Workplace Exposure Standard (WES) review

ARSENIC
(CAS NO: 7440-38-2)

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New Zealand Government

WORKSAFE
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appendices

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1.0
Introduction

This WorkSafe New Zealand (WorkSafe) review considers whether the **WES** for arsenic and soluble arsenic compounds (as As) should be changed.

The WES review considers the potential for exposure to arsenic in New Zealand, the health effects and risks, exposure standards from other jurisdictions around the world, and the practicability of measuring exposures.

The review includes a recommendation to change the WorkSafe WES for arsenic and soluble compounds (as As), which is currently set at a **WES-TWA** of 0.05**mg/m³** for **inhalable fraction**, as published in the special guide *Workplace Exposure Standards and Biological Exposure Indices*, 11th Ed., November 2019 (WorkSafe, 2019).

The gas arsine, AsH_3 [CAS No.: 7784–42–1], has its own WES-TWA (WorkSafe, 2019).

Terms that are **bold** (first occurrence only) are further defined in the Glossary.
Synonyms: As, As^{III}, AsIII, As^{V}, AsV, As^{3+}, As3+, As^{5+}, As5+.

2.0 Chemical and physical properties

Arsenic is a grey, crystalline solid with a metallic lustre at room temperature (**ECHA**, 2017; **ACGIH®**, 2001).

Arsenic can exist in four oxidation states: -3, 0 (metal), +3 and +5. In water, arsenic is mostly found in inorganic forms as oxyanions of arsenite (As III) or arsenate (As V). Under moderately reducing conditions, arsenite (+3) may be the dominant form, but arsenate (+5) is generally the stable oxidation state in oxygenated environments. In strongly reducing environments, elemental arsenic and arsine (-3) can exist (ECHA, 2017). As a consequence of arsenic's chemical properties, a large number of inorganic arsenic compounds exist with ECHA noting about 40 salts of arsenic acid [H_3AsO_4; CAS No.: 7778-39-4], commonly sodium, calcium and iron (ECHA, 2017).

Chemical and physical properties of some arsenic compounds include:

SUBSTANCE	ARSENIC	ARSENIC ACID	ARSENIC TRIOXIDE	POTASSIUM ARSENATE	SODIUM ARSENITE
CAS No.:	7440-38-2	7778-39-4	1327-53-3	7784-41-0	7784-46-5
Molecular weight [g/mol]	74.9	141.9	197.8	180.0	129.9
Formula	As	H_3AsO_4	As_2O_3	KH_2AsO_4	$NaAsO_2$
Physical form	Crystalline	Hygroscopic crystals	Solid	Solid	Hygroscopic solid
Specific gravity/Density [g/cm³]	5.73	2.0-2.5	3.74	2.900	1.870
Melting point	Sublimes at 613°C	35.5°C	312°C	288°C	–
Boiling point	–	Loses H_2O at 160°C	465°C	–	–
Vapour pressure (KPa at 25°C)	3.3×10^{-10}	7.6×10^{-20}	3.7×10^{-11}	–	8×10^{-19}
Water solubility	Insoluble	–	Soluble in water (37g/L at 20°C)	Soluble in cold water (190g/L at 6°C)	Very soluble in water (1000g/L at 25°C)

ECHA, 2016

TABLE 1: Physicochemical properties of some arsenic compounds

Health-related hazard classifications for arsenic and some arsenic compounds:

HSNO CLASSIFICATIONS					
Substance	**Arsenic**	**Arsenic acid**	**Arsenic (III) oxide**	**Arsenic acid, trisodium salt**	**Sodium arsenate, bibasic, heptahydrate**
CAS No.:	7440-38-2	7778-39-4	1327-53-3	13464-38-5	10048-95-0
Classification	6.1B (All); 6.1B (O); 6.1B (I); 6.6B; 6.7A; 6.9A (All); 6.9A (O); 6.9A (I)	6.1B (All); 6.1B (O); 6.1B (I); 6.3B; 6.4A; 6.7A; 6.8A; 6.9A (All); 6.9A (O)	6.1B (All); 6.1B (O); 6.7A; 8.2C; 8.3A	6.1C (All); 6.1C (O); 6.1C (I); 6.7A	6.1C (All); 6.1C (O); 6.1C (I); 6.7A

TABLE 2: HSNO hazard classifications of arsenic and some arsenic compounds (**EPA**, 2019a-e)

For a full listing of all HSNO health-related hazardous substances classification codes and their descriptions, see Appendix 2.

[All] Overall classification for that endpoint.

[O] Oral exposure route.

[D] Dermal exposure route.

[I] Inhalation exposure route.

3.0
Uses

Arsenic and arsenic compounds have been produced and used for centuries (ECHA, 2017).

Current and historical uses of arsenic include pharmaceuticals; wood preservatives; agricultural chemicals (for example, as a cotton desiccant/defoliant); feed additives for poultry and swine; applications in the mining industry; in the production of non-ferrous alloys; in glass-making (for example, as a decolouriser and fining agent in the production of bottle glass and the manufacture of speciality glass); in the semiconductor industry; and, in the production of copper foil for printed circuit boards (ECHA, 2017).

Processing of non-ferrous metals, such as zinc and copper refining, can lead to significant waste streams containing arsenic, including metal arsenates (ECHA, 2017).

Arsenic is present in the environment, as a result of natural and anthropogenic sources, with food and water the primary sources of arsenic exposure in the general population, particularly in arsenic-rich geological areas (ECHA, 2017; **IARC**, 2012).

Occupational exposure to arsenic can occur during production, storage, transportation and end-use.

Workers can be exposed to arsenic via inhalation or ingestion and dermal (skin-to-mouth) contact (ECHA, 2017; IARC, 2012).

The number of workers exposed or potentially exposed to arsenic in New Zealand workplaces is unknown.

Statistics New Zealand 2018 data indicate that 8,260 New Zealand workers were working in the areas of:

- gold ore mining
- other metal ore mining
- timber resawing and dressing
- glass and glass product manufacturing
- copper, silver, lead and zinc smelting and refining
- non-ferrous metal casting
- other basic non-ferrous metal product manufacturing
- computer and electronic equipment manufacturing (NZ Stat, 2019).

4.0
Health effects

IN THIS SECTION:

4.1 Non-cancer

Humans

The ECHA opinion on arsenic acid and its inorganic salts summarised the acute toxicity in exposed humans:

> "Inorganic arsenic is acutely toxic and ingestion of large doses leads to gastrointestinal symptoms, disturbances of cardiovascular and central nervous system functions, multi-organ failure and eventually death. In survivors, bone marrow depression, haemolysis, hepatomegaly, melanosis, polyneuropathy and encephalopathy may be observed (**WHO-IPCS** 2001/**ATSDR** 2007).
>
> "Among existing data (Enterline *et al* 1982; Jarup *et al*, 1989; Lee-Feldstein, 1986) there are no cases of death in humans from inhalation exposure to inorganic arsenicals following acute exposure, even at very high exposure levels.
>
> "According to **WHO**/ATSDR (WHO-IPCS 2001/ATSDR 2007). Data [sic], dermal exposure to inorganic arsenicals did not cause lethality in humans.
>
> "The studies of Levin-Scherz *et al* (1987) and Saady *et al*, (1989) revealed that acute lethality caused by ingestion of inorganic arsenic is usually attributable to cardiopulmonary collapse. Delayed lethality results from failure of one or more of many tissues injured by arsenic. Estimates of the minimum lethal oral dose in humans ranged from 1–3**mg** As/kg bw/day (Armstrong *et al*, 1984; JW, 1904; Vallee, 1960)." (References cited in ECHA, 2017).

The New Zealand EPA classifies arsenic, arsenic acid, and arsenic (III) oxide as 6.1B substances – substances that are acutely toxic (EPA, 2019).

The New Zealand EPA classifies arsenic acid, trisodium salt and sodium arsenate, bibasic, heptahydrate as 6.1C substances – substances that are acutely toxic (EPA, 2019).

The **NIOSH** Skin Notation Profile for arsenic and inorganic arsenic containing compounds summarised the irritation/corrosion potential in humans:

> "No human or animal *in vivo* studies on corrosivity of arsenic or *in vitro* tests for corrosivity using human or animal skin models or *in vitro* tests of skin integrity using cadaver skin were identified. However, several occupational cases or human studies have reported irritant contact dermatitis or cutaneous effects in patients or workers exposed to arsenic [Pinto and McGill 1953; Bourrain 1998; Mohamed 1998]. Skin reactions were mostly in the form of itching, dryness, hyperpigmentation, folliculitis, superficial ulceration, erythema, swelling, and papules, with vesicle formation in severe cases. In mice treated twice daily with 50μmL of 0.4% potassium arsenite solution in 80% ethanol extensive ulceration was observed [Boutwell 1963]. Mir [2017] investigated the proteome level changes in human skin keratinocyte cells exposed to 100 millimolars of sodium arsenite over a period of 6 months. An increase in reactive oxygen species (**ROS**) was noted, as well as overexpression of 42 proteins (including **NAD(P)H** dehydrogenase, glutamate9cysteine ligase catalytic subunit (**GCLC**), aldo-keto reductase family 1 member C2 (**AKR1C2**) and (**AKR1C3**) and downregulation of proteins essential for terminal differentiation of keratinocytes (including periplakin, envoplakin, and involucrin) [Mir ea 2017]."

