Substance name: Calcium arsenate
EC number: 231-904-5
CAS number: 7778-44-1

MEMBER STATE COMMITTEE SUPPORT DOCUMENT FOR IDENTIFICATION OF

CALCIUM ARSENATE

AS A SUBSTANCE OF VERY HIGH CONCERN BECAUSE OF ITS CMR[1] PROPERTIES

Adopted on 24 November 2011

[1] CMR means carcinogenic, mutagenic or toxic for reproduction

CONTENTS

TABLES

Substance Name(s): Calcium arsenate

EC Number(s): 231-904-5

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The substance is identified as a substance meeting the criteria of Article 57 (a) of Regulation (EC) 1907/2006 (REACH) owing to its classification as carcinogen 1A[2] which corresponds to classification as carcinogen category 1[3].

Summary of how the substance meets the Carcinogen 1A criteria

Calcium arsenate is covered by index number 033-005-00-1, "arsenic acid and its salts", in Regulation (EC) No 1272/2008, Annex VI, Part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) , as amended and adapted to technical and scientific progress by Regulation (EC) No 790/2009, and classified as carcinogen Carc. 1A (H350: "May cause cancer"). The corresponding classification in Annex VI, Part 3, Table 3.2 (the list of harmonised and classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008 is carcinogen, Carc. Cat. 1 (R45;"May cause cancer").

Consequently, this classification of the substance in Regulation (EC) No 1272/2008, as amended and adapted to technical and scientific progress by Regulation (EC) No 790/2009, shows that calcium arsenate meets the criteria for classification as carcinogenic in accordance with Article 57(a) of REACH.

Registration dossiers submitted for the substance: YES

[2] Classification in accordance with Regulation (EC) No 1272/2008 Annex VI, part 3, Table 3.1 List of harmonised classification and labelling of hazardous substances.

[3] Classification in accordance with Regulation (EC) No 1272/2008, Annex VI, part 3, Table 3.2 List of harmonised classification and labelling of hazardous substances (from Annex I to Council Directive 67/548/EEC).

JUSTIFICATION

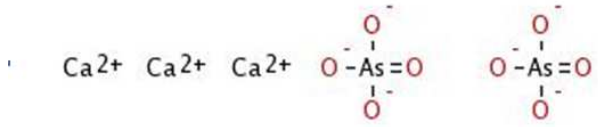
1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Table 1: Substance identity

EC number:	231-904-5
EC name:	Calcium arsenate
CAS number (in the EC inventory):	7778-44-1
CAS number:	7778-44-1
CAS name:	Arsenic acid (H3AsO4), calcium salt (2:3)
IUPAC name:	Tricalcium(2+) diarsenate
Index number in Annex VI of the CLP Regulation	033-005-00-1
Molecular formula:	$As_2Ca_3O_8$
Molecular weight range:	398,1
Synonyms:	Arsenic acid calcium salt; calcium orthoarsenate; tricalcium arsenate;

Structural formula:



Source: ESIS

1.2 Composition of the substance

Name: Calcium arsenate

Description:

Degree of purity:

Table 2: Constituents

Constituents	Typical concentration	Concentration range	Remarks
Calcium arsenate			

Table 3: Impurities

Impurities	Typical concentration	Concentration range	Remarks

Table 4: Additives

Additives	Typical concentration	Concentration range	Remarks

Further details on the composition of the substance are confidential and can be found in the technical dossier.

1.3 Physico-chemical properties

Table 5: Overview of physicochemical properties

Property	Value	Remarks	Source
Physical state at 20°C and 101.3 kPa	Colourless amorph powder Calcium arsenate is a colourless to white, odourless, solid powder.		IPCS Health and Safety Guide No. 70 ECHA website
Melting point	1455°C		IPCS Health and Safety Guide No. 70
Boiling point	Decomposes	No data for starting temperature for decomposition available	IPCS Health and Safety Guide No. 70 ECHA website
Vapour pressure	0 mm Hg at 20 °C .		IPCS Health and Safety Guide No. 70 ECHA website
Water solubility	0.13 g/L in water at 25°C		HSDB ECHA website
Partition coefficient n-octanol/water (log value)			
Dissociation constant			

