Committee for Risk Assessment

RAC

Opinion on

Arsenic acid and its inorganic salts

ECHA/RAC/A77-O-0000001412-86-148/F

Adopted

29 May 2017

Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu

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OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON THE EVALUATION OF THE OCCUPATIONAL EXPOSURE LIMITS (OELs) FOR ARSENIC ACID AND ITS INORGANIC SALTS

Pursuant to Article 77(3)(c) of Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (the REACH Regulation), the Committee for Risk Assessment (RAC) has adopted an opinion on the evaluation of the scientific relevance of occupational exposure limits (OELs) for arsenic acid and its inorganic salts.

Commission request

The Commission, in view of the preparation of the third and fourth proposal for an amendment of Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (CMD), and in line with the 2017 Commission Communication '*Safer and Healthier Work for All*' - Modernisation of the EU Occupational Safety and Health Legislation and Policy'[1], has decided to ask the advice of RAC to assess the scientific relevance of occupational exposure limits for some carcinogenic chemical substances.

Therefore, the Commission has made a request (8 March 2017[2]) in accordance with Article 77 (3)(c) of the REACH Regulation, to evaluate, in accordance with Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work (CAD) and/or Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (CMD), the following chemical compounds: 4,4'-methylenebis[2-chloroaniline] (MOCA), arsenic acid and its inorganic salts, nickel and its compounds, acrylonitrile and benzene.

I PROCESS FOR ADOPTION OF THE OPINION

Following a request from the European Commission, in the mandate of 15 March 2017[3], the Executive Director of ECHA requested RAC to draw up an opinion on the evaluation of the scientific relevance of occupational exposure limits (OELs) for arsenic acid and its inorganic salts.

The aim of the opinion is to provide scientific advice in support of the Commission action on the Proposal to amend Directive 2004/37/EC (3rd wave of amendment). This advice must include a recommendation to be given to the Advisory Committee on Safety and Health at Work (ACSH) in line with the relevant OSH legislative procedures and in the format used by SCOEL in drafting its opinion.

An initial proposal was prepared by the European Chemicals Agency for the consideration by RAC. The current opinion was reviewed by RAC in a written commenting round from 05 May 2017 to 23 May 2017 and at the RAC-41 meeting,. Due to imposed time constraints, the opinion was not subject to a Public Consultation.

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[1] http://ec.europa.eu/social/main.jsp?langId=en&catId=148&newsId=2709&furtherNews=yes

[2] https://echa.europa.eu/documents/10162/13641/ec_note_to_echa_oels_en.pdf/f72342ef-7361-0d7c-70a1-e77243bdc5c1

[3] https://echa.europa.eu/documents/10162/13641/rac_mandate_oels_en.pdf/9f9b7fb9-545a-214c-69f0-dff5f5092174

II ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by the RAC: **Tiina Santonen.**

The RAC opinion was adopted by consensus on **29 May 2017.**…

Table of Contents

Figures

Tables

Assessment of the Scientific Relevance of OELs for arsenic acid and its inorganic salts

RECOMMENDATION

The opinion of RAC for the assessment of the scientific relevance of OELs for arsenic acid and its inorganic salts, is set out in the table below and in the following summary of the evaluation.

SUMMARY TABLE

The table summarises the outcome of the RAC evaluation to derive limit values for the inhalation route and the evaluation for dermal exposure and a skin notation. The table also includes carcinogenicity classifications.

Derived Limit Values

OEL	not established
8-hour TWA:	not derived
STEL:	not derived
BLV:	not derived
BGV:	10 µg As/l urine (post-shift sample at end of a working week) as combined As3+, As5+ and MMA and DMA.* ** *Dietary sources, especially seafood may have a significant impact on total MMA (monomethylarsonic acid) and DMA (dimethylarsinic acid) levels. ** BGV is recommended to be updated when more data becomes available on the speciated As3+ and As5+ levels among European population

Carcinogenicity Classification

CLP Harmonised classification for carcinogenicity	Carc 1A; H350
IARC	arsenic and inorganic arsenic compounds: Group 1 – carcinogenic to humans
SCOEL Classification of carcinogens scheme [4]	non threshold genotoxic carcinogen; "Group B -genotoxic carcinogens, for which the existence of a threshold cannot be sufficiently supported at present. In these cases the LNT model may be used as a default assumption, based on the scientific uncertainty".

