Annex XV dossier

PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE AS A CATEGORY 1A OR 1B CMR, PBT, vPvB OR A SUBSTANCE OF AN EQUIVALENT LEVEL OF CONCERN

Substance Name(s): Arsenic acid

EC Number(s): 231-901-9

CAS Number(s): 7778-39-4

Submitted by: Climate and Pollution Agency, Norway

PUBLIC VERSION: This report does not include the confidential annexes referred to in the document.

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

PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE AS A CMR 1A OR 1B, PBT, VPVB OR A SUBSTANCE OF AN EQUIVALENT LEVEL OF CONCERN

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In addition this dossier is intended to cover all hydrated forms of arsenic acid

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

Summary of how the substance meets the CMR (1A or 1B) criteria

Arsenic acid 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) 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 shows that arsenic acid meets the criteria for classification as carcinogenic in accordance with Article 57(a) of REACH.

Registration dossiers submitted for the substance? YES

[1] 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.

[2] 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).

PART I

JUSTIFICATION

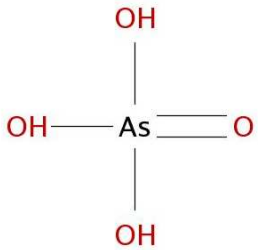
1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Table 1: Substance identity

EC number:	231-901-9
EC name:	Arsenic acid
CAS number (in the EC inventory):	7778-39-4
CAS number:	7778-39-4
CAS name:	Arsenic acid (H_3AsO_4)
IUPAC name:	arsenic acid trihydroxidooxidoarsenic (IUPAC 2005)
Index number in Annex VI of the CLP Regulation	033-005-00-1
Molecular formula:	AsH_3O_4
Molecular weight range:	141.94
Synonyms:	Orthoarsenic acid,

Structural formula:



Source: ESIS

1.2 Composition of the substance

Name: Arsenic acid

Description:

Degree of purity:

Table 2: Constituents

Constituents	Typical concentration	Concentration range	Remarks
Arsenic acid,	>80% (w/w)	90-100 % (w/w)	Mono- constituent, ECHA website

Table 3: Impurities

Impurities	Typical concentration	Concentration range	Remarks
			Information provided in the Confidential Annex

Table 4: Additives

Additives	Typical concentration	Concentration range	Remarks

1.3 Physico-chemical properties

Arsenic acid, anhydrous, Cas nr. 7778-39-4 has not been isolated, but is only found in solution where it is largely ionized. Its hemihydrate form, arsenic acid, hemihydrate (As2H8O9), with Cas nr. 7774-41-6 does form stable crystals.

Table 5: Overview of physicochemical properties

Property	Value	Remarks	Source
Physical state at 20°C and 101.3 kPa	Liquid, solid	Arsenic acid, anhydrous, has not been isolated, but is only found in solution where it is largely ionized. Its hemihydrate form ($As_2H_8O_9$), with Cas nr 7774-41-6 does form stable crystals.	CRC Handbook of Chemistry and Physics ,ECHA website
Melting/freezing point	35°C 36.1°C 35.5°C	Values are for arsenic acid hemihydrate,	HSDB; ATSDR (2007) CRC Handbook of Chemistry and Physics ECB (2000), ECHA website
Boiling point	160 °C at 1013 hPa	The boiling point of arsenic acid (hemihydrate) is reported to be 160°C which corresponds to the loss of water	HSDB; ECB (2000), ECHA website
Vapour pressure	55 mBar at 50°C 110 mBar at 65°C 12.58 hPa at 15 °C		GESTIS (2010) ECB (2000) ECHA website
Water solubility	302 g/L at 12.5 °C Very soluble*		HSDB 2010 ATSDR (2007) ECHA website
Partition coefficient n-octanol/water (log value)			
Dissociation constant	Ca. 2.3 pKa pKa 1 = 2.22, pKa 2 = 6.98 and pKa 3 = 11.53 pKa 2 = 7.089 +/- 0.01.		Cotton et al. (1972) NRC (1999) HSDB (2010) ECHA website;

*Very soluble is defined as (> 10000 mg/L) according to ATSDR (2007)

2 HARMONISED CLASSIFICATION AND LABELLING

Arsenic acid 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 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 *1		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	-	-	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	-	-	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 this dossier.