2 HARMONISED CLASSIFICATION AND LABELLING

Calcium arsenate is covered by Index number 033-005-00-1, "arsenic acid and its salts" in Part 3 of Annex VI, of Regulation (EC) No 1272/2008, as updated by Commission Regulation No 790/2009 (ATP01), as follows:

Table 6: Classification according to part 3 of Annex VI, Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
033-005-00-1	arsenic acid and its salts with the exception of those specified elsewhere in this Annex	-	-	Carc. 1A Acute Tox. 3 * Acute Tox. 3 * Aquatic Acute 1 Aquatic Chronic 1	H350 H331 H301 H400 H410	GHS06 GHS08 GHS09 Dgr	H350 H331 H301 H410			A

Table 7: Classification according to part 3 of Annex VI, Table 3.2 (list of harmonized classification and labelling of hazardous substances from Annex I of Council Directive 67/548/EEC) of Regulation (EC) No 1272/2008

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
033-005-00-1	arsenic acid and its salts with the exception of those specified elsewhere in this Annex	-	-	Carc. Cat. 1; R45 T; R23/25 N; R50-53	T; N R: 45-23/25-50/53 S: 53-45-60-61		AE

3 ENVIRONMENTAL FATE PROPERTIES

Not relevant for the identification of the substance as SVHC in accordance with Article 57(a).

4 HUMAN HEALTH HAZARD ASSESSMENT

See section 2 on harmonised classification and labelling.

A summary on carcinogenic effects of arsenic acid and its salts is provided in appendix 1.

5 ENVIRONMENTAL HAZARD ASSESSMENT

Not relevant for the identification of the substance as SVHC in accordance with Article 57(a).

6 CONCLUSIONS ON THE SVHC PROPERTIES

6.1 PBT, vPvB assessment

Not relevant for the identification of the substance as SVHC in accordance with Article 57(a).

6.2 CMR assessment

Calcium arsenate is covered by index number 033-005-00-1, “arsenic acid and its salts”, in Regulation (EC) No 1272/2008, Annex VI, Part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) , as amended and adapted to technical and scientific progress by Regulation (EC) No 790/2009, and classified as carcinogen Carc. 1A (H350: “May cause cancer”). The corresponding classification in Annex VI, Part 3, Table 3.2 (the list of harmonised and classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008 is carcinogen, Carc. Cat. 1 (R45; ”May cause cancer”).

Therefore, this classification of calcium arsenate in Regulation (EC) No 1272/2008, as amended and adapted to technical and scientific progress by Regulation (EC) No 790/2009, shows that it meets the criteria for classification as carcinogen in accordance with Articles 57 (a) of REACH.

6.3 Substances of equivalent level of concern assessment

Not relevant for the identification of the substance as SVHC in accordance with Article 57(a).

7 REFERENCES

ECHA website, European Chemicals Agency database.
http://apps.echa.europa.eu/registered/registered-sub.aspx.

HSDB (2011): Hazardous Substances Data Bank (HSDB®). National Library of Medicine's (NLM) Toxicology Data Network (TOXNET®).
http://www.nlm.nih.gov/pubs/factsheets/hsdbfs.html#

IPCS (1992): Inorganic arsenic compounds other than arsine. Health and Safety Guide 70.IPCS International Programme on Chemical Safety, Geneva.
http://www.inchem.org/documents/hsg/hsg/hsg070.htm

8 DEFINITION OF ARSENIC COMPOUNDS AND GLOSSARY

Arsenic and its compounds are ubiquitous in nature. They exhibit both metallic and nonmetallic properties. From both the biological and the toxicological points of view, arsenic compounds can be classified into three major groups: inorganic arsenic compounds; organic arsenic compounds; and arsine gas. Arsenic can exist in four valence states: –3, 0, +3 and +5. Under reducing conditions, the +3 valence state as arsenite (As^{III}) is the dominant form; the +5 valence state as arsenate (As^{V}) is generally the more stable form in oxygenated environments. Inorganic As^{III} and As^{V} are the major arsenic species identified in natural water, whereas minor amounts of monomethylarsonic acid (MMA^{V}) and dimethylarsinic acid (DMA^{V}) can also be present.

Glossary:

Arsenic acid

Formula H_3AsO_4 . Colourless crystals, soluble in water and alcohol.