[4] SCOEL 'Methodology for the Derivation of Occupational Exposure Limits' (SCOEL, 2013; version 7) https://circabc.europa.eu/sd/a/1bd6666f-5c8c-4d13-83c2-18a73dbebb67/SCOEL%20methodology%202013.pdf.

Notations

Notations[5]:	not assigned

SUMMARY

Background

This opinion concerns arsenic acid and its inorganic salts, however it must be noted that the toxicological and exposure data in particular, often do not discriminate between different arsenic species. In addition, taking into account the carcinogenicity and mutagenicity data on different inorganic arsenic compounds and mechanistic data, the carcinogenicity of inorganic arsenic is not limited only to arsenic acid and its salts. Therefore this evaluation also applies to **arsenic and its inorganic compounds** in general.

The aim of the recommendation is to provide scientific advice on the relevance of OELs for arsenic acid and its inorganic salts particularly with reference to its carcinogenicity.

This evaluation on **arsenic acid and its inorganic salts** requested by the Commission takes into account the RAC dose-response function, (RAC, 2013; attached as Appendix 1) and the recent recommendations of the Council's Dutch Expert Committee on Occupational Safety (DECOS, 2012) both covering these substances. The evaluation has been supplemented by a limited review of more recently published papers, focussing on the mode of action of carcinogenicity of arsenic acids and its salts, as well as the uses and exposure of workers to it, with special emphasis on the waste cycle. Despite mechanistic indications of a threshold mode of action, the available data do not allow the identification of a threshold. The current opinion may need to be reviewed should new scientific data/reviews become available in the future; it should be noted that the US EPA are currently reviewing arsenic and its compounds to update their 2007 report.

Key conclusions of the evaluation

- 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), i.e. 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[6], 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*

[5] SCOEL 'Methodology for the Derivation of Occupational Exposure Limits' (SCOEL 2013; version 7)

[6] See Appendix 2 for SCOEL Classification of Carcinogens scheme

the LNT 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.

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, cannot be derived from the scientific evidence.

However a Biological Guidance Value (BGV) value of 10 µg/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)

Carcinogenicity and mode of action

Arsenic compounds produce lung tumours in both animals and humans, following inhalation, oral or parenteral exposures (see Section 7.7.1). Exposure to high levels of

arsenic compounds in drinking water has been associated with skin, and urinary tract or bladder cancer or both in humans. Tumours at other sites including the adrenal glands, bladder and liver have also been reported in some animal studies.

Arsenic, arsenic acid and inorganic arsenic compounds have potential to damage chromosomes, positive results having been reported both in cultured mammalian cells and in somatic cells in rodents and humans. Although these substances do not appear to induce point mutations in bacteria or in mammalian cells, this genotoxic potential may contribute to their carcinogenicity.

The following secondary genotoxic processes maybe relevant in consideration of the carcinogenicity of arsenic compounds (see Section 7.9.1):

- Arsenic species can bind to thiol-groups in proteins, which may lead to inhibition of DNA repair enzymes or perturb other processes connected with the maintenance of damage free DNA;
- Arsenic species in cells do not generate reactive oxygen directly but they inhibit scavenging systems of reactive oxygen. This leads indirectly to the increase of reactive oxygen species, which in turn has potential to increase the level of DNA damage.

Furthermore, exposure to arsenic compounds can influence the activity of DNA methyltransfereases, resulting in hypo- or hypermethylation of DNA. Such epigenetic changes have potential to influence gene expression and DNA repair. They may also contribute to the carcinogenicity of these compounds.

The above mentioned processes suggest that the carcinogenicity of arsenic compounds is underpinned by a potentially diverse series of non-stochastic genotoxic and other activities. The mechanistic evidence supports the view that genotoxicity is mainly caused via secondary processes which are triggered by arsenic.

However, 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. In recognition of the lack of a clear exposure threshold for the carcinogenicity of arsenic and its inorganic compounds RAC recommends that the linear dose-response model may be used as a default assumption for cancer risk assessment. According to SCOEL classification scheme arsenic and its inorganic compounds would be classified as SCOEL carcinogen group B (see Bolt and Huici-Montagud, 2008).

Biological Monitoring

A health-based biological limit value (BLV) cannot be recommended at present, because it is not possible to identify a threshold for the carcinogenicity of arsenic acid and its salts.