> "Case reports and human studies [Pinto and McGill 1953; Bourrain 1998; Mohamed 1998] demonstrate that chronic or high-dose dermal exposure to arsenic can result in irritant contact dermatitis. Some of the irritant symptoms observed could possibly reflect other ingredients. However, the effects are consistent with irritation and are supported by the finding that prolonged exposure to arsenic following dermal application resulted in extensive ulceration at the site of application in mice [Boutwell 1963]. Therefore, on the basis of the data for this assessment, arsenic is assigned the **SK: DIR (IRR)** notation." (References cited in NIOSH, 2017).

The New Zealand EPA classifies arsenic acid as a 6.3B and 6.4A substance – a substance that is mildly irritating to the skin and irritating to the eye (EPA, 2019).

The New Zealand EPA classifies arsenic (III) oxide as an 8.2A and 8.3A substance – a substance that is corrosive to dermal tissue and ocular tissue (EPA, 2019).

The NIOSH Skin Notation Profile for arsenic and inorganic arsenic containing compounds summarised the sensitisation potential in humans:

> "Several studies were identified that evaluated the potential of arsenic to cause skin sensitiza-tion in humans and animals. Wahlberg and Boman [1986] reported two out of 379 (0.5%) eczema patients patch tested with arsenic compounds [0.1% sodium arsenate in distilled water (pH 8.5) and 0.05% sodium arsenite in distilled water (pH 10.0)] that showed positive test results. The patients had no known previous exposure to arsenic compounds and the positive response might have been due to a cross reactivity with nickel. In a guinea pig maximization test (**GPMT**), arsenic compounds (1.0% sodium arsenate and 0.1% sodium arsenite) were not sensitizing to the skin, and were not rated as Grade I Allergens [Wahlberg and Boman 1986].
>
> "An *in vivo* animal study using the GPMT did not support the weak skin sensitization data in humans [Wahlberg and Boman 1986]. This assessment concludes that data are too limited to conclude that arsenic and its inorganic compounds have the potential to cause skin sensitization in humans. Therefore, on the basis of the data for this assessment, arsenic is not assigned the **SK: SEN** notation." (References cited in NIOSH, 2017).

The ECHA opinion on arsenic acid and its inorganic salts summarised the genotoxic potential in humans:

> "Genotoxicity studies have included exposed and unexposed individuals from several populations and analyses have been based on various tissues, including blood, buccal and bladder cells as well as sections from tumour biopsies (WHO-IPCS, 2011/ATSDR, 2007).
>
> "Even with some negative findings, the overall weight of evidence indicated that arsenic can cause clastogenic damage in different cell types, with different endpoints, (such as **DNA** damage, plasmid unwinding and oxidative stress) in exposed individuals. Clastogenic effects have also been observed in cells from cancer patients. Therefore it suggests that arsenic is clastogenic in humans in vivo (WHO-IPCS, 2011/ATSDR, 2007).
>
> "No **HPRT** gene mutation was seen in the single study in lymphocytes or increases in **ras** or **p53** gene expression in cells from cancer patients with long-term exposure to arsenic, except for one study with increased p53 expression in Bowen's disease patients with such exposure compared to patients without exposure (WHO-IPCS, 2011/ATSDR, 2007).

> "Further, studies of humans have detected higher-than-average incidence of chromosomal aberrations in peripheral lymphocytes, both after inhalation and oral exposure. However, these studies must be interpreted with caution, since in most cases there was only a small number of subjects and a number of other chemical exposures was possible (WHO-IPCS, 2011/ATSDR, 2007).
>
> "Additional available human data (both from in vivo and in vitro studies) showed chromosome aberrations and sister chromatid exchanges in different cell types of people exposed to relatively high arsenic concentrations in drinking water (Basu *et al*, 2004; Mahata *et al*, 2003; Mahata *et al*, 2004a; Mahata *et al*, 2004b; Moore *et al*, 2002; Tian *et al*, 2001; Ghosh *et al*, 2006; Chakraborty *et al*, 2006; Martinez *et al*, 2005; Jarup *et al*, 1989).
>
> "Coelho *et al*, (2014;2013) investigated occupational exposures to arsenic and other metals in a group of 122 subjects working in the Panasqueira mining industry or living in the same region in central Portugal. Arsenic was, among other metalloids, the element with the highest increase in exposed populations. The results showed that the metal (loid) contamination in the Panasqueira mine area induced genotoxic damage including induction of oxidative stress and damage to DNA and the presence of interferences with DNA repair systems and signal transduction pathways, these were observed in both in individuals working in the mine or living in the area. The study suggested that the findings were significant and conclude that there was an urgent intervention of authorities is required to protect exposed populations.
>
> "Wen *et al*, (2011) investigated occupational exposures in two arsenic plants, which produce arsenic trioxide by smelting arsenic ore, in the Yunnan province, in China. The study examined the effects of inorganic arsenic, monomethylarsonic acid, and dimethylarsinic acid on the DNA damage of exons 5, 6, and 8 of p53 gene in arsenic-exposed population. The main findings are that there are significant increased damage of exons 5 and 8 of p53 gene in workers from arsenic plants, and damage indexes of exon 5 increase with urinary **MMA**, **DMA**, and **tAs**. Further the study suggested a positive correlation between the damage index of exon 5 and the PMI was found, also for MMA%, but a negative correlation between the damage index of exon 5 and the **SMI**." (References cited in ECHA, 2017).

The New Zealand EPA classifies arsenic as a 6.6B substance – a substance that is a suspected human mutagen (EPA, 2019).

The ECHA opinion on arsenic acid and its inorganic salts summarised the reproductive/developmental toxicity in humans:

> "Several studies have examined reproductive endpoints in humans.
>
> "No effects of arsenic on fertility were observed upon inhalatory and/or oral exposure.
>
> "In older inhalatory and oral human studies (Nordström *et al*, 1978a; 1978b; 1979;a; 1979b; Aschengrau *et al*, 1989; Zierler *et al*, 1988) the populations were exposed to a number of other chemicals beyond arsenic. In these studies, Nordström *et al* (1978a; 1978b; 1979;a; 1979b) investigated female workers of the Rönnskär copper smelter and four populations of different distances from the smelter. As the result of these observations, the following findings were reported. The birth weights of the offspring of female employees and of the women living close to the smelter was statistically significantly decreased. In the population located close to the smelter a
>
> statistically significant increase of the abortion frequency was found compared to more distantly located populations. Further the women

occupied in close connection with the smelting processes had a significantly higher abortion frequency than other employees. The lowest birth weights were found in the offspring of women working in close contact with the smelting processes. In the offspring of women who had worked at the smelter during pregnancy the frequency of congenital malformations was increased. All the observed effects should be interpreted with caution as other chemicals may have contributed to the effects and causal relationship with arsenic and its inorganic compounds is uncertain.

"Recent human studies (Hopenhayn-Rich *et al*, 2000; Ahmad *et al*, 2001) on arsenic exposure from drinking water in different parts of the world (for example, Chile, Bangladesh) suggest an association as a causal factor for spontaneous abortion, stillbirth, preterm delivery and reduced birth weight as well as neuropsychological development.

"In a retrospective study, infant mortality was investigated in two regions of Chile between 1950 and 1996. In Antofagasta, contamination of the drinking water with arsenic was documented, while in Valparaiso the levels were comparatively low. Investigation of the temporal development of late foetal mortality, mortality of newborn babies and mortality in early childhood revealed a quantitative relationship with the arsenic level in drinking water (Hopenhayn-Rich *et al*, 2000).

"In another study in Bangladesh, two groups of 96 women aged between 15 and 49 were compared. One group had consumed ≥0.1mg arsenic per litre drinking water (43.8% of the women for 5 to 10 years), and the other group had not. The two groups were matched for age, social status, education and age at marriage. In the group of exposed women were [sic] the frequencies of spontaneous abortions, stillbirths and premature births significantly higher than in the control group (Ahmad *et al*, 2001)." (References cited in ECHA, 2017).