Arsenate

Arsenate is a salt or ester of arsenic acid having a negative ion of AsO_4^{3-}, Example of an arsenate salt is calcium arsenate $As_2Ca_3O_8$

Arsenite

Arsenite is a salt or ester of arsenious acid having a negative ion of AsO_3^{3-} derived from aqueous solutions of As_4O_6. Example of an arsenite salt is sodium arsenite Na_3AsO_3.

Arsenide

Arsenide is a negative, trivalent binary arsenic compound having a negative ion of As^{3-}. Example of an arsenide is gallium arsenide (GaAs).

Arsine

A colorless, highly poisonous gas with an unpleasant odor with the formula $As H_3$.

Arsinic acid

An acid of general formula R_2AsO_2H, derived from trivalent arsenic; an example is dimethylarsinic acid, $(CH_3)_2AsO(OH)$.

Arsonic acid

An acid derived fromarsenic acid H_3AsO_4, the type formula is generally considered to be $RAsO(OH)_2$, an example is monomethylarsonic acid $CH_3AsO(OH)_2$

Monomethylarsonic acid (MMA ^{V})

$CH_3AsO(OH)_2$

Monomethylarsonous acid (MMA^{III})

$CH_3As(OH)_2$

Dimethylarsinic acid (DMA^{V}):

$(CH_3)_2AsO(OH)$

Dimethylarsinous acid (DMA^{III}):

$(CH_3)_2AsOH$

APPENDIX 1: SUMMARY OF CARCINOGENIC EFFECTS OF ARSENIC ACID AND ITS SALTS

1 INTRODUCTION

A review of the documentation for the carcinogenic effects of arsenic acid and selected salts is presented in this section to support the proposal of "Arsenic acid and its salts" as Substances of Very High Concern under REACH. The classification of arsenic acid and its salts are presented in table 6 according to criteria in the Regulation (EC) No 1272/2008 (CLP Regulation), as amended and adapted to technical and scientific progress by Regulation (EC) No 790/2009

The substances listed in table 1 are the target for this review.

Table 1 Overview of arsenic compounds addressed by this review

Substance name	Molecular formula	CAS no.	Water solubility[1]
Arsenic acid	AsH3O4	7778-39-4	302 g/L at 12.5 °C
Calcium arsenate	Ca3(AsO4)2	7778-44-1	0.13 g/L at 25 °C
Trilead diarsenate	Pb3(AsO4)2	3687-31-8	Sparingly soluble

[1]data from IUCLID5

For all three substances arsenic is in the pentavalent (+5) state. The water solubility is presented in table 1.

Arsenic acid and the two mentioned arsenates are all covered by Index number 033-005-00-1, “arsenic acid and its salts” in Part 3 of Annex VI, of the CLP Regulation as amended with a harmonised classification as carcinogens in category 1A. The full classification is shown in table 2.

Table 2 CLP classification of arsenic acid and its salts

International Chemical Identification	Hazard Class and category code(s)	Hazard Statement Code(s)
arsenic acid and its salts	Carc. 1A	H350
	Acute Tox. 3 *	H331
	Acute Tox. 3 *	H301
	Aquatic Acute 1	H400
	Aquatic Chronic 1	H410

Trilead diarsenate is also covered by Index number 082-001-00-6 “Lead compounds with the exception of those specified elsewhere in this Annex” in Annex VI, of the CLP Regulation with harmonised classification as toxic for reproduction Repr 1A; H360Df .

2 EXPOSURE

For the general population the main route of exposure is by the oral route, whereas occupational exposure is predominantly through inhalation and to a much lesser degree through dermal exposure.