Occupational exposure to arsenic can be biomonitored by measuring urinary excretion of inorganic arsenic and its metabolites (DMA and MMA). A commonly applied method is to measure the sum of As3+, As5+ and DMA and MMA. However, consumption of fish and shellfish has a significant elevating effect on urinary DMA and MMA levels. Therefore, arsenic intake with food of maritime origin should be considered for several days prior to every sampling (see Section 7.1.5) and if elevated levels of are noted, the individuals should be specifically asked about any fish consumption over the last few days, and if necessary the arsenic concentration should be re-determined after a period without fish.

Speciation of different urinary arsenic species provides a more comprehensive picture of occupational exposure. However, there is a lack of proper reference values for individual arsenic species. In population studies, the levels of inorganic As3+ and As5+ in urine have remained in the majority of samples below the available level of detection of the analytical methods, which has resulted in an inability to set a reference level for these

individual species. Recently however, UK HSE[7] published a sensitive µLC-ICP-MS based method for the speciation of different arsenic species, which is able to detect As3+ and As5+ levels as low levels as 0.02-0.04 µg/l (LOQ), respectively. They also established 95th percentiles of 0.54 and 0.23 µg/l for As3+ and As5+, respectively, based on the sample of 95 volunteers.

With respect to setting a Biological Guidance Value (BGV) specifically for As3+ and As5+, the current database is limited, due to the limitations in the sensitivity of commonly used analytical techniques . There are some data available on the general population levels of the sum of As3+, As5+ and DMA and MMA. Based on the data from France showing 95th percentile of 8.9 µg/l in adults after controlling of seafood consumption, and from Belgium showing 90th percentile of 10.7 µg/l in 20-40 year old mothers, a BGV of 10 µg/l is proposed for the sum of As3+, As5+ and DMA and MMA.

The German Research Foundation (DFG) has estimated that an 8 h TWA exposure to 0.01 mg/m3 results in urinary arsenic levels (sum of As3+, As5+, MMA and DMA) of 50 µg/l, 0.05 mg/m^3 in 90 µg/l and 0.1 mg/m^3 in 130 µg/l.

Notations

Absorption by the dermal route has not been well characterised, but according to the available data it is likely to be low compared to the other routes. According to the SCOEL methodology[8], a skin notation should only be applied if skin uptake is likely to result in substantial contribution (of the order of 10% or more) to the total body burden. The rate of absorption of arsenic and arsenic compounds through the skin does not warrant a skin notation.

RAC agrees that a skin notation is not warranted.

[7] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4481610/

[8] https://circabc.europa.eu/sd/a/1bd6666f-5c8c-4d13-83c2-18a73dbebb67/SCOEL%20methodology%202013.pdf

REPORT

1. Chemical Agent Identification and Physico-Chemical Properties

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.

Arsenic is a grey, crystalline solid with metallic luster. Elemental arsenic sublimes at 613°C, has a very low vapour pressure and a log Poctanol/water of 0.680. In contrary, arsenic compounds are crystalline, amorphous or hygroscopic substances, which occur in trivalent and pentavalent forms. For instance arsenic trioxide, the major arsenic compound with regard to occupational exposure, melts at 312°C, boils at 465°C, and has also a very low vapour pressure and a log $P_{octanol/water}$ of -0.130.

Arsenic acid, according to Kirk-Othmer (2014) and Ullmann (2008) has the formula H_3AsO_4. This substance has an EINECS entry (231-901-9) and an associated CAS entry (7778-39-4) and in the EU, there are registration, authorization and restriction dossiers that use this name and EINECS entry[9]. Its hemihydrate form ($H_3AsO_4 \cdot ½H_2O$) forms stable crystals. Arsenic acid is prepared by treating arsenic trioxide (As_2O_3) with concentrated nitric acid and dinitrogen trioxide is produced as a by-product.

The descriptor 'arsenic acid and its inorganic salts' thus covers the triprotic H_3AsO_4, and its salts, i.e. part of the As (V) group of compounds. ECHA (2011) identified ca. 40 salts of arsenic acid; sodium, calcium and iron being the most commonly encountered – see Annex I, Table 1; the list is not exhaustive.