The New Zealand EPA classifies arsenic acid as a 6.8A substance – a substance that is a known or presumed human reproductive or developmental toxicant (EPA, 2019).

The **SCOEL** opinion on arsenic acid and its inorganic salts summarised the repeated exposure toxicity in humans:

"The literature on sub-chronic and chronic exposure on arsenic has been reviewed by IARC (2004). Most reports of chronic arsenic toxicity focus on skin manifestations such as pigmentation, with depigmentation affecting trunks and limbs and keratosis affecting hands and feet. Chronic lung disease, peripheral neuropathy, hepatomegaly and peripheral vascular disease have frequently been reported in cases of chronic exposure to arsenic. Exposure to arsenic has been associated with an increased risk for diabetes mellitus. Other systemic manifestations include cardiovascular effects, abdominal pain, anorexia, nausea, diarrhoea, cerebrovascular disease, non-pitting oedema of hands, feet or legs, anaemia and generalised weakness. In Taiwan a significantly higher mortality from cardiovascular and peripheral vascular disease was reported among patients with Blackfoot disease compared with the general population of Taiwan or with unaffected residents in endemic areas of Blackfoot disease.

"The major effects of subacute oral exposure are gastrointestinal, haematological (such as hematopoietic and immune system changes) cardiovascular, respiratory, effects on the reproductive and nervous systems and dermal (such as skin lesions including hyperkeratinisation and hyperpigmentation of the skin) (WHO- IPCS, 2001/ATSDR, 2007).

"In various epidemiological studies, peripheral vascular effects such as acrocyanosis, Raynaud's disease (episodes of ischaemia resulting from spasms in vessels, usually in the arteries of the fingers) and tissue necrosis on the extremities (Blackfoot disease) were described after long-term inhalation exposure to arsenic (ATSDR 2007, Lagerkvist *et al*, 1988).

"Feldman *et al* (1979) reported that in a copper smelting plant, peripheral neuropathy was investigated in 70 employees exposed to arsenic trioxide and 41 control persons who were not exposed. The results show that the level of arsenic, which was determined by analysing urine, hair and finger nails, was associated with a higher number of cases of sensory and motor neuropathy and electrophysiological changes.

"Sinczuk-Walczak *et al*, (2014) investigated a group of 21 men employed in copper smelting; they were selected on the basis of highest exposure from 61 workers at 10 different Polish factories (tasks: refiners, copper electrolysers and crane operators). Significantly, the authors concluded that exposure levels in excess of the ACGIH (2016) **TLV** (10µg/**m³**) and **BEI** (35µg/l; inorganic As plus methylated metabolites in urine) generates neuropathic disorders in the peripheral nervous system." (References cited in ECHA, 2017).

Animals

The ECHA opinion on arsenic acid and its inorganic salts summarised the acute toxicity in experimental animals:

"Inorganic arsenic can be lethal to experimental animals and humans. Arsenic toxicity depends on its solubility, chemical form and route of administration and varies among experimental animals (see Table 16.) (WHO-IPCS 2001/ATSDR 2007).

"Generally, trivalent arsenic is more toxic than the pentavalent forms. For example, the more soluble sodium arsenite is more toxic than arsenic trioxide (WHO 2011;-Done & Peart, 1971). Also, the inorganic arsenicals are more toxic than **MMAV** and **DMAV**.

"Holson *et al*, (1999) reported 100% mortality in pregnant rats after 1 day of inhalation exposure to arsenic trioxide at concentrations ≥100mg/m³ (76mg As/m³). In another study (Gaines, 1960), the acute dermal **LD50** for the pentavalent arsenicals calcium arsenate and lead arsenate in the rat was ≥2400**mg/kg bw** (≥400mg As/kg bw)." (References cited in ECHA, 2017).

The New Zealand EPA classifies arsenic and arsenic acid as a 6.9A substance – a substance that is toxic to human target organs or systems (EPA, 2019).

The ECHA opinion on arsenic acid and its inorganic salts summarised the irritation/corrosion and sensitisation potentials in experimental animals:

"Animal data regarding irritation of arsenic and arsenic compounds are limited.

"No animal data on local effects on the respiratory tract and no studies on ocular effects in animals were reported (WHO-IPCS, 2011/ATSDR, 2007)." (References cited in ECHA, 2017).

"Sodium arsenite and sodium arsenate were not allergenic in the guinea-pig maximisation test (WHO-IPCS, 2001/ATSDR, 2007): Wahlberg and Boman, 1986).

> "In one study, Fukuyama *et al* (2008) used the local lymph node assay to evaluate the ability of chromated copper arsenate (**CCA**) and its components to cause sensitizing reactions. In addition, total levels of chromium and arsenic in blood samples were measured. In all groups treated with CCA, all parameters assessed, including lymph node (**LN**) weight and lymphocyte proliferation, increased in a dose-dependent manner. It was discussed by the authors that all three components of CCA (chromium oxide, arsenic oxide and copper oxide) had sensitising properties." (References cited in ECHA, 2017).

The ECHA opinion on arsenic acid and its inorganic salts summarised the genotoxic potential in experimental animals and *in vitro* test systems:

> "The major underlying mechanisms of the genotoxic effects of arsenic compounds include the rapid induction of oxidative DNA damage and DNA repair inhibition and slower changes in DNA methylation patterns, aneuploidy and gene amplification. Gene amplification, altered DNA methylation and aneuploidy lead to altered gene expression and genomic instability. Inhibition of DNA repair leads to co-mutagenicity as well. These effects are consistent with the experimental animal carcinogenicity data, in which arsenite is a transgenerational carcinogen, with exposure being present during many cell generations, and with co-carcinogenicity (EFSA, 2009; IARC, 2012)." (References cited in ECHA, 2017).

The ECHA opinion on arsenic acid and its inorganic salts summarised the reproductive/developmental toxicity in experimental animals:

> "There are no reported studies in animals showing effects on fertility of inorganic arsenic via the inhalatory route, but exposure to inorganic arsenic via the oral and intraperitoneal route has shown interference with spermatogenesis and degeneration of follicular cells. In addition, developmental effects such as reduced birth weight, a variety of foetal malformations (both skeletal and soft tissues) and increased foetal mortality have been noted following inhalation exposure of mice and rats, oral exposure of mice, rats, hamsters and rabbits, and intraperitoneal or intravenous exposure of mice, rats and hamsters. Malformations have usually been seen at levels showing also maternal toxicity." (ECHA, 2017).

The ECHA opinion on arsenic acid and its inorganic salts summarised the repeated exposure toxicity in experimental animals:

> "Effects have been seen in animal studies, although no recent studies are available." (ECHA, 2017).

4.2 Cancer

The International Agency for Research on Cancer [IARC] evaluation of arsenic and arsenic compounds concluded that:

> "There is *sufficient evidence* in humans for the carcinogenicity of mixed exposure to inorganic arsenic compounds, including arsenic trioxide, arsenite, and arsenate. Inorganic arsenic compounds, including arsenic trioxide, arsenite, and arsenate, cause cancer of the lung, urinary bladder, and skin. Also, a positive association has been observed between exposure to arsenic and inorganic arsenic compounds and cancer of the kidney, liver, and prostate.

> "There is *sufficient evidence* in experimental animals for the carcinogenicity of dimethylarsinic acid, calcium arsenate, and sodium arsenite.
>
> "There is *limited evidence* in experimental animals for the carcinogenicity of sodium arsenate, gallium arsenide, arsenic trioxide, and trimethylarsine oxide.
>
> "There is *inadequate evidence* in experimental animals for the carcinogenicity of monomethylarsonic acid and arsenic trisulfide.
>
> "In view of the overall findings in animals, there is *sufficient evidence* in experimental animals for the carcinogenicity of inorganic arsenic compounds". (IARC, 2012).

With an overall evaluation that:

> "Arsenic and inorganic arsenic compounds are *carcinogenic to humans (Group 1)*.
>
> "Dimethylarsinic acid and monomethylarsonic acid are *possibly carcinogenic to humans (Group 2B)*.
>
> "Arsenobetaine and other organic arsenic compounds *not metabolized in humans, are not classifiable as to their carcinogenicity to humans (Group 3)*.
>
> "The Working Group made the overall evaluation on 'arsenic and inorganic arsenic compounds' rather than on some individual arsenic compounds, based on the combined results of epidemiological studies, carcinogenicity studies in experimental animals, and data on the chemical characteristics, metabolism, and modes of action of carcinogenicity.
>
> "Elemental arsenic and inorganic arsenic species share the same metabolic pathway: arsenate→arsenite→methylarsonate→dimethylarsenite. Thus, independent of the mechanisms of the carcinogenic action, and independent of which of the metabolites is the actual ultimate carcinogen, different inorganic arsenic species should be considered as carcinogenic." (IARC, 2012).