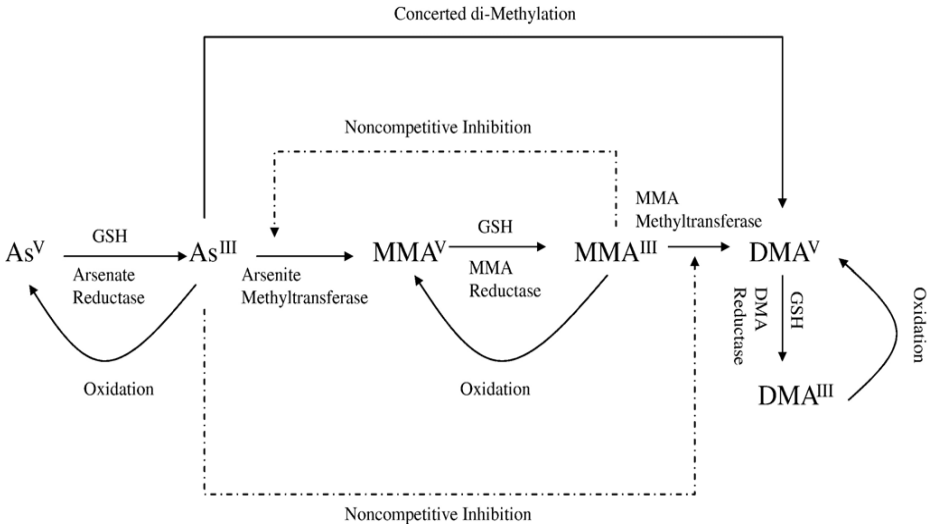
3 TOXICOKINETICS

3.1 Biotransformation of inorganic arsenic compounds

Soluble inorganic arsenic compounds are rapidly absorbed after oral exposure (about 70–90%) (Pomroy et al., 1980; Vahter and Norin, 1980; Freeman et al., 1995), but less well after inhalation (Beck et al., 2002), and dermal exposure (1 – 6%) (Wester et al., 1993). Absorbed arsenic is transported, mainly bound to SH groups in proteins and low-molecular-weight compounds such as glutathione (GSH) and cysteine, to different organs in the body (IARC, 2004).

Biotransformation of inorganic arsenic is characterized by two main types of reactions, i.e. reduction reactions where pentavalent arsenic is reduced to trivalent arsenic, and oxidative methylation where the trivalent arsenic forms are methylated to form mono- and dimethylated products. Once absorbed, arsenates in the pentavalent state (As^{V}) are rapidly reduced to arsenates (As^{III}) through a reaction requiring glutathione (GSH) and the distribution of As^{V} and As^{III} metabolites is therefore very similar as long as the methylation capacity is not exceeded (IARC, 2004). Inorganic arsenic is metabolized via methylation. The methylation occurs through alternating reductive and oxidative methylation reactions, that is, reduction of As^{V} to As^{III} followed by addition of one or two methyl groups. The methylation to monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) occurs mainly in the liver and S-adenosylmethionine is considered to be the main methyl donor (IARC, 2004). The glutathione (GSH) complexes formed in the reactions can decompose to yield GSH and MMA^{III} or DMA^{III}, which can then form MMA^{V} and DMA^{V} respectively. Limited short-term studies on humans indicate that the capacity to methylate inorganic arsenic is progressively, but not completely, saturated when daily intake exceeds 0.5 mg (WHO, 2003). An illustration of the biotransformation of inorganic arsenic is shown in figure 1.

Figure 1.Biotransformation of inorganic arsenic (from Clewell et al. 2007)



In humans most of the arsenic in blood is rapidly cleared, following a three-exponential clearance curve (Pomroy et al., 1980). The majority of arsenic in blood is cleared with a half-time of about 2 or 3 h. The half-times of the second and third phases are about 168 and 240 h, respectively (IARC 2004). In human subjects exposed chronically to arsenic, the hair and nails generally show the highest concentrations. Thus, arsenic appears to concentrate in tissues with a high content of cysteine-containing proteins like hair and nails, liver, kidney, blood, squamous epithelium of the upper gastrointestinal tract, epididymis, thyroid, skeleton and lens (IARC, 2004). Inorganic arsenic and methylated metabolites cross the placenta barrier, but do not readily cross the blood–brain barrier (IARC, 2004). In humans most inorganic arsenic is excreted in the urine as a mixture of As^{III}, As^{V}, MMA, and DMA and smaller amounts via faeces. The relative amounts of species in urine are generally 10–30% inorganic arsenic, 10–20% MMA_{total} and 60–80% DMA_{total} although there is a wide variation among individuals (Vahter and Concha, 2001). Hamsters are considered a suitable animal model for toxicokinetic studies since its urinary profile of arsenic species resembles that of humans following exposure to inorganic arsenic.

