mg/m^3	1.2 mg/m^3

The cancer risk values (Appendix C) are lower than the AEGL-2 values.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of human data relevant to AEGL-3

No quantitative acute inhalation data with arsenic trioxide in humans are available. The highest mean occupational concentration was 0.670 mg As/m^3, equal to 0.885 mg arsenic trioxide/m^3 (Hakala and Pyy 1995) for area samples, and the highest mean 8-h TWA was 0.746 mg As/m^3, equal to 0.985 mg arsenic trioxide/m^3 for breathing zone samples (Jakubowski et al. 1998). Because these concentrations are normal workplace exposures, they can be considered as non-lethal, at least with regard to short exposure durations.

7.2. Summary of animal data relevant to AEGL-3

In a preliminary study of developmental toxicity in rats, Holson et al. (1999) reported 100% lethality in pregnant rats exposed to arsenic trioxide at 100 mg As_2O_3/m^3 and higher for 6 hours. All rats

exposed to 25 and 50 mg As_2O_3/m^3 survived a 6-h exposure. The (6-h) NOEL for lethality in rats is therefore 50 mg/m^3.

7.3. Derivation of AEGL-3

The NOEL for lethality of 50 mg/m^3 in rats (Holson et al. 1999) can be used as the point of departure for the development of the AEGL-3 values for arsenic trioxide. However, extrapolation of animal data to humans is complicated by differences in metabolism and perhaps also in sensitivity (WHO 2001, ATSDR 2000). Applying standard safety factors (10x10) to the above NOEL in rats would result in a 6-h AEGL-3 of 0.5 mg/m^3, which is well within the range of normal workplace exposures and therefore not a good estimate for a lethality threshold in humans. Even a safety factor of 30 would result in a 6-h value that is only just above normal workplace exposure concentrations. Therefore, supported by the human workplace exposure data, a total safety factor of 10 (3x3) is considered sufficient. The resulting 6-h value is 5 mg/m^3.
Time-concentration effects are not available for arsenic trioxide. Therefore, standard time-scaling according to Ten Berge will be applied, using $C^n \times t = k$, with n=3 for shorter time points and n=1 for longer time points. Because the starting point for time extrapolation is 4 hours or longer, the AEGL-3 10-minute value is the same as the AEGL-3 30-minute value. The following AEGL-3 values were derived:

TABLE 7. AEGL-3 Values for Arsenic trioxide

10-minute	30-minute	1-hour	4-hour	8-hour
11 mg/m^3	11 mg/m^3	9.1 mg/m^3	5.7 mg/m^3	3.7 mg/m^3

8. SUMMARY OF AEGLS

8.1. AEGL values and toxicity endpoints

TABLE 8. Summary of AEGL Values

Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	3.7 mg/m^3	3.7 mg/m^3	3.0 mg/m^3	1.9 mg/m^3	1.2 mg/m^3
AEGL-3 (Lethal)	11 mg/m^3	11 mg/m^3	9.1 mg/m^3	5.7 mg/m^3	3.7 mg/m^3

These values are expressed as arsenic trioxide (mg As_2O_3/m^3)
The cancer risk values (Appendix C) are lower than the AEGL-2 values.

8.2. Comparison with other standards and guidelines

TABLE 9. Extant Standards and Guidelines for arsenic trioxide

Guideline	Exposure Duration				
	10 minute	**30 minute**	**1 hour**	**4 hour**	**8 hour**
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	3.7 mg/m^3	3.7 mg/m^3	3.0 mg/m^3	1.9 mg/m^3	1.2 mg/m^3
AEGL-3	11 mg/m^3	11 mg/m^3	9.1 mg/m^3	5.7 mg/m^3	3.7 mg/m^3
ERPG-1 (AIHA)[a]	-	-	-	-	-
ERPG-2 (AIHA)	-	-	-	-	-
ERPG-3 (AIHA)	-	-	-	-	-
EEGL (NRC)[b]					
PEL-TWA (OSHA)[c]					0.010 mg/m^3 (as As) 0.013 mg/m^3 (as As_2O_3)
PEL-STEL (OSHA)[d]					
IDLH (NIOSH)[e]		5 mg/m^3 (as As) 6.6 mg/m^3 (as As_2O_3)			
REL-TWA (NIOSH)[f]					
REL-STEL (NIOSH)[g]	0.002 mg/m^3 (as As) 0.003 mg/m^3 (as As_2O_3)				
TLV-TWA (ACGIH)[h]					
TLV-STEL (ACGIH)[i]					
MAK (Germany)[j]					
MAK Peak Limit (Germany)[k]					
MAC (The Netherlands)[l]					0.025 mg/m^3 (as As)

					0.033 mg/m^3 (as As_2O_3)

The cancer risk values (Appendix C) are lower than the AEGL-2 values.