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 this dossier.

6 CONCLUSIONS ON THE SVHC PROPERTIES

6.1 PBT, vPvB assessment

Not relevant for this dossier.

6.2 CMR assessment

Arsenic acid 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) 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 shows that arsenic acid meets the criteria for classification as carcinogenic in accordance with Articles 57 (a) of REACH.

6.3 Substances of equivalent level of concern assessment

Not relevant for this dossier.

PART II

INFORMATION ON USE, EXPOSURE, ALTERNATIVES AND RISKS

1 MANUFACTURE, IMPORT AND EXPORT

1.1 Manufacturing sites

As of June 2011 arsenic acid is not manufactured by any companies in the EU according to information obtained from the Arsenic Acid Consortium [3] (2011).

In 2010 arsenic acid was manufactured in the EU.

1.2 Manufacturing process

Arsenic acid can be manufactured by different proprietary or patented processes. A typical process involves the reaction of arsenic trioxide with nitric acid in the presence of a catalyst in a contained process (Arsenic Acid Consortium, 2011). Liquid arsenic acid is produced with a consistently high yield and is purified, filtered and analyzed before shipment.

1.3 Manufacture, import and export of the substance on it own

The total import and manufacture of arsenic acid was in the range of 100-1000 tonnes in 2010. The total manufactured and imported volumes are described in the Confidential Annex to this report.

[3] Consortium constituted for REACH processes by companies involved in activities related to arsenic acid. The Arsenic Acid Consortium is managed by Patric Levy, Patrick Levy Consulting, France. For a number of other arsenic substances, another consortium, the Arsenic Consortium lead by WirtschaftsVereinigung Metalle WVM, has been established.

According to Minerals Yearbook for 2009, 89 tonnes of arsenic acid was imported into the USA from France in 2008. For 2009, the reported import was 0 tonnes (Brooks, 2009). No information, that confirms the export of arsenic acid from the EU, has been obtained.

1.4 Trends

Based on data reported in registration dossiers, a decreasing trend in the total manufactured and imported volume can be assumed.

Information on the trend over a more extended time period is not available.

1.5 Import of the substance in mixtures and articles

No import into the EU of arsenic acid in mixtures and articles has been identified.

Household appliances with ceramic glass produced by use of arsenic acid may be imported from countries outside the EU. However, by the manufacturing of the glass the arsenic acid is converted to a non-crystalline or vitreous inorganic macromolecular structure, that might not be bioavailable. The arsenic acid as such would not be present in the final articles.

Arsenic acid is still widely used as a biocide for wood preservatives in countries outside EU, and some import with treated wood may take place. According to Annex XVII of the REACH Regulation, wood treated by arsenic shall not be placed on the market, but by derogation wood treated with Copper Chromium Arsenic (CCA) may be placed on the market for professional and industrial use under certain conditions. The possible import of arsenic acid as a biocide in articles is beyond the scope of this report, and has not been investigated further.

Arsenic acid used for printed circuit boards will be present in the final boards in the form of elemental arsenic (As) on the surface of the copper foil. It must be expected that arsenic is present in imported printed circuit boards in various electronic equipment, as well as in printed circuit boards imported for manufacturing of electronic equipment in the EU.

1.6 Releases from manufacture

As of 2011, arsenic acid is not manufactured in the EU. More information is provided in the Confidential Annex.

2 USES OF THE SUBSTANCE

The following current uses of arsenic acid have been identified:

- Use as fining agent in the manufacture of speciality glass;
- Use in the production of copper foil for printed circuit boards.

2.1 Use as fining agent in the manufacture of glass

The volumes for the use as fining agent are provided in the Confidential Annex.