3.2 Toxicokinetics

Arsenic acid is very soluble in water (302 g/L at 12.5ºC; IUCLID5). Very few studies on toxicokinetics of arsenic acid are available in the open literature. However, in one study by Odanaka and co-workers (1980) arsenic acid was administered orally to mice, hamsters and rats. In all species the absorption via GI was above 40% and DMA, MMA and inorganic-As compounds were measured in urine and faeces.

In the open literature there are few studies examining toxicokinetics of calcium arsenate. The water-solubility of calcium arsenate is 0.13 g/L at 25ºC (IUCLID5) and it has been shown that after six days in 0.9% saline solution (50 mg As/L at 37ºC) 23% of the added calcium arsenate was dissolved (Pershagen et al., 1982). In hamsters given weekly intratracheal instillations of calcium arsenate dust suspension (for 2 to 5 weeks), arsenic was measured in both liver and hair. High concentration of calcium arsenate was retained in the lungs (Pershagen et al., 1982). Calcium arsenate has also been found in lungs after intratracheal instillations for a long period of time (50% retained after 7 days) in rats (Inamasu et al., 1982).

The available data for trilead diarsenate and toxicokinetic is sparse. Trilead diarsenate is sparingly soluble in water (IUCLID5). In a study by Marafante and Vahter (1987) the absorption and biotransformation following intratracheal and oral administration of radiolabel ^{74}As in trilead diarsenate (suspension) was examined. Groups of four hamsters were administrated 2 mg/kg bw intratracheally or orally. Three days after intratracheal administration, approximately 45% of the trilead diarsenate was retained in the lungs, while 1.2% was found in the carcase. The excretion via urine and faeces was 33% and 6%, respectively (Table 3). Hence, the absorption after intratracheal administration was approximately 40%. After oral administration, 70-80% of the dose was detected in the faeces. The faecal elimination following intratracheal administration was low (6%) and indicate that biliary and intestinal excretion most likely contribute little to the total elimination following oral administration. Twenty two percent of the dose was found in urine. The absorption of trilead diarsenate via the gastrointestinal tract is estimated to be between 20-30% (Table 3). After oral administration, most of the ^{74}As was measured as DMA metabolite in the urine (17%), while after intratracheal administration only 9% of the ^{74}As was found as DMA and 20% was detected as As^{V}.

Table 3: Faecal and urinary elimination of total ^{74}As and urinary excretion of ^{74}As-metabolites in hamsters during three days following intratracheal or oral administration of ^{74}As trilead diarsenate

				^{74}As-metabolites in urine		
Compound	**Administration route**	**Faeces**	**Urine**	**As^{III}**	**As^{V}**	**DMA**
$Pb_3(AsO_4)_2$	intratracheal	6.5±0.8	32.8±1.5	2.2±0.4	20.2±1.5	9.0±0.2
$Pb_3(AsO_4)_2$	oral	68.8±4.4	22.2±3.4	1.9±0.8	5.8±1.0	17.0±2.4

Figures represent percentage of the dose. Mean of four hamsters ± SE.

3.3 Summary of toxicokinetics

Arsenic acid is soluble in water and absorption following oral administration of experimental animals is high. Inorganic arsenic species and metabolites were measured in urine from arsenic acid exposed animals. Calcium arsenate is soluble in water and in saline solution *in vitro*. Its bioavailability is supported by the measurement of arsenic in hair and liver after intratracheal instillation in hamsters. Trilead diarsenate is sparingly soluble in water, but absorption via intratracheal or oral administration in hamsters was found to be 40% and 30%, respectively. The As-species As^{III}, As^{V} and DMA were measured in urine after trilead diarsenate exposure in hamsters. These findings show that arsenic acid, calcium arsenate and trilead diarsenate are bioavailable and that exposure to these substances leads to systemic exposure to inorganic arsenic.

4 GENOTOXICITY

Arsenicals (inorganic and organic arsenic compounds) have not been shown to have mutagenic effects in Ames test (reviewed in IARC, 2004). The methylated forms of trivalent arsenic are the only arsenic species that cause DNA damage *in vitro.* Arsenicals do not react directly with DNA but oxidative damage is seen in cells treated with low concentrations of $As^{III.}$.