The US National Toxicology Program [**NTP**] Report on Carcinogens [**RoC**], Fourteenth Edition concluded that:

> "Arsenic and inorganic arsenic compounds are *known to be human carcinogens* based on sufficient evidence of carcinogenicity in humans." (NTP RoC, 2016).

The New Zealand EPA classifies arsenic and several inorganic arsenic compounds including: arsenic acid; arsenic (III) oxide; arsenic acid, trisodium salt; and, sodium arsenate, bibasic, heptahydrate as 6.7A – a substance known or presumed to be a human carcinogen (EPA, 2019a-e).

Humans

The IARC Monograph on arsenic and arsenic compounds summarised the carcinogenicity data in exposed humans:

> "The Working Group reviews a large body of evidence that covers ecological studies, case-control studies and cohort studies in a variety of settings and populations exposed either by ingestion (primarily to As^{III} and As^{V} in drinking-water) or inhalation (with exposure to a mixture of inorganic arsenic compounds). The evidence also relates to historical exposure from pesticidal and pharmaceutical uses. The epidemiological evidence from drinking-water

exposure permits the evaluation of the carcinogenicity that is related to exposure to As^{III} and As^{V}. The epidemiological evidence from inhaled arsenic mixtures permits the evaluation of the carcinogenicity that is related to inorganic arsenic compounds. However, it does not allow a separation of the carcinogenic risk associated with particular arsenic species that occur in these mixtures.

"The observed associations between exposure to arsenic in drinking-water and lung cancer, and between exposure to arsenic in air and lung cancer, cannot be attributed to chance or bias. The evidence is compelling for both the inhalation and ingestion routes of exposure. There is evidence of dose-response relationships within exposed populations with both types of exposure.

"The observed association between exposure to arsenic in drinking-water and bladder cancer cannot be attributed to chance or bias. There is evidence of dose-response relationships within exposed populations.

"The observed association between exposure to arsenic in drinking-water and skin cancer cannot be attributed to chance or bias. There is evidence of dose-response relationships within exposed populations. The evidence is primarily for squamous cell carcinoma of the skin.

"Although the data for kidney cancer are suggestive of a relationship with exposure to arsenic in drinking-water, overall, the small possibility of chance or bias cannot be completely ruled out.

"The evidence for an association between liver cancer and long-term exposure to arsenic in drinking-water relies on mortality data. Although the data strongly suggest a causal association with some evidence of a dose-response relationship, the Working Group could not rule out possible chance or bias. The evidence comes mainly from Taiwan (China) where hepatitis B is highly prevalent.

"The evidence for an association for prostate cancer and long-term exposure to arsenic in drinking water relies on mortality data. In the studies from Taiwan (China), there is some evidence of a dose-response relationship. However, the data from South America are not consistent with this observation. Although the evidence on prostate cancer suggests the possibility of a causal association, the Working Group could not rule out the possibility of chance or bias." (IARC, 2012).

Animals

The IARC Monograph on arsenic and arsenic compounds summarised the carcinogenicity data in experimental animals:

"Oral administration of sodium arsenate and **DMA^{V}** induced lung tumours in mice. Calcium arsenate induced lung tumours in hamsters by oral and intratracheal administration. Pre- and postnatal exposure in mice to arsenic trioxide, through subcutaneous injections (maternal and postnatal), induced lung tumours in the offspring. Transplacental exposure via maternal oral exposure in mice to sodium arsenate during gestation induced lung, liver, ovary and adrenal tumours in the offspring in several studies, and the uterus in one study. Early life transplacental and perinatal exposure to sodium arsenite appears to be a time of particular sensitivity in terms of carcinogenesis.

"Oral exposure to DMAV induced urinary bladder tumours in several studies in rats and among studies in mice, only one showed negative results. Oral trimethylarsine induced liver tumours in rats. Chronic oral exposure to **MMA^{V}** did not produce tumours in rats and mice. [The Working Group considered that previous traditional bioassays for arsenicals for adult rodents were frequently negative in their final evaluations.]

"Inhalation of gallium arsenide causes lung and adenal [sic] tumours in rats but not in mice.

"In multiple studies, initiating, promoting or co-carcinogenic activity was demonstrated in the urinary bladder, skin, female reproductive tract, kidney, lung, liver and thyroid after exposure to inorganic arsenicals or DMAV in drinking-water or by transplacental exposure." (IARC, 2012).

4.3 Absorption, distribution, metabolism and excretion

The ECHA opinion on arsenic acid and its inorganic salts summarised the ADME:

"Arsenic absorption depends on its chemical form. The rate of absorption of arsenic in highly insoluble forms (for example, arsenic sulphide, lead arsenate) is much lower than that of more soluble forms via both oral and inhalation routes.

"In humans, AsIII, AsV, monomethylarsonic acid (MMA), and dimethylarsinic acid (DMA) are orally absorbed ≥ 80% (WHO–IPCS, 2001/ATSDR, 2007).

"Arsenic is also absorbed via inhalation. In lung cancer patients exposed to arsenic in cigarette smoke, deposition was estimated to be about 40% and absorption was 75–85% (Holland, 1959). Thus, overall absorption (expressed as a percentage of inhaled arsenic) was about 30–34%.

"Absorption by the dermal route has not been well characterised, but is considered to be low compared to the other routes (WHO–IPCS, 2001/ ATSDR, 2007).

"Hazelton *et al*, (2001) found indications for accumulation of arsenic in the lung. In this study, a two-stage clonal expansion model was used to analyse lung cancer mortality in a cohort of Yunnan tin miners. Particles containing arsenic accumulated in the lung with very slow clearance (6 years or longer).

"Data on distribution after inhalation exposure are limited, but it appears that arsenic is available to nearly all tissues. Also arsenic accumulates in keratin-rich tissues such as skin, hair and nails (WHO-IPCS, 2001/ATSDR, 2007).

"In pregnant women, exposure to arsenic resulted in the death of the foetus and of toxic levels of arsenic in foetal organs. This demonstrates that the material had passed through the placenta (Lugo *et al*, 1969), (Bolliger *et al*, 1992). Concha *et al*, (1998) reported that arsenic concentrations were similar in cord blood and maternal blood (~9µg/L) of mother-infant pairs exposed to drinking water containing high levels of arsenic (~200µg/L). This study also showed that arsenic metabolites originating from inorganic As in the blood of the newborns and their mothers was in the form of DMA.

"Hall *et al* (2007) investigated 101 pregnant women in Bangladesh exposed to waterborne arsenic. They observed strong associations between maternal and cord blood concentrations for total As (**r**=0.93, **p**<0.0001); DMA (r=0.94, p<0.0001); MMA (r=0.80, p<0.0001); arsenite (r=0.8, p<0.0001) and arsenate (r=0.89, p<0.0001).

> "Arsenic and its metabolites are largely excreted in urine. Excretion also occurs via faeces; a minor excretion pathway is nails and hair. Arsenic was also found in human milk.
>
> "In many animal species arsenic metabolism is characterised by two main reactions: (1) two-electron reduction reactions of pentavalent to trivalent arsenic, and (2) oxidative methylation of trivalent arsenic, mono- and trimethylated products." (References cited in ECHA, 2017).

The ECHA opinion on arsenic acid and its inorganic salts summarised the mechanistic data for carcinogenesis:

> "Arsenic was considered by **DECOS** (DECOS, 2012) to act as a non-stochastic carcinogen. Clastogenic damage was observed in human and animal studies in vivo and in vitro. For point mutations, the results are negative. With regards to the mechanism of the genotoxic effects, there are hypotheses that are not fully clarified and which cause controversy.
>
> "It is assumed that inorganic arsenic compounds do not affect DNA directly in the form of DNA-adducts or DNA-protein crosslinks. Exposure to arsenic per se does not cause point mutations, which are observed during simultaneous exposure to arsenic and physical factors (UV radiation, X-radiation or gamma radiation). This means that arsenic could act as a co-mutagen, enhancing mutagenicity of other agents (Li *et al*, 1989).
>
> "Further evidence shows reactivity of arsenicals with thiol-groups in proteins, which has been viewed in conjunction with the inhibition of DNA repair enzymes.
>
> "Other data (Zhao *et al*, 1997; Dizik *et al*, 1991; Christman *et al*, 1993; Hseieh *et al*, 1989; Mass *et al*, 1997) suggest that inorganic arsenic compounds lead to altered gene expression together with disturbance of DNA methylation as an effect of methyltransferases. According to US EPA, hypermethylation of DNA is caused by arsenic, particularly in the promoter region, which results in inactivation of tumour suppressor genes or genes involved in DNA repair.
>
> "In the recent review, Bustaffa *et al* (2014) demonstrated that a growing body of evidence indicates that epigenetic modifications play a role in the induction by arsenic of adverse effects on human health. Arsenic induces epimutations both at a genome-wide level and at specific gene promoter regions, and is also able to induce histone modifications such as methylation, acetylation, and phosphorylation of histone tails, changing the expression of several genes. Furthermore, several findings demonstrated that the exposure to arsenic induces gene-specific alteration of **miRNA** expression likely resulting in an impaired expression of all the genes which expression is regulated by those miRNA.
>
> "Furthermore, arsenic induces oxidative stress (Shimizu *et al*, 1998; Guyton *et al*, 1996). Although it does not generate reactive oxygen by itself, it inhibits scavenging systems for reactive oxygen.
>
> "Since all these processes support a non-stochastic mechanism of genotoxicity (DECOS, 2012), a **NOAEL** for arsenic and arsenic compounds might theoretically be derived using a threshold model. However, the available epidemiological and experimental studies do not allow the numerical identification of such threshold. DECOS, in this situation, performed an evaluation of so-called **HBC-OCRV** (Health-Based Calculated Occupational Cancer Risk Values), using mathematical modelling and extrapolation as described in Section 8.