[a]**ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association** (AIHA 1994)
The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.
The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual=s ability to take protection action.
The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects.

[b]**EEGL (Emergency Exposure Guidance Levels, National Research Council** (NRC 1985)
The EEGL is the concentration of contaminants that can cause discomfort or other evidence of irritation or intoxication in or around the workplace, but avoids death, other severe acute effects and long-term or chronic injury.

Check to see if your chemical has CEELs or SMACs (NRC) Provide the definition...
For example, SMACs provide guidance on chemical exposures during normal operations of spacecraft as well as emergency situations. The one-hour SMAC is a concentration of airborne substance that will not compromise the performance of specific tasks by astronauts during emergency conditions or cause serious or permanent toxic effects. Such exposure may cause reversible effects such as skin or eye irritation, but they are not expected to impair judgment or interfere with proper responses to emergencies.

[c]**OSHA PEL-TWA (Occupational Safety and Health Administration, Permissible Exposure Limits - Time Weighted Average)** (OSHA 19??) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.

[d]**OSHA PEL-STEL (Permissible Exposure Limits - Short Term Exposure Limit)**

[e]**IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health)** represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects.

[f]**NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average)** is defined analogous to the ACGIH-TLV-TWA.

[g]**NIOSH REL-STEL (Recommended Exposure Limits - Short Term Exposure Limit)**
is defined analogous to the ACGIH TLV-STEL.

[h]**ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** is the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[i]**ACGIH TLV-STEL (Threshold Limit Value - Short Term Exposure Limit)**
is defined as a 15-minute TWA exposure which should not be exceeded at any time during the workday even if the 8-hour TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 minutes and should not occur more than 4 times per day. There should be at least 60 minutes between successive exposures in this range.

[j]**MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration])** (Deutsche Forschungsgemeinschaft [German Research Association] 2000) is defined analogous to the ACGIH-TLV-TWA.

[k]**MAK Spitzenbegrenzung (Peak Limit [give category])** (German Research Association 2000)

constitutes the maximum average concentration to which workers can be exposed for a period up to 30 minutes with no more than 2 exposure periods per work shift; total exposure may not exceed 8-hour MAK.

We don=t have Einsatztoleranzwert levels, so skip at this time.

[l]**MAC (Maximaal Aanvaaarde Concentratie [Maximal Accepted Concentration])** (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000) is defined analogous to the ACGIH-TLV-TWA.

8.3. Data quality and research needs

Human or animal data on AEGL-1 and AEGL-2 endpoints are lacking. Only few animal data are available on lethality. Data on ADME, developmental toxicity, genotoxicity and carcinogenicity are available.

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APPENDIX A: Derivation of AEGL Values

Derivation of AEGL-1

Key study:	no data available relevant to AEGL-1 endpoints
Toxicity Endpoint:	
Time scaling:	
Uncertainty factors:	
Calculations:	
10-minute AEGL-1	not recommended
30-minute AEGL-1	not recommended
1-hour AEGL-1	not recommended
4-hour AEGL-1	not recommended
8-hour AEGL-1	not recommended