Kligerman *et al.* (2003) have evaluated the arsenicals As^{V}, As^{III} and their MMA and DMA counterparts, in different assays[4] and found that MMA^{III} and DMA^{III} were the most potent clastogens of the six arsenicals in human lymphocytes and the most potent mutagens at the Tk(+/-) locus in mouse lymphoma cells. The dimethylated arsenicals were also spindle poisons, suggesting that they may be ultimate forms of arsenic that induce aneuploidy. Although the arsenicals were potent clastogens, none were potent SCE inducers, similar to

[4] Induction of chromosome aberrations, sister chromatid exchanges (SCE), toxicity in cultured human peripheral blood lymphocytes, mutagenicity in L5178Y/Tk(+/-) mouse lymphoma cells, the Salmonella reversion assay; and prophage-induction in Escherichia coli.

clastogens that act via reactive oxygen species. None of the six arsenicals (As^{V}, As^{III} and their MMA and DMA counterparts) were gene mutagens in Salmonella TA98, TA100, or TA104; and neither MMA^{III} nor DMA^{III} induced prophage. The results show that both methylated As^{V} compounds were less cytotoxic and genotoxic than As^{V}, whereas both methylated As^{III} compounds were more cytotoxic and genotoxic than As^{III}. The results support the view that MMA^{III} and DMA^{III} are candidate ultimate genotoxic forms of arsenic and that they are clastogens and not gene mutagens. The authors suggest that the clastogenicity of the other arsenicals is due to their metabolism by cells to MMA^{III} or DMA^{III}.

Other studies of micronuclei (MN) induced by As^{III} in human fibroblasts have shown that at lower (relatively non-toxic) doses, As^{III} acts as an aneugen, while at high (toxic) doses it acts as a clastogen and that aneuploidy is seen after treatment with As^{III} concentrations lower than those that cause chromosomal aberration (Sciandrello *et al.*, 2004). Studies of humans in West Bengal, India exposed to high concentrations of inorganic arsenic in drinking water also showed a significantly higher frequency of micronuclei in oral mucosal cells, bladder epithelial cells and peripheral lymphocytes (IARC, 2004).

Jensen *et al.* (2008) have demonstrated that malignant transformation of human urothelial cells by arsenicals is also associated with changes in histone acetylation and DNA methylation in gene promoter regions. Other studies have also shown altered DNA methylation in arsenic-exposed humans.

Fischer *et al.* (2005) have shown that As^{III} can act as a co-mutagen and enhance the mutagenicity of other agents like BaP. Other studies have shown that this may occur by interference with both nucleotide-excision repair and base-excision repair (BER). BER is crucial for development and for the repair of endogenous DNA damage. However, unlike nucleotide excision repair, the regulation of BER is not well understood. Arsenic is known to produce oxidative DNA damage, which is repaired primarily by BER, whilst high doses of arsenic can also inhibit DNA repair. Studies by Sykora and Snow (2008) have shown that there is evidence that changes in BER due to low doses of arsenic could contribute to a non-linear, threshold dose response for arsenic carcinogenesis.

Arsenic induces cell transformation in Syrian hamster embryo cells (SHE), BALB/3T3 cells and in the rat liver cell line TRL1215. Inoculation of the latter cells into nude mice gave rise to malignant tumours (fibrosarcoma and metastases to the lung) (IARC, 2004). The SHE cell-transformation assay represents a short-term in vitro assay capable of predicting rodent carcinogenicity of chemicals with a high degree of concordance. Induction of malignant transformation in the normally non-tumorigenic rat liver epithelial cell line (TRL 1215), and the chronic arsenic-exposed cells produce invasive and metastatic tumours upon inoculation into nude mice (the immunodeficient nude mice do not reject tumour transplantations from other species).

5 CARCINOGENICITY

5.1 CLP classification

In Annex VI of the CLP Regulation, as amended and adapted to technical and scientific progress by Regulation (EC) No 790/2009, the arsenic compounds shown in table 4 are classified as carcinogenic in category 1A.