"More recently Lewis *et al* (2015) explored the option to perform a quantitative risk analysis for the general population employing a nonlinear threshold model. They argued that taking all information together, that is, occupational studies, information on the mode of action of ingested inorganic arsenic, and mechanistic data, a possible threshold for arsenic-induced lung cancer via inhalation is supported. Combining the data of the Tacoma and Anaconda cohorts (Enterline *et al*., 1995 and Lubin *et al*., 2008) they performed a pooled analysis using the cumulative exposure and reported SMR to derive a calculated NOAEL concentration for the general US population of 1.28μg/m^3. Furthermore, based on the dose-response data on concentrations of airborne arsenic and respiratory cancer mortality as reported by Lubin *et al*. (2008) they calculated a LOAEL for the general population of 0.1mg/m^3. With regards to an estimated exposure of the general population via inhalation in the range of 30ng/m^3, they argued for a sufficient margin of safety. Lewis summarised that to date, all assessments of arsenic's carcinogenic potency via inhalation have assumed a low-dose linear dose–response relationship. This assumption has been made despite the biological plausibility for a carcinogenic threshold for arsenic and consistent findings across cohorts that exposure concentration is a critical dose–response consideration. He concluded that an exploration into both a threshold model and the impact of exposure concentration is critical to achieve a robust characterization of arsenic's carcinogenic potential via inhalation." (References cited in ECHA, 2017).

5.0 Exposure standards

IN THIS SECTION:

5.1 Other exposure standards

Table 3 below shows some of the arsenic and arsenic compounds exposure standards from around the world, as published by the Institute for Occupational Safety and Health of the German Social Accident Insurance (**IFA**, 2019).

JURISDICTION OR ADVISORY BODY	8-HOUR LIMIT VALUE[1]	SHORT-TERM LIMIT VALUE[1]
	mg/m³	mg/m³
Australia	0.05	
Austria	0.1[2]	0.4[2]
Belgium	0.01[9]	
Canada – Ontario	0.01[3]	0.05[3]
Canada – Québec	0.1	
Denmark	0.01	0.02
Finland	0.01	
Germany – **AGS**	0.0083[2,4] 0.00083[2,5]	0.066[2,4,6]
Hungary		0.01
Ireland	0.01	
Israel	0.01[9] 0.2[13]	
Japan – **MHLW**	0.003[7]	
Japan – **JSOH**	0.003[10,12] 0.0003[11,12]	
New Zealand	0.05	
People's Republic of China	0.01	0.02[6]
Poland	0.01	
Romania	0.01[9]	0.1[6,9]
Singapore	0.01	
South Korea	0.01	
Spain	0.01	
Sweden	0.01	
Switzerland	0.1[2]	
USA – **NIOSH**		0.002[8]
USA – **OSHA**	0.01	
UK	0.1	

TABLE 3: Exposure standards for arsenic and arsenic compounds, as As, from around the world

[1] As As, as total dust – unless otherwise specified.
[2] Inhalable aerosol/fraction.
[3] And organic compounds (only where both inorganic and organic compounds are present).
[4] Workplace exposure concentration corresponding to the proposed **tolerable cancer risk**.
[5] Workplace exposure concentration corresponding to the proposed preliminary **acceptable cancer risk**.
[6] 15 minutes average value.
[7] Not GaAs (gallium arsenide).
[8] **Ceiling limit value** (15 min).
[9] Arsenic and inorganic compounds.
[10] Reference value corresponding to an individual excess lifetime risk of cancer 10^{-3}.
[11] Reference value corresponding to an individual excess lifetime risk of cancer 10^{-4}.
[12] Both inorganic and organic arsenic compounds as As.
[13] Organic arsenic compounds as As.

It is noted that the only organisations from whom we obtained information as to how and why they set occupational exposures standards on arsenic and arsenic compounds were ECHA, **DFG**, DECOS, ACGIH® and Safe Work Australia.

5.2 ECHA

The European Chemicals Agency [ECHA] Committee for Risk Assessment opinion on arsenic acid and its inorganic salts (ECHA, 2017) concluded:

- "The critical endpoint for establishing an **OEL** is carcinogenicity. However, health-based OELs cannot be established for arsenic acid and its salts because the available data do not allow the identification of a threshold for the genotoxic and carcinogenic effects of arsenic.
- "Arsenic acid and its salts are classified as Carcinogen 1A under the Classification, Labelling and Packaging Regulation (**EC**) 1272/2008 (**CLP**), that is, they are known human carcinogens, largely based on human evidence.
- "The broader group Arsenic, and inorganic arsenic compounds are considered to be human carcinogens (Group 1) by the International Agency for Research on Cancer (IARC). IARC (2012) noted that *"there is sufficient evidence in humans for carcinogenicity of mixed exposure to inorganic arsenic compounds, including arsenic trioxide, arsenite and arsenate*. The composition of arsenic compounds to which a patient has been exposed and the specific components causing cancer are often unclear.
- "According to the SCOEL Classification scheme, arsenic acid and its inorganic salts would most likely be classified as "*Group B: Genotoxic carcinogens, for which the existence of a threshold cannot be sufficiently supported at present. In these cases the **LNT** [Linear Non Threshold] model may be used as a default assumption, based on the scientific uncertainty*" (see Bolt and Huici-Montagud, 2008).
- "Inhalation is the primary route of occupational exposure for arsenic while non-occupational exposure occurs mainly through food (see Section 7.1.5) and through the drinking water in areas with high levels of arsenic in drinking water resources (see Section 7.7.1).
- "Epidemiological studies of populations occupationally exposed to arsenic consistently demonstrate an excess lung cancer risk (see Section 7.7.1). In addition, epidemiological studies in the general population also show that the oral exposure to arsenic via drinking water increases the risk of skin and urinary bladder cancer (see Section 7.7.1).
- "Absorption by the dermal route is considered to be low compared to the other routes thus a skin notation is not warranted." (ECHA, 2017).

Derived limit values

"Arsenic, arsenic acid and inorganic arsenic compounds are categorised as genotoxic carcinogens for which health based limit values, including the 8-hour TWA, **STEL** (15 min), and BLV [biological limit value], cannot be derived from the scientific evidence.

"However a Biological Guidance Value (BGV) value of 10µg/L is recommended by **RAC** based on the 95th percentile of general population data established for the sum of As3+, As5+, and DMA and MMA (see below).

Cancer risk assessment

"Based on the risk assessment of DECOS (2012), RAC previously defined cancer dose-response relationships for arsenic compounds based on linear extrapolation from the observed range (see Appendix 1 for details of ranges). The Committee has found no significant new information to justify a change to this position. However, extrapolating outside the range of observation inevitably introduces uncertainties. As the mechanistic evidence is suggestive of non-linearity, it is acknowledged that the excess risks in the low exposure range might be an overestimate.

Inhalation exposure cancer risk

"Workers: based on a 40 year working life (8 h/day, 5 days/week):
An excess lifetime lung cancer mortality risk = 1.4 x 10^{-4} per µg As/m^3 (derived for the inhalable particulate fraction).

Systemic cancer risk dermal route:

"Although arsenic and inorganic arsenic compounds are likely to have limited skin permeability RAC has derived a dose-response also for the carcinogenicity via the skin: this dose-response assumes skin permeability of 1%. This is based on the **BMDL0.5** derived from human epidemiology data from the Taiwanese drinking water cohorts (Chen *et al*, 2010a, 2010b) and assuming linearity of the dose-response.