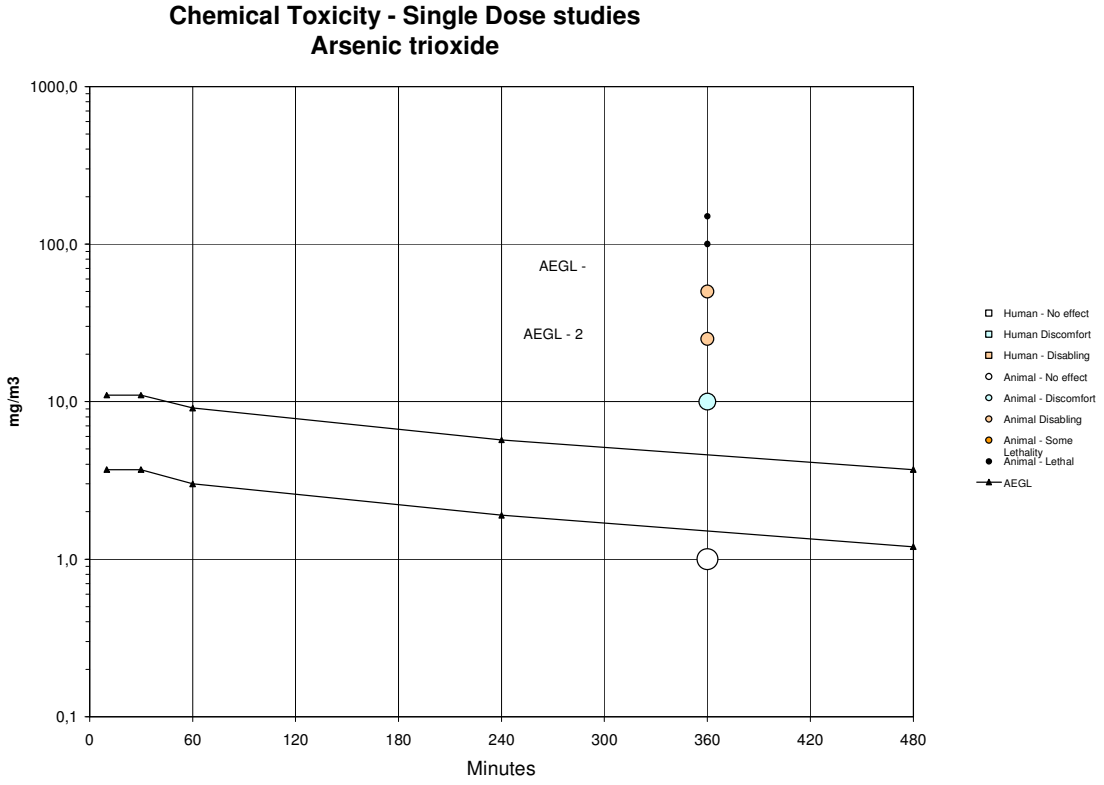
Derivation of AEGL-2

Key study:	Jakubowski et al. 1998
Toxicity Endpoint:	In absence of dose-response data for AEGL-2 effects, the AEGL-2 values are based on 1/3 of the AEGL-3 values.The proposed AEGL-2 values are supported by the absence of AEGL-2 effects in rats after repeated 6-h exposures to 25 mg/m^3 (Holson et al. 1999).
Time scaling:	Not applicable.
Uncertainty factors:	Not applicable.
Calculations:	
10-minute AEGL-2	3.7 mg/m^3
30-minute AEGL-2	3.7 mg/m^3
1-hour AEGL-2	3.0 mg/m^3
4-hour AEGL-2	1.9 mg/m^3
8-hour AEGL-2	1.2 mg/m^3

Derivation of AEGL-3

Key study:	Holson et al. 1999
Toxicity Endpoint:	NOEL for lethality (50 mg/m^3) after a single 6-h exposure of rats.
Time scaling:	$C^n \times t = k$, with n=3 for shorter time points and n=1 for longer time points. Because the starting point for time extrapolation is 4 hours or longer, the AEGL-3 10-minute value is the same as the AEGL-3 30-minute value.
Uncertainty factors:	A total UF of 10 (3x3) was proposed, because larger factors would result in AEGL-3 values within or just above normal workplace exposures.
Calculations:	
10-minute AEGL-3	11 mg/m^3
30-minute AEGL-3	11 mg/m^3
1-hour AEGL-3	9.1 mg/m^3
4-hour AEGL-3	5.7 mg/m^3
8-hour AEGL-3	3.7 mg/m^3

APPENDIX B: Category plot for Arsenic trioxide


Chemical Toxicity - Single Dose studies
Arsenic trioxide
1000,0
100,0
10,0
1,0
0,1
mg/m3
AEGL -
AEGL - 2
0
60
120
180
240
300
360
420
480
Minutes
Human - No effect
Human Discomfort
Human - Disabling
Animal - No effect
Animal - Discomfort
Animal Disabling
Animal - Some Lethality
Animal - Lethal
AEGL

1

APPENDIX C: Carcinogenicity Assessment

CARCINOGENICITY ASSESSMENT OF ARSENIC TRIOXIDE

An inhalation slope factor of 5.00E+01 (mg/kg/day) and an inhalation unit risk of 4.30E-03 (µg As/m^3) are currently available for inorganic arsenic (U.S. EPA, 1966; 1997).

The slope factor for inorganic arsenic is 5.0E+01 (mg/kg per day) which, based upon a human inhalation rate of 20 m^3/day and a body weight of 70 Kg, is equivalent to 14.29 (mg As/m^3).