Table 4 Arsenic compounds classified as carcinogenic in category 1A

Index No.	CAS No.	Substance name
033-003-00-0	1327-53-3	diarsenic trioxide
033-004-00-6	1303-28-2	diarsenic pentaoxide
033-005-00-1	-	arsenic acid and its salts with the exception of those specified elsewhere in this Annex
601-067-00-4	15606-95-8	triethyl arsenate
028-038-00-3	13477-70-8	trinickel bis (arsenate)
082-011-00-0	7784-40-9	lead hydrogen arsenate
028-051-00-4	12068-61-0 [1] 27016-75-7 [2]	nickel diarsenide nickel arsenide

5.2 IARC Classification

Arsenic and arsenic compounds were evaluated previously as being carcinogenic to humans (Group 1) on the basis of sufficient evidence of an increased risk for skin cancer among patients exposed to inorganic arsenic through medical treatment, and an increased risk for lung cancer among workers involved in mining and smelting, who inhaled inorganic arsenic (IARC, 1980, 1987). In a more recent report, IARC concluded that there is sufficient evidence in humans that arsenic in drinking-water causes cancers of the urinary bladder, lung and skin (IARC, 2004).

In 2009 IARC reconfirmed the classification of arsenic and inorganic arsenic compounds as “carcinogenic to humans” (group 1) (Straif *et al.*, 2009; IARC monograph vol 100C, in press). The working group made the overall evaluation on a group "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. The common metabolic pathway of elemental and inorganic arsenic species was underlined.

5.3 Human information

There is evidence from a large number of epidemiological studies and case reports that exposure to inorganic arsenic increases the risk of developing cancer (reviewed in IARC, 2004; ATSDR, 2007). In humans exposed chronically to inorganic arsenic by the oral route, from food or drinking water, skin tumours are the most common type of cancer, but other internal tumours in bladder and lungs, and to a lesser extent, liver, kidney, and prostate are also reported from epidemiological studies and case reports.

In drinking water, arsenic in the form of arsenic acid (arsenate, As^{V}) and arsenous acid (arsenite, As^{III}) are considered the causative agents behind the carcinogenicity demonstrated in a broad range of epidemiological studies. Epidemiological studies form the basis for the classification of arsenic in drinking-water and they reveal a dose-response trend of ingested arsenic on skin and lung cancer risk. A few of the studies on exposure to arsenic in drinking-

water and risk of skin or lung cancers are summarised in Table 5. Some central studies showing an association between exposure and cancer are shortly presented below.

Several studies conducted in arseniasis (i.e. chronic arsenic poisoning) endemic areas have found elevated risks for skin, lung and bladder cancer associated with levels of arsenic in drinking water. An ecological study from south-west Taiwan, Tseng et al. (1968) found an eightfold difference in the prevalence of skin cancer lesions from the highest (>600 μg/L) to the lowest category (<300 μg/L) of arsenic concentration in artesian wells, after an extensive examination survey of 40421 inhabitants in 37 villages. A more recent ecological study from northern Chile showed that the relative risks for lung and bladder cancer peaked in the years 1980–2000 in a region that experienced strong increases in drinking-water arsenic contamination in the years between 1950-1970 (Marshall et al., 2007).

A case-control study from northern Chile revealed significantly increasing risks of lung cancer with increasing levels of arsenic in drinking-water (Ferreccio et al., 2000). Clear trends in dose-response were found when concentrations were averaged over the years 1930–1994 and also when the peak exposure period 1958–1970 was considered.

In a cohort from south-west Taiwan, Chen et al. (1986) observed a dose–response relationship between the duration of consumption of artesian well water containing high levels of arsenic and lung cancer mortality risk. A study of combined cohorts in south-west and north-east Taiwan found a synergistic interaction between arsenic in drinking water and cigarette smoking (Chen et al., 2004).

A summary of epidemiological studies of workers exposed to As_2O_3 in smelters is presented in the background document to the opinion proposing harmonised classification and labelling at community level for gallium arsenide (RAC, 2010).