2.1.1 Function of the substance

Arsenic acid is used in the manufacturing of ceramic glass as a fining agent to remove bubbles from the glass melt (Arsenic Acid Consortium, 2011). According to Bray (2001) an addition of 0.04% arsenous oxide plus 1% nitre (potassium nitrate) works by releasing quantities of oxygen late in the fining which makes the bubbles more easily absorbed to the melt. The arsenous oxide is usually introduced in the form of arsenic acid (Bray, 2001). The arsenic acid used for this application is sometimes referred to as oxidizing agent.

For diarsenic trioxide, with a similar use in the glass making, it has been discussed to what extent the substance can be considered used as intermediate. By the application, the arsenic substances are transferred to a non-crystalline or vitreous inorganic macromolecular structure by the high temperature of the melt, thereby changing their chemical speciation and properties as described in the background document for diarsenic trioxide prepared by ECHA (2010a).

For diarsenic trioxide, ECHA has concluded that the substance is not used in the synthesis of the glass, but as a processing agent modifying the properties of the glass, and consequently, the substance cannot be considered an intermediate (ECHA, 2010a).

As arsenic acid is used in a similar way, the conclusion for diarsenic trioxide would also apply for this use of arsenic acid.

Arsenic acid, diarsenic trioxide and, possibly, diarsenic pentaoxide has been reported also to be used (under different processing conditions) as decolourising agents in glass and enamels (RPA, 2009). According to information from the Arsenic Consortium in the speciality glass sector the only use of arsenic acid is as fining agent. The refining action, however, leads to a reduction of arsenic oxide and consequently to emission of oxygen in the glass bath. The redox state changes and can influence the colour of the glass if multivalent agents are present due to balancing between one state to another one (Arsenic Acid Consortium, 2011).

2.1.2 Applications and sector of use

Arsenic acid is used in the industrial Special Glass Sector. Arsenic acid is in particular used in the production of black and white ceramic glass (Arsenic Acid Consortium, 2011). No information indicating the use of the substance in the artisanal glass sector has been obtained.

Special glass will tend to be produced in a few large facilities. According to the IPPC Reference Document on Best Available Techniques in the glass manufacturing industry, in Europe, ceramic glass products are principally made by three manufacturers (IPPC, 2009).

According to information obtained from the Arsenic Acid Consortium (2011), arsenic is used by a limited number of industrial glass manufactures in the EU. Names of manufacturing sites are provided in the Confidential Annex.

The ceramic glass is mainly used for vitro-ceramic (glass-ceramic) plates for cookware and other high-temperature domestic appliances (Arsenic Acid Consortium, 2011).

2.1.3 Quantities involved

Manufacture of ceramic glass is the principal application area for arsenic acid, and the total consumption for this application is in the range of 100-1000 tonnes.

2.1.4 Processes involved

The IPPC Reference Document on Best Available Techniques in the glass manufacturing industry makes several references to the use of diarsenic trioxide, but no references to the use of arsenic acid in the glass industry (IPPC, 2009).

The arsenic acid is used in the industrial speciality glass sectors and the processes are quite similar to the processes described for diarsenic trioxide. The arsenic acid is mixed with raw materials for the glass making and transferred by conveyer belts to the furnace.

The processes involved, which are further described in the following sections and the Confidential Annex, include:

- Transfer from container to weighing, mixing reactor and tunnel compo in closed system;
- Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities;
- Raw material loading;
- Waste management.

2.1.5 Use in articles

The ceramic glass is mainly used for cookware and other high-temperature domestic appliances. As mentioned above, by the application of arsenic acid in the glass melt, the arsenic substances are transferred to a non-crystalline or vitreous inorganic macromolecular structure. Consequently arsenic acid would not be present in the final articles.

2.2 Use in the production of copper foil

More information on volumes is provided in the Confidential Annex

2.2.1 Function of the substance

The description of the use of arsenic acid for production of copper foil is based on a questionnaire response from industry and is provided in the Confidential Annex.

2.2.2 Applications and sector of use

The arsenic acid is used in the electronic components sector (manufacturing of foils for printed circuit boards). The printed circuit boards are used in a variety of electronic equipment. The copper foils are both used within the EU and exported to countries outside the EU.

According to information from industry, the arsenic is not used for special purpose printed circuit boards, but is in general used on copper foils for printed circuit boards.