To convert to a level of inorganic arsenic that would cause an excess cancer risk of 10^{-4}:
Risk of 1 x 10^{-4} = (1 x 10^{-4}/14.29) x 1 mg As/m^3 = 7 x 10^{-6} mg As/m^3 (virtually safe dose)

To convert a 70-year exposure to a 24-hour exposure:

24-hr exposure = d x 25,600 = (7 x 10^{-6} mg As/m^3) x 25,600 days
= 0.16 mg As/m^3

To account for uncertainty regarding the variability in the stage of the cancer process at which arsenic or its metabolites may act, a multistage factor of 6 is applied (NRC, 2001):
(0.16 mg As/m^3)/6 = 0.027 mg As/m^3

Therefore, based upon the potential carcinogenicity of inorganic arsenic, an acceptable 24-hr exposure would be 0.027 mg As/m^3

If the exposure is limited to a fraction (f) of a 24-hr period, the fractional exposure becomes 1/f x 24 hrs.

24-hr exposure = 0.027 mg As/m^3
8-hr = 0.080 mg As/m^3
4-hr = 0.16 mg As/m^3
1-hr = 0.64 mg As/m^3
0.5 hr = 1.3 mg As/m^3

This assessment is based upon inorganic arsenic rather than arsenic trioxide. Because arsenic trioxide is only 75.8% arsenic, a 1.32-fold increase in the aforementioned calculated exposure values would be required to provide equivalent levels of inorganic arsenic. These exposures would be:

24-hr exposure = 0.035 mg As_2O_3/m^3
8-hr = 0.11 mg As_2O_3/m^3
4-hr = 0.21 mg As_2O_3/m^3
1-hr = 0.84 mg As_2O_3/m^3
0.5 hr = 1.69 mg As_2O_3/m^3

APPENDIX D: Derivation Summary for Arsenic trioxide AEGLs

ACUTE EXPOSURE GUIDELINE LEVELS FOR ARSENIC TRIOXIDE (CAS Reg. No. 1327-53-3) DERIVATION SUMMARY

AEGL-1 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
NR	NR	NR	NR	NR

Key Reference:

Test Species/Strain/Number:

Exposure Route/Concentrations/Durations:

Effects:
ppm
ppm
ppm
ppm
ppm
ppm

Endpoint/Concentration/Rationale:

Uncertainty Factors/Rationale:
Total uncertainty factor:
Interspecies:
Intraspecies:

Modifying Factor:

Animal to Human Dosimetric Adjustment:

Time Scaling:

Data Adequacy:

AEGL-2 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
3.7 mg/m^3	3.7 mg/m^3	3.0 mg/m^3	1.9 mg/m^3	1.2 mg/m^3
Key Reference: 1/3 AEGL-3				
Test Species/Strain/Number: NA				
Exposure Route/Concentrations/Durations: NA				
Effects: NA				
Endpoint/Concentration/Rationale: 1/3 of the AEGL-3 values				
Uncertainty Factors/Rationale: NA				
Modifying Factor: NA				
Animal to Human Dosimetric Adjustment: NA				
Time Scaling: NA Data Adequacy: Poor				

1

AEGL-3 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
11 mg/m^3	11 mg/m^3	9.1 mg/m^3	5.7 mg/m^3	3.7 mg/m^3

Key Reference: Holson et al. 1999

Test Species/Strain/Number: Rat Crl:CD(SD)BR, groups of ten females

Exposure Route/Concentrations/Durations:

arsenic trioxide was given by inhalation used whole-body exposure chambers

Exposure concentrations were 25, 50, 100, 150, 200 mg As_2O_3/m^3

The duration was 6 hours

Effects:

25 mg As_2O_3/m^3	no mortality
50 mg As_2O_3/m^3	no mortality
100 mg As_2O_3/m^3	100 % mortality
150 mg As_2O_3/m^3	100 % mortality
200 mg As_2O_3/m^3	100 % mortality

Endpoint/Concentration/Rationale: Point of departure is the NOEL of 50 mg As_2O_3/m^3 for lethality

Uncertainty Factors/Rationale: A total UF of 10 (3x3) was proposed, because larger factors would result in AEGL-3 values within or just above normal workplace exposures.

Total uncertainty factor: 10

Interspecies: 3

Intraspecies: 3

Modifying Factor: N.a.

Animal to Human Dosimetric Adjustment: None

Time Scaling: $C^n \times t = k$, with n=3 for shorter time points and n=1 for longer time points. Because the starting point for time extrapolation is 4 hours or longer, the AEGL-3 10-minute value is the same as the AEGL-3 30-minute value.

Data Adequacy: Limited to data in rats.