Table 5. Summary of selected epidemiological studies of inorganic arsenic in drinking water and risk of skin or lung cancer; From RAC 2010

Design	**Country**	**Study size**	**Adjusted for confounders**	**Comment**	**Concentration µg/L water**	***No. of observations,* Risk estimate#, (95% confidence interval)**	**Reference**
Ecologic	Taiwan	40,421		Incidence of skin cancer was measured as a function of exposure level in over 40,000 people residing in 37 villages, and compared to a control group of 7,500 people with low arsenic exposure. No skin cancers were found in the control group.	>600	Skin cancer, *428* Prevalence rate (per 1000) Overall: 10.6, 21.4	Tseng et al. 1968
Cohort study	Taiwan	10,591	Adjusted for risk factors, including cigarette smoking	Relative risk of lung cancer was related to arsenic exposure level in 2503 residents in southwester and 8088 in northeastern arseniasis-endemic areas.	≥700 (village median)	Lung cancer, *139* Relative Risk Overall: 3.29 (1.60-6.78), Non-smokers: 2.21 (0.71-6.86)	Chen et al. 2004
Case-control study	Chile	570	Adjusted for risk factors, including cigarette smoking and working in copper smelting industry	Hospital based study using frequency-matched hospital controls. Relative risk of lung cancer was related to arsenic exposure level.	200-400 (average value 1930-94) ≥700 (average concentration 1958-1970; peak exposure period)	Lung cancer, *151* Odds Ratio 8.9 (4.0-19.6) 7.1 (3.4-14.8)	Ferreccio et al. 2000

5.4 Non-human information

In general, animal models seem to be less sensitive than humans to the carcinogenic effect of arsenic. However, mouse models with transplacental or whole life exposures induces tumours in multiple tissues including lung and liver that are known or suspected human target sites of inorganic arsenic compounds (reviewed in Tokar et al., 2010; Waalkes et al., 2003, 2004, 2006a, 2006b; Tokar et al., 2011). Furthermore, oral sodium arsenate in the drinking water enhanced lung tumour multiplicity and lung tumor size in male mice (Cui et al., 2006) and several animal studies on DMA, has demonstrated carcinogenicity (reviewed in Tokar et al., 2010). In two hamster studies, weekly intratracheal administration of calcium arsenate induced significant increase in lung tumours (adenomas and an adenocarcinoma) when the animals were observed over their life span (Pershagen and Björklund, 1985; Yamamoto et al., 1987).

5.5 Mechanism of carcinogenicity

The knowledge of arsenic biotransformation holds the trivalent methylated and non-methylated species accountable for most arsenic toxicity. Effects such as oxidative DNA damage, genomic instability, aneuploidy, gene amplification, epigenetic effects, DNA-repair inhibition leading to mutagenesis and cell proliferation, oxidative stress, co-carcinogenesis and tumour promotion have been suggested as mechanisms for the carcinogenic effects of arsenic (Straif *et al.*, 2009). Transgenic animal model deficient in methylation or in repair of oxidative DNA lesions have been used to study mechanisms of toxicity and carcinogenicity of arsenic compounds (Yokohira, 2011; Kinoshita, 2007). However, most of these mechanisms remain poorly understood with regard to the various organs affected by the inorganic arsenic compounds. A better understanding is also required with regard to the exact dose at which arsenic induces tumours *in vivo*.

Available data indicates a complex mode of action for the toxicity of inorganic arsenicals and no threshold has been established for the induction of cancer.

6 CONCLUSION

Several inorganic arsenicals, including arsenic acid and its salts are classified as carcinogenic to humans in category 1A (CLP regulation, Annex VI; IARC 1980, 1987, 2004) based on epidemiological studies of carcinogenicity from occupational inhalation exposure and exposure via drinking water. Although animal models seem to be less sensitive than humans to the carcinogenic effect of arsenic, recent rodent studies confirm the carcinogenicity of inorganic arsenicals.

There is no human data for the individual arsenates *per se*, but substantial documentation of carcinogenicity in humans of arsenic and arsenic compounds in the trivalent and pentavalent state is available. Results from animal cancerstudies are available for specific compounds including calcium arsenate. Furthermore, animal studies support that arsenic acid, calcium arsenate and trilead arsenate are bioavailable and lead to systemic release of arsenic species.

Due to the classification of, “Arsenic acid and its salts” as carcinogenic in category 1A it is recommended to identify arsenic acid, calcium arsenate and trilead diarsenate as SVHC's based on this classification .

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