2.2.3 Quantities involved

The total quantity of arsenic acid used for this application is estimated to be in the range of 10-100 tonnes.

The manufacturing of printed circuit boards in the EU has been decreasing as most electric components are today manufactured in Asia.

2.2.4 Processes involved

Process description is provided in the Confidential Annex.

2.2.5 Use in articles

The arsenic from the arsenic acid will be present in the final articles as elemental arsenic in printed circuit boards. The surface of the circuit boards will be lacquered, and the users are consequently not exposed to the arsenic when touching the boards.

It must be expected that arsenic is present in imported printed circuit boards in electronic equipment, and also is present in imported printed circuit boards for manufacturing of electronic equipment in the EU. It is indicated by industry that the foil contains arsenic (As) in the concentration of <0.02 % by weight.

2.3 Other potential uses

No other actual uses of arsenic acid have been identified in the registration dossiers which has been confirmed by the Arsenic Acid Consortium and data search via the internet.

A number of applications of arsenic acid are indicated in the literature, but actual use of arsenic acid for these applications in the EU has not been confirmed.

Uses in the USA
The Minerals Yearbook for 2009 mentions three applications of arsenic acid in the USA: agricultural chemical, fining agent in glass making (bubble dispersant) and decolouring agent in glass making (Brooks, 2009). US EPA (1998) mentions the following applications of arsenic aid: Manufacture of arsenates, glass making, wood treating process, defoliant, desiccant for cotton (until 1993 in the USA) and soil sterilant.

Applications indicated in the Nordic Product Registers
No quantities have been reported in the SPIN database (Substances in Preparations in Nordic countries; i.e. Sweden, Denmark, Finland and Norway).

Synthetization of diarsenic pentaoxide
According to RPA (2009), diarsenic pentaoxide can be synthesised by dehydration of crystalline arsenic acid at temperatures above 200°C. The updated background document for diarsenic pentaoxide indicates that, according to information provided by industry, diarsenic pentaoxide seems neither to be manufactured in nor imported to the EU (ECHA, 2010b).

Use as a biocide
Traditionally arsenic acid has been used as a biocide for wood treatment and as a pesticide.

The marketing and use of biocidal products are regulated by Directive 98/8/EC concerning the placing of biocidal products on the market. According to the Commision Regulation (EC) No 1451/2007 of 4 December 2007 on the second phase of the 10-year work programme referred to in Article 16(2) of Directive 98/8/EC, biocidal products containing active substances not listed in Annex II to this Regulation or in Annex I or IA to Directive 98/8/EC shall no longer be placed on the market (unless used for research). Arsenic acid is neither included in Annex II of Commision Regulation (EC) No 1451/2007 nor the Annex I or IA to the Directive 98/8/EC. As consequence, any manufacture of the substance for export for use as biocide outside the EU would need to be registered under REACH. The Biocidal Products directive does, however, not apply to imported preparations that may contain an active biocide substance, if the preparation is not within the definition of a biocidal product, nor does it apply to imported articles treated with a substance as a biocide. The biocidal product directive is currently under revision.

Annex XVII of the REACH Regulation, lays down restrictions on the use of arsenic compounds as antifouling product, for treatment of industrial waters and for treatment of wood and furthermore restrictions on the use of wood treated with arsenic compounds. However, by way of derogation, wood treated with CCA (chromium, copper, arsenic) solutions in industrial installations under certain conditions, may be placed on the market for professional and industrial use for specified applications provided that the structural integrity of the wood is required for human or livestock safety and skin contact by the general public during its service life is unlikely. As arsenic acid is not used as a biocide in the EU this has no practical relevance for wood treated in the EU. CCA concentrates with arsenic acid are marketed outside the EU, and wood treated outside the EU may be imported for the specific, exempted uses. Such import may in principle take place, but has not been further investigated.

3 RELEASES FROM USES

The information on releases from uses, including occupational and consumer exposure and environmental releases is mainly provided in the Confidential Annex.