"Workers: based on a 40 year working life (8 h/day, 5 days/week):
An excess lifetime lung cancer mortality risk = 6.4 x 10^{-6} per µg As/kg bw/day (as dermal exposure) (ECHA, 2017).

The ECHA RAC concluded that a skin notation was not warranted, based on the available data and the SCOEL methodology (ECHA, 2017).

5.3 DFG

The Deutsche Forschungsgemeinschaft [DFG, German Research Foundation] review of arsenic and its inorganic compounds (with the exception of arsine) noted that arsenic and its inorganic arsenic compounds have been classified in Category 1 as human carcinogens, and in Category 3A for germ cell mutations (DFG, 2016). As Category 1 (human carcinogens) and Category 3A (germ cell mutagens), no MAK value or peak limitations have been derived (DFG, 2016).

DFG also noted that:

"Arsenic and its inorganic arsenic compounds are not designated with an **"H"** (for substances which can be absorbed through the skin) … In studies with rats, even after occlusive dermal application of 10,000mg gallium arsenide for 24 hours, no evidence of clinical changes indicating toxicity could be found. As, in addition, no other data are available which indicate any relevant absorption through the skin, gallium arsenide is not designated with an "H"."

"The sensitizing effects of "arsenic and its inorganic arsenic compounds" were evaluated in the documentation completed in 2002 (documentation "Arsenic and its inorganic compounds (with the exception of arsine)" 2005), and designation with **"Sa"** or **"Sh"** (for substances which cause sensitization of the airways or skin) was not considered necessary. For gallium arsenide only one local lymph node assay with negative results is available. Therefore, sensitizing effects of arsenic and its inorganic arsenic compounds cannot be derived from the available data, and the substance has not been designated with "Sa" or "Sh"." (DFG, 2016).

5.4 DECOS

The Dutch Expert Committee on Occupational Standards [DECOS] review of arsenic and inorganic arsenic compounds concluded that the concentration of arsenic in air that corresponded to an excess cancer mortality:

- of 4 per 1,000 [4 x 10^{-3}], for 40 years of occupational exposure, is 28**µg/**m^3, and
- of 4 per 100,000 [4 x 10^{-5}], for 40 years of occupational exposure, is 0.28µg/m^3 (DECOS, 2012).

The rationale:

> "The Committee considers lung cancer as the critical effect in humans after inhalation exposure to arsenic and arsenic compounds. Studies of populations occupationally exposed (primarily by inhalation) to arsenic, such as smelter workers, pesticide manufacturers and miners in many different countries, consistently demonstrated an excess lung cancer risk among the arsenic-exposed. Sufficient quantitative information from human studies on the levels of occupational arsenic exposure to ensure reliable assessment of the exposure-response relationship was available for three copper smelter cohorts: Tacoma (USA), Anaconda (USA) and Rönnskär (Sweden) (Enterline *et al*., 1995; Lubin *et al*., 2000; Järup *et al*., 1989). Increased risks have been observed in relatively low cumulative exposure categories: exposure category of < 250µg/m^3.year (Rönnskär, Sweden) and exposure category of < 750µg/m^3.year (Tacoma, USA). Furthermore, in the Tacoma smelter, daily exposure to 213µg/m^3 arsenic for 30 years or more was associated with a statistically significant SMR of 238.7 for lung cancer (Enterline *et al*., 1987). Studies indicated that smoking had a synergistic effect on the development of lung cancer of arsenic exposure.
>
> "The Committee considers arsenic as a non-stochastic genotoxic compound (see Annex I and J). Clastogenic damage was observed in human and animal studies in vivo and in vitro. For point mutations, the results are largely negative. With regard to the mechanism which caused the genotoxic effects, there is evidence that arsenicals bind to thiol-groups in proteins which may lead to inhibition of (for example, DNA repair enzymes). There is also evidence that arsenic exposure can result in hypo- or hypermethylation of cellular DNA; these changes can be caused by (for example, an effect of arsenic on DNA methyltransferases). Furthermore, arsenic does not generate reactive oxygen by itself but inhibits the scavenging systems of reactive oxygen species, which indirectly leads to an increase of reactive oxygen species. Since all these processes support a non-stochastic mechanism of genotoxicity a NOAEL for arsenic and arsenic compounds should theoretically be derived using a threshold model. However, the available epidemiological studies do not allow derivation of such a threshold (that is, a no-effect concentration).
>
> "Therefore the Committee decided not to pursue a threshold approach but to calculate excess lifetime cancer mortality risks (health-based calculated occupational cancer risk values (HBC-OCRV)), using mathematical modeling and extrapolation."
>
> "The Committee selected four epidemiological studies on lung or respiratory cancer mortality among workers exposed to arsenic. The studies by Lubin *et al*. (2000), Lubin *et al*. (2008), Järup *et al*. (1989) and Enterline *et al*. (1995) were considered for quantitative hazard assessment."

> "Considering the quality of the papers and fit of the models, the Committee decides to use the outcomes of the Lubin *et al*. (2000) study and calculates that exposure to 28µg As/m^3 for 40 years results in 4 additional death cases per per 1,000 ($4x10^{-3}$) deaths and exposure to 0.28µg As/m^3 for 40 years result [in] 4 additional death cases per per [sic] 100,000 ($4x10^{-3}$) deaths.
>
> The Committee concludes that the concentration level of 28µg/m^3 associated with a lifetime cancer risk level of 4 $x10^{-3}$ is well below any health based occupational exposure limit derived from data other than carcinogenicity." (References cited in DECOS, 2012).

DECOS also noted that the available data did not warrant the setting of a STEL or Ceiling value; and, that the rate of absorption of arsenic and arsenic compounds through the skin does not warrant a *skin* notation (DECOS, 2012).

5.5 ACGIH®

The ACGIH® review of arsenic and its inorganic compounds recommended a **TLV-TWA** of 0.01 mg/m^3, measured as arsenic [As] for occupational exposure to elemental arsenic and its inorganic compounds, excluding arsine (ACGIH®, 2001). The TLV-TWA is intended to minimise the potential for adverse effects on the skin, liver, peripheral vasculature, upper respiratory tract, and lungs, including cancer. The ACGIH® noted that the conclusive evidence that arsenic is a human carcinogen warrants an A1, Confirmed Human Carcinogen notation, and accordingly, worker exposure by all routes should be carefully controlled to levels as low as possible below the TLV. The ACGIH® also noted that sufficient data was not available to recommend **Skin** or **SEN** notations, nor a **TLV-STEL**, but that BEIs had been recommended (ACGIH®, 2001).

The rationale:

> "In addition to effects on the upper respiratory tract, skin, liver, and peripheral vasculature (Hamilton and Hardy, 1974; Tseng, 1977; Borgono *et al*., 1977), there is consistent evidence from numerous epidemiologic studies linking lung cancer excesses with occupational exposures of smelter workers and pesticide workers and linking skin cancer excesses with persons who used arsenical compounds for medicinal reasons or who drank water contaminated with arsenic. The evidence is conclusive that arsenic is a human carcinogen. The quantitative air monitoring data presented by Enterline *et al*. (1987) indicate a significant excess of lung cancer risk for workers exposed to a mean level of 0.2 mg/m^3 of arsenic. This is based on an SMR of 213, where there were 47 observed lung cancer deaths. It is the lowest level at which an excess risk of cancer in humans has been found. To allow some measure of safety, a TLV-TWA of 0.01 mg/m^3, as arsenic, with an A1, Confirmed Human Carcinogen, designation is recommended." (References cited in ACGIH®, 2001).

5.6 Safe Work Australia

Safe Work Australia has recommended an 8-h TWA of 0.01 mg/m^3 to protect for excess skin, lung and liver cancers in exposed workers. There are insufficient data to recommend a STEL or peak limitation.

In their review, they say, "An assessment of mutagenicity is complicated by the variety of compounds within the arsenic group. A detailed examination of these data is recommended to be prioritised during subsequent reviews.

> "The TWA is based on an epidemiological study of arsenic exposed workers in which the lowest exposure level associated with an excess risk of lung cancer is 0.2 mg/m^3. A no effect level for cancer risk for these compounds has not been established (ACGIH, 2018). A factor of 20 was applied to account for uncertainties in mutagenicity data and no clear NOAEL for carcinogenic effects" (Safe Work Australia, 2019).

6.0 Analytical methods for the assessment of airborne arsenic and soluble arsenic compounds

A common method in New Zealand to measure airborne arsenic is using a modification of NIOSH Method 7303 (NIOSH, 2003).

Using this method, an air sample is collected onto a cellulose ester membrane filter using a sampling train set at a flow rate of 2 litres of air per minute. Following exposure of the filter for an appropriate period of time, the filter is subjected to acid digestion followed by analysis using inductively coupled plasma – atomic emission spectroscopy (ICP-AES). The limit of quantitation of this method has been quoted as 0.075µg of arsenic per sample.