Salts of arsenic acid

Sodium arsenate has the formula Na_3AsO_4. However, related salts are also called sodium arsenate, including Na_2HAsO_4 (disodium hydrogen arsenate) and NaH_2AsO_4 (sodium dihydrogen arsenate). The trisodium salt is a white or colourless solid that is highly toxic. It is usually handled as the dodecahydrate $Na_3AsO_4 \cdot 12H_2O$

Iron and calcium arsenate are the most important salts and have respectively the formulas:

- Ferrous arsenate $Fe(II)_3(AsO_4)_2$
- Calcium arsenate $Ca_3(AsO_4)_2$

Tables 1 and 2 present the substance identification and physical-chemical properties of arsenic and different inorganic arsenic compounds. See also Appendix 3 for a list of Arsenic compounds.

Other important inorganic arsenic compounds

In addition to arsenic acid and its salts, DECOS (2012) in their report on 'arsenic and inorganic arsenic compounds', covered arsenic metal, diarsenic trioxide (III), arsenous acid (III) and its salts, diarsenic pentaoxide (V) and arsenic acid (V) and its salts as well as cupric acetoarsenate. These have also been included to Table 1.

[9] https://echa.europa.eu/substance-information/-/substanceinfo/100.029.001

Table 1: Substance identification

(a) Arsenic acid and its salts

Substance	CAS No,	EINECS No.	Molecular formula	Molar mass (g/mol)
Arsenic acid	7778-39-4	231-901-9	H_3AsO_4	141.9
Arsenic acid, trisodium salt	13464-38-5	236-682-3	Na_3AsO_4	-
Potassium arsenate	7784-41-0	232-065-8	KH_2AsO_4	180.0
Arsenic acid, calcium salt	7778-44-1	231-904-5	$Ca_3(AsO_4)_2$	-
Lead arsenate	7784-40-9	232-064-2	Pb3(AsO4)2	347.1
Magnesium arsenate	10103-50-1	233-285-7	$Mg_3(AsO_4)_2$	350.8

(b) Other important arsenic species

Substance	CAS No,	EINECS No.	Molecular formula	Molar mass (g/mol)
Arsenic	7440-38-2	231-148-6	As	74.9
Arsenic trioxide	1327-53-3	215-418-4	As_2O_3	197.8
Arsenic pentoxide	1303-38-2	215-116-9	As_2O_5	229.8
Arsenic trichloride	7784-34-1	232-059-5	$AsCl_3$	181.3
Arsenic trisulphide	1303-33-9	215-117-4	As_2S_3	246.0
Sodium arsenite	7784-46-5	232-070-5	$NaAsO_2$	129.9
Arsenous acid, potassium salt	13464-35-2	-	$KH(AsO_2)_2$	-
Calcium arsenite	52740-16-6	258-147-3	$CaAsO_3H$	-
Copper(II) arsenite	10290-12-7	233-644-8	$Cu(AsO_2)_2$	277.4
Cupric acetoarsenite	12002-03-8	-	$C_4H_6As_6Cu_4O_{16}$	1013.8

Table 2: Physical and chemical properties

(a) Arsenic acid and its salts

Substance	Solubility in water	Melting point (°C)	Boiling point (°C)	Vapour pressure (kPa, 25°C)	Density (g/cm^3)	Log $P_{octanol/water}$
Arsenic acid	-	35.5	loses H_2O at 160	7.6×10^{-20}	2.0 – 2.5	3.140
Potassium arsenate	Soluble in cold water (190 g/l at 6°C), very soluble in hot water	288	-	-	2.900	-

Substance	Solubility in water	Melting point (°C)	Boiling point (°C)	Vapour pressure (kPa, 25°C)	Density (g/cm^3)	Log $P_{octanol/water}$
Lead arsenate	Soluble in water (8.5×10^5 mg/l at 25°C)	Decomposition at 720	-	1.9×10^{-19}	-	-2.490
Magnesium arsenate	Soluble in water (2.7×10^5 mg/l at 17°C)	86.3	-	-	-	-7.290