3.1 Use as fining agent in manufacture of glass

3.1.1 Operational conditions and existing risk management measures

Arsenic acid is mainly used in glass manufacturing in industrial processes. Specific information on releases from the companies using arsenic acid in the manufacture of ceramic glass is included in the Confidential Annex. More generally, the glass industry consider manufacture of arsenic containing glass as carried out under closed conditions (ECHA, 2010a).

According to information from industry regarding the use of diarsenic trioxide (and here confirmed to apply to arsenic acid by the Arsenic Acid Consortium with small additions), in the industrial glass sector material is pumped hydro pneumatically or under closed conditions into closed silos and transported on covered conveyor belts to the furnace. Air releases from the conveyer belts are treated by bag big filters and the filtered dust is returned in closed moving systems as recycled material onto the conveyor belts with the full mixture of raw materials. Smaller quantities are handled with big bags or even polyethylene bag lined drums.

With respect to the high toxicity of the material in industrial facilities they are emptied and handled under strictly controlled conditions (SCC) (ECHA, 2010a).

The process descriptors and environmental release categories for this application of arsenic acid in glass as reported in ECHA website is shown in Table 8 below. As discussed above it is questionable whether ERC 6a, "Industrial use resulting in manufacture of another substance (use of intermediates)" can be applied for this application.

Table 8: Process descriptors and environmental release categories for the use of arsenic acid in industrial glass making (ECHA website)

Process	**Process descriptor**		**Environmental release category**		**Market sector by type of chemical product and sector of end use**	
Arsenic acid in industrial use	PROC 1	Use in closed process, no likelihood of exposure	ERC 3	Formulation in materials		
	PROC 3	Use in closed batch process (synthesis or formulation)	ERC 5	Industrial use resulting in inclusion into or onto a matrix		
	PROC 8a	Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities	ERC 6a	Industrial use resulting in manufacture of another substance (use of intermediates)		
	PROC 8b	Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities				

Source: ECHA website, Information on Registered Substances, arsenic acid

3.1.2 Occupational exposure

Exposure estimates are provided in the Confidential Annex.

3.1.3 Consumer exposure

During product use consumers will not be exposed to the arsenic acid as it is not present (as the original compounds) in the glass. Furthermore, because the arsenic is bound into the glass matrix, the potential for migration and exposure (to arsenic) would be expected to be very low (RPA, 2009). One detailed study into elemental migration from glass (including lead crystal) in contact with food found that, in general, accelerated migration testing did not result in detectable levels of various elements including arsenic (GTS, 2002 as cited by RPA, 2009).

3.1.4 Releases of the substance to the environment

According to RPA (2009) there are several glass manufacturing facilities across the EU, each with arsenic emissions in the range 0.1 to 0.7 tonnes per year. The sources are arsenic acid, diarsenic trioxide and possibly other arsenic compounds used in the glass making.

Information on releases of arsenic to the environment for the users of arsenic acid is included in the Confidential Annex.

3.2 Use in the production of copper foil

Operational conditions and existing risk management measures, and occupational, consumer and environmental exposure to the substance are described in the Confidential Annex.

4 CONCLUSIONS ON MANUFACTURE, USES, RELEASES AND EXPOSURE

Based on the available information the following can be concluded:

- As of June 2011, arsenic acid is not manufactured in the EU, but manufacturing took place until 2010.
- The total import and use of arsenic acid is in the range of 100-1000 tonnes per year.
- The principal use of arsenic acid is as fining agent in the manufacture of ceramic glass which is mainly used for vitro-ceramic household appliances.
- A part of the arsenic acid is used for manufacturing of copper foils for printed circuit boards.
- The majority of the arsenic acid will be present in the articles as arsenic bound into the glass matrix or as arsenic in a surface layer; consumer exposure to the arsenic is expected to be low.

5 CURRENT KNOWLEDGE ON ALTERNATIVES

5.1 Glass making

Confidential information on the current status on the development of alternatives to arsenic acid in glass production, obtained from the Arsenic Acid Consortium (2011), is included in the Confidential Annex.