Collecting an air sample for 8 hours at a flow rate of 2L/min would allow a minimum concentration of approximately 0.00008mg of arsenic per m^3 of air to be measured based on the quoted limit of quantitation.

7.0
Discussion

WorkSafe's WES for arsenic and soluble arsenic compounds, as As, has been unchanged since 1994.

The toxicological database reviewed above indicates that arsenic and soluble arsenic compounds are locally and systemically toxic to humans, causing irritant contact dermatitis and other skin and respiratory tract effects; and systemically causing genotoxicity, developmental toxicity, peripheral neuropathy, peripheral vascular disease and other adverse effects. Arsenic and several arsenic compounds are confirmed human carcinogens.

Based on the aforementioned documentation, informed by the conclusions of the ECHA, DFG, DECOS, ACGIH® and Safe Work Australia reviews, and in particular the findings listed below, WorkSafe considers its current WES-TWA of 0.05mg/m³ for inhalable fraction of arsenic and soluble arsenic compounds, as As, to be inadequate to manage health risks from possible workplace exposure:

- Arsenic and several arsenic compounds cause lung, urinary bladder and skin cancer in exposed humans. Positive associations have also been observed for cancer of the kidney, liver and prostate (IARC, 2012).
- ECHA noted that arsenic species have the potential to cause: chromosomal damage; secondary genotoxic processes such as inhibition of the maintenance of damage free DNA, and the scavenging of reactive oxygen; and, alterations in the levels of DNA methylation (ECHA, 2017).
- The mechanism(s) by which arsenic species induce cancer appear to be a diverse series of non-stochastic genotoxic and other activities, with genotoxicity mainly caused by secondary processes triggered by arsenic (ECHA, 2017; IARC, 2012).
- ECHA also noted that although the balance of evidence suggests that the carcinogenic hazards of arsenic and compounds may be driven by key events that each have a threshold below which they will not occur, the available data do not allow the identification of such threshold exposure levels (ECHA, 2017).
- Linear risk extrapolations for additional cancer deaths expected from arsenic inhalation, for 40 years of occupational exposure, have been reported as 4 per 1,000 at 28µg As/m³ and 4 per 100,000 at 0.28µg As/m³ [1.4 x 10-4 per µg As/m³] (DECOS 2012; ECHA, 2017).
- ACGIH® recommended a TLV-TWA of 0.01mg As/m³, based on an LOAEL of 0.2mg/m³ for lung cancer deaths in exposed workers reported by Enterline *et al*. (1987 cited in ACGIH®, 2001); and, ECHA noted a NOAEL of 1.28µg As/m³ with a LOAEL of 0.1mg/m³ for the general US population calculated by Lewis *et al*. (2015 cited in ECHA, 2017).
- Safe Work Australia recommended a WES of 0.01mg/m³, based on the ACGIH® recommendation.

- The proposed WES-TWA for arsenic and soluble arsenic compounds of 1µg/m³ [inhalable fraction] is set to be protective against all non-carcinogenic endpoints, and represents an estimated increase in the incidence of lung cancer deaths of 1.4 per 10,000 over a 40-year working life; and slightly lower than the NOAEL of 1.28µg As/m³ and 100x below the LOAEL of 0.1mg/m³ calculated for the general US population by Lewis *et al*. (2015 cited in ECHA, 2017).
- As cumulative rather than peak concentrations of arsenic exposure appear to be significant in the development of lung cancer and other toxicity in exposed workers, a **WES-STEL** is not warranted.
- A ***skin*** *notation* is not justified for arsenic, due to the low rate of dermal absorption reported.
- Available information indicates that arsenic is not a sensitiser, and a ***sen*** *notation* is not warranted.
- It is noted that a Biological Exposure Index [BEI] of 35µg/L of urine is currently set for the sum of inorganic arsenic and its methylated metabolites. Based on data from the DFG this would be equivalent to around 5µg/m³ of air (see the WorkSafe BEI review for arsenic, 2020).

8.0
Recommendations

WorkSafe considers its current WES-TWA of 0.05 mg/m^3 (50µg/m^3) for inhalable fraction of arsenic and soluble arsenic compounds, as As, to be inadequate to protect workers exposed in the workplace, based on today's scientific understanding.

It is proposed that WorkSafe:

1. adopt a WES-TWA for arsenic and soluble arsenic compounds of 0.001mg/m^3 (1µg/m^3), as As [inhalable fraction].

Noting that the proposed WES-TWA of 0.001mg/m^3 [inhalable fraction] for arsenic may not eliminate all risk, due to the uncertainty as to the carcinogenic threshold for arsenic species and the potential for exposures from non-occupational sources, so workplace exposures should be minimised.

Appendices

IN THIS SECTION:

Appendix 1: Glossary

TERM	MEANING
Acceptable (cancer) risk	EU criterion: 4 extra cases in a population of 10,000 until 2013; 4 extra cases in a population of 100,000 after 2013 (see Tolerable risk).
ACGIH®	The American Conference of Governmental Industrial Hygienists (ACGIH®) is a member-based organisation, established in 1938, that advances occupational and environmental health. Examples of this include their annual edition of the TLVs® and BEIs® book and work practice guides.
ADME	Absorption, Distribution, Metabolism and Excretion.
AGS	Ausschuss für Gefahrstoffe [Committee for Hazardous Substances] is a consultative body of the German Federal Ministry of Labour and Social Affairs on issues of the Ordinance on Hazardous Substances. Administered by the BAuA.
AKR1C2	Aldo-keto reductase family 1 member C2, also known as bile acid binding protein, 3α-hydroxysteroid dehydrogenase type 3, and dihydrodiol dehydrogenase type 2.
AKR1C3	Aldo-keto reductase family 1 member C3 (AKR1C3), also known as 17β-hydroxysteroid dehydrogenase type 5 (17β-HSD5, HSD17B5) is a key steroidogenic enzyme.
ATSDR	Agency for Toxic Substances and Disease Registry is a federal public health agency of the US Department of Health and Human Services.
BEI	Biological Exposure Index.
BMD(L)0.5 BMDL 0.5	Bench Mark Dose, lower limit of a 0.5% extra risk.
CCA	Chromated copper arsenate or copper chrome arsenate.
Ceiling Ceiling value Ceiling Limit Value	Ceiling Limit Value – absolute exposure limit that should not be exceeded at any time.
CLP	Classification, Labelling and Packaging – EU program.
DECOS	Dutch Expert Committee on Occupational Standards [DECOS]- a Committee of the Health Council of the Netherlands. The latter was established in 1902 as an independent scientific advisory body with a remit: "to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research..." (Section 22, Health Act).
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation), the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Federal Republic of Germany. The science-based MAK values are recommended to the German Minister of Labour and Social Affairs for possible adoption under the German Hazardous Substances Ordinance.
DMA DMAV DMA^V	Dimethylarsinic acid.
DNA	Deoxyribonucleic acid.
ECHA	The European Chemicals Agency (an agency of the European Union).
EPA	The New Zealand Environmental Protection Authority.
GCLC	Glutamate-cysteine ligase, also known as gamma-glutamylcysteine synthetase is the first and rate-limiting enzyme of glutathione synthesis.
GPMT	Guinea pig maximization test.
"H"	DFG MAK designation: *danger of percutaneous absorption*.
HBC-OCRV	Health based calculated occupational cancer risk value. A DECOS term.
hprt; HPRT; HGPRT	Hypoxanthine phosphoribosyltransferase or hypoxanthine-guanine phosphoribosyltransferase gene that codes for the enzyme.