More generally, the following information applies to the use of arsenic compounds in glass making:

Fining agents
Arsenic acid and diarsenic trioxide (under different processing conditions) are used as a fining agent to remove bubbles from the glass melt. Due to concerns over the use of arsenic compounds, there are various other established alternative substances including (RPA, 2009):

- Sodium sulphate (used in lead crystal);
- Antimony trioxide (used in lead crystal);

- Sodium/potassium nitrates with antimony trioxides (used in special glasses);
- Cerium oxide.

The European Glass Industry (CPIV) has for the consultation for diarsenic trioxide highlighted a number of applications where there are technical difficulties in replacing arsenic in special glass (ECHA, 2010a). The industry states that although some glass-ceramic hobs (cooker tops) are now arsenic-free, producing clear glass hobs remain a difficult challenge.

Many of the alternatives to the use of arsenic in glass/enamel processing, e.g. antimony trioxide, may be considered potentially harmful to human health and the environment (ECHA, 2010a).

Decolourising agents
Arsenic acid, diarsenic trioxide and, possibly, pentaoxide have been reported to be used (under different processing conditions) as decolourising agents in glass and enamels. As discussed above, the use of arsenic acid as decolourising agent has not been confirmed by the Arsenic Acid Consortium.

5.2 Production of copper foil

According to the questionnaire response from one manufacturer of copper foil, an alternative to the arsenic acid has been tested successfully. The alternative is considered confidential.

According to the manufacturer, no additional work would be needed to develop the alternative, but the alternative has to be further tested by the customers to ensure that the foil comply with the technical requirements. The manufacturer of the foils suggests that the arsenic containing boards could be replaced within a timeframe of 5 years.

5.3 Conclusions regarding alternatives

- Conclusions regarding alternatives to arsenic acid as fining agent in the manufacture of ceramic glass are provided in the Confidential Annex.
- For manufacturing of copper foil, alternatives have been developed, but not fully tested by the customers.

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7 DEFINITION OF ARSENIC COMPOUNDS AND GLOSSARY

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 as amended (CPL regulation).

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

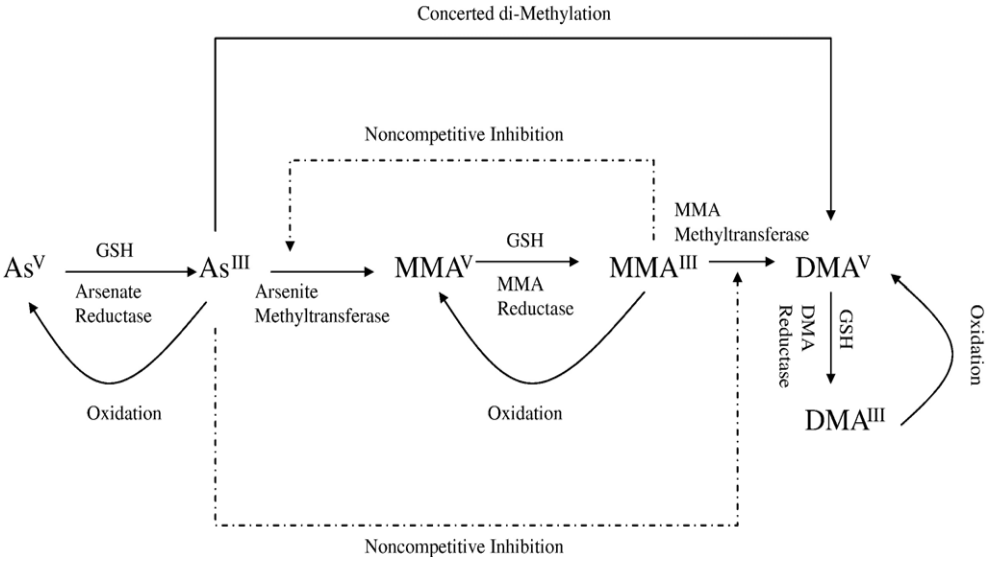
3.1 Biotransformation of inorganic arsenic compounds

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 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

[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.

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 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 40 421 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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APPENDIX 2: CONFIDENTIAL ANNEX