TERM	MEANING
HSNO	Hazardous Substances and New Organisms Act, New Zealand.
IARC	International Agency for Research on Cancer, World Health Organization.
IFA	Institut für Arbeitsschutz der Deutschen Gestzlichen Unfallversicherung (Institute for Occupational Safety and Health of the German Social Accident Insurance).
Inhalable fraction	Inhalable particulate fraction is that fraction of dust that can be breathed into the nose or mouth. Particulate size: mostly < 100µm, 50% cut point. For sampling purposes the inhalable dust is to be collected according to the method set out in AS 3640-2009: Workplace Atmospheres – Method for Sampling and Gravimetric Determination of Inhalable Dust (Standards Australia, 2009b). (*cf*. Respirable fraction) (Also referred to as: inhalable aerosol; inhalable particulate matter)
JSOH	Japan Society for Occupational Health.
LD_{50}	Lethal Dose 50%: Dose resulting in 50% mortality.
LN	Lymph node.
LNT	Linear non-threshold.
LOAEL	Lowest Observed Adverse Effect Level.
µg/L	Microgram or one millionth of a gram per litre.
µg/m^3	Micrograms of substance per cubic metre of air.
mg	Milligram or one thousandth of a gram.
mg/kg bw	Milligrams of substance per kilogram body weight.
mg/m^3	Milligrams of substance per cubic metre of air.
MHLW	Japanese Ministry of Health, Labour and Welfare
miRNA	Micro-RNA. A microRNA (abbreviated miRNA) is a small non-coding RNA molecule (containing about 22 nucleotides) found in plants, animals and some viruses, that functions in RNA silencing and post-transcriptional regulation of gene expression.
MMA MMAV MMAV	Monomethylarsonic acid.
NAD(P)H NADPH	Nicotinamide adenine dinucleotide phosphate, reduced.
NIOSH	The National Institute for Occupational Safety and Health is the United States federal agency responsible for conducting research and making recommendations for the prevention of work-related injury and illness.
NOAEL	No Observed Adverse Effect Level.
NTP	National Toxicology Program, US Department of Health and Human Services.
OEL	Occupational Exposure Limit (equivalent to a WES).
OSHA	Occupational Safety and Health Administration, US Department of Labor.
p	Calculated probability value.
p53	Also known as TP53 or tumour protein (EC :2.7.1.37) is a gene that codes for a protein that regulates the cell cycle and hence functions as a tumour suppression. It is very important for cells in multicellular organisms to suppress cancer.
r	Coefficient of correlation.
RAC	Committee for Risk Assessment, European Chemicals Agency.
Ras ras	Ras protein family members belong to a class of protein called small GTPase, and are involved in transmitting signals within cells (cellular signal transduction).

TERM	MEANING
Respirable fraction	Respirable particulate fraction is that fraction of inhaled airborne particles that can penetrate beyond the terminal bronchioles into the gas-exchange region of the lungs (alveoli). Particulate size: mostly < 4µm, 50% cut point. For sampling purposes the respirable dust samples are to be collected according to the method set out in the Standards Australia publication AS 2985-2009: Workplace Atmospheres – Method for Sampling and Gravimetric Determination of Respirable Dust (Standards Australia, 2009a). (*cf*. Inhalable fraction) (Also referred to as: respirable aerosol; respirable particulate matter)
RoC ROC	Report on carcinogens.
ROS	Reactive Oxygen Species.
"Sa"	Sensitising to airways. A DFG MAK notation.
SCOEL	The Scientific Committee on Occupational Exposure Limits is a committee of the European Commission, established in 1995 to advise on occupational health limits for chemicals in the workplace within the framework of Directive 98/24/EC, the chemical agents directive, and Directive 90/394/EEC, the carcinogens at work directive.
sen	A substance that can 'sensitise' the respiratory system, inducing a state of hypersensitivity to it, so that on subsequent exposures, an allergic reaction can occur (which would not develop in non-sensitised individuals). It is uncommon to become sensitised to a compound after just a single reaction to it. A WorkSafe term.
SEN	A notation indicating the substance is a sensitiser. DSEN and RSEN are used in place of SEN when specific evidence of sensitisation by the dermal or respiratory route, respectively, is confirmed by human or animal data. An ACGIH® term.
"Sh"	DFG MAK designation: *danger of sensitisation of the skin*.
skin	Skin absorption – applicable to a substance that is capable of being significantly absorbed into the body through contact with the skin. A WorkSafe term.
Skin	A notation indicating the potential for significant contribution to the overall exposure, by the cutaneous route, including mucous membranes and the eyes, by contact with vapours, liquids and solids. An ACGIH® term.
SK:DIR(IRR)	Skin notation indicating the potential for direct irritant effects following exposure of the skin. A NIOSH term.
SK:SEN	Skin notation indicating the potential for immune-mediated reactions following exposure of the skin. A NIOSH term.
SMI	Standardised Mortality Index.
SMR	Standardised Mortality Ratio (SMR) is a measure of the strength or association between exposure and mortality; a form of Relative Risk (RR) in which the outcome is death. The SMR is the ratio of the number of deaths (due to a given disease arising from exposure to a specific risk factor) that occurs within the study population to the number of deaths that would be expected if the study population had the same rate of mortality as the general population (the standard). By convention, the figure is usually multiplied by 100 [an SMR of 200 corresponds to a RR of 2.0]. *A value greater than 100/1.0 indicates a positive association between exposure and disease*. (This may be causal, or have other explanations, such as bias, chance or confounding). (WHEC, 2017).
STEL (WES-STEL)	The 15-minute time weighted average exposure standard. Applies to any 15-minute period in the working day and is designed to protect the worker against adverse effects of irritation, chronic or irreversible tissue change, or narcosis that may increase the likelihood of accidents. The WES-STEL is not an alternative to the WES-TWA; both the short-term and time-weighted average exposures apply. Exposures at concentrations between the WES-TWA and the WES-STEL should be less than 15 minutes, should occur no more than four times per day, and there should be at least 60 minutes between successive exposures in this range. A WorkSafe term.
tAs	Total arsenic.
TLV®	Threshold Limit Value (see TLV-STEL and TLV-TWA below). An ACGIH® term. Please see the Statement of Position Regarding the TLVs® and BEIs® and Policy Statement on the Uses of TLVs® and BEIs®

TERM	MEANING
TLV-STEL	TLV-Short-Term Exposure Limit; a 15 minute TWA exposure that should not be exceeded at any time during a work day, even if the 8-hour TWA is within the TLV-TWA. An ACGIH® term.
TLV-TWA	TLV – Time-Weighted Average; the TWA concentration for a conventional 8-hour workday and a 40-hour workweek, to which it is believed that nearly all workers may be repeatedly exposed to, day after day, for a working lifetime without adverse effect. An ACGIH® term.
Tolerable (cancer) risk	EU criterion: 4 extra cases in a population of 1,000 (see Acceptable risk).
WES	Workplace Exposure Standard – WES are values that refer to the airborne concentration of substances, at which it is believed that nearly all workers can be repeatedly exposed to, day after day, without coming to harm. The values are normally calculated on work schedules of five shifts of eight hours duration over a 40 hour week. A New Zealand term.
WES-STEL	The 15-minute time weighted average exposure standard. Applies to any 15-minute period in the working day and is designed to protect the worker against adverse effects of irritation, chronic or irreversible tissue change, or narcosis that may increase the likelihood of accidents. The WES-STEL is not an alternative to the WES-TWA; both the short-term and time-weighted average exposures apply. Exposures at concentrations between the WES-TWA and the WES-STEL should be less than 15 minutes, should occur no more than four times per day, and there should be at least 60 minutes between successive exposures in this range.
WES-TWA	The average airborne concentration of a substance calculated over an eight-hour working day. A New Zealand term.
WHO	World Health Organisation, Geneva.
WHO-IPCS	World Health Organisation – International Programme on Chemical Safety.

Appendix 2: HSNO health-related hazardous substance classifications

This is the full list of all health-related hazardous substances classifications that are listed by the NZ EPA, including those that apply to this substance.

CLASSIFICATION CODE	MEANING
Acutely toxic	
6.1A	Substances that are acutely toxic – Fatal
6.1B	Substances that are acutely toxic – Fatal
6.1C	Substances that are acutely toxic – Toxic
6.1D	Substances that are acutely toxic – Harmful
6.1E	Substances that are acutely toxic – May be harmful, aspiration hazard
Skin irritant	
6.3A	Substances that are irritating to the skin
6.3B	Substances that are mildly irritating to the skin
Eye irritant	
6.4A	Substances that are irritating to the eye
Sensitisation	
6.5A	Substances that are respiratory sensitisers
6.5B	Substances that are contact sensitisers
Mutagens	
6.6A	Substances that are known or presumed human mutagens
6.6B	Substances that are suspected human mutagens
Carcinogens	
6.7A	Substances that are known or presumed human carcinogens
6.7B	Substances that are suspected human carcinogens
Reproductive/developmental toxicants	
6.8A	Substances that are known or presumed human reproductive or developmental toxicants
6.8B	Substances that are suspected human reproductive or developmental toxicants
6.8C	Substances that produce toxic human reproductive or developmental effects on or via lactation
Target organ toxicants	
6.9A	Substances that are toxic to human target organs or systems
6.9B	Substances that are harmful to human target organs or systems
Skin corrosive	
8.2A	Substances that are corrosive to dermal tissue (UN PGI)
8.2B	Substances that are corrosive to dermal tissue (UN PGII)
8.2C	Substances that are corrosive to dermal tissue (UN PGIII)
Eye corrosive	
8.3A	Substances that are corrosive to ocular tissue

Source: www.epa.govt.nz/industry-areas/hazardous-substances/rules-for-hazardous-substances/hazardous-substances-classification-codes

Appendix 3: References

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