(b) Other important arsenic species

Substance	Solubility in water	Melting point (°C)	Boiling point (°C)	Vapour pressure (kPa, 25°C)	Density (g/cm^3)	Log $P_{octanol/water}$
Arsenic	Insoluble	Sublimation at 613	-	3.3×10^{-10}	5.727	0.680
Arsenic trioxide	Soluble in water (37 g/l at 20°C and 115 g/l at 100°C)	312	465	3.7×10^{-11}	3.738	-0.130
Arsenic pentoxide	Soluble in water (1500 g/l at 16°C and 767 g/l at 100°C)	Decomposition at 315	-	-	4.320	-
Arsenic trichloride	Decomposed by water	-16	130	1.3 (23.5°C)	2.100	1.610
Arsenic trisulphide	Insoluble in cold water, slightly soluble in hot water	300–325	707	-	-	-
Sodium arsenite	Very soluble in water (1×10^6 mg/l at 25°C)	-	-	8×10^{-19}	1.870	-3.280
Copper(II) arsenite	-	Decomposition	-	-	-	-
Cupric acetoarsenite	-	-	-	-	-	-

2. EU Harmonised Classification and Labelling - CLP (EC)1271/2008

Arsenic acid and its salts are all classified as known human carcinogens (Carc. 1A), as are diarsenic trioxide, diarsenic pentaoxide, lead hydrogen arsenate, nickel diarsenide, nickel arsenide, trinickel bis(arsenate), nickel(II) arsenate, trinickel bis(arsenite) and triethyl arsenate.

Arsenic metal is not classified as a carcinogen and significantly, '*arsenic compounds, with the exception of those specified elsewhere in this Annex*', i.e. with the exception of the compounds mentioned above are not classified as carcinogens.

Gallium arsenide is separately classified as a presumed human carcinogen (Carc 1B) and presumed human reproductive toxicant (Repro 1B) and may have different properties due to the presence of Gallium, although As seems to be the more toxic moeity and has been shown to be bioavailable under physiological conditions (RAC, 2011; p9).

Arsine (AsH_3) and tertbutyl arsine are not classified as carcinogens, probably due to their gaseous state/volatility and acute toxicity.

The classification of arsenic and all arsenic compounds based on EC Regulation 1272/2008 on classification, labelling and packaging of substances and mixtures is presented in Table 3. No concentration limits are specified for different arsenic compounds.

As requested by the Commission in this evaluation by RAC, the specific descriptor 'arsenic acid and its salts' matches the second CLP entry given below.

Thus, a group of arsenic (III) compounds are not classified as carcinogens (this consists mainly of arsenous acid and its salts). Given the way in which international reviews (e.g. IARC, 2012) on the carcinogenic properties of arsenic and its inorganic compounds have generally treated the whole inorganic group as being carcinogenic, this anomaly in EU classification may need further attention. As noted above, arsenic metal is not classified as a carcinogen in the EU.

Table 3: EU classification: CLP (EC) 1271/2008, Annex VI listing of arsenic and compounds

Index No	International chemical ID	Oxidation state	Chemical formula	EC No	CAS No	Annex VI of CLP hazard class and category	Hazard statement code
033-001-00-X	arsenic	(0)	As	231-148-6	7440-38-2	Acute Tox. 3 * Acute Tox. 3 * Aquatic Acute 1 Aquatic Chronic 1	H331 H301 H400 H410
033-005-00-1	arsenic acid and its salts with the exception of those specified elsewhere in this Annex	(V)	H_3AsO_4	-	-	**Carc. 1A** Acute Tox. 3 * Acute Tox. 3 * Aquatic Acute 1 Aquatic Chronic 1	H350 H331 H301 H400 H410
033-002-00-5	arsenic compounds, with the exception of those specified elsewhere in this Annex	(all)				Acute Tox. 3 * Acute Tox. 3 * Aquatic Acute 1 Aquatic Chronic 1	H331 H301 H400 H410
033-004-00-6	diarsenic pentaoxide; arsenic pentoxide; arsenic oxide	(V)	As_2O_5	215-116-9	1303-28-2	**Carc. 1A** Acute Tox. 3 * Acute Tox. 3 * Aquatic Acute 1 Aquatic Chronic 1	H350 H331 H301 H400 H410
033-003-00-0	diarsenic trioxide; arsenic trioxide	(III)	As_2O_3	215-481-4	1327-53-3	**Carc. 1A** Acute Tox. 2 * Skin Corr. 1B Aquatic Acute 1 Aquatic Chronic 1	H350 H300 H314 H400 H410
031-001-00-4	gallium arsenide	(0)	GaAs	215-114-8	1303-00-0	**Carc. 1B** Repr. 1B STOT RE 1	H350 H360F H372 (respiratory and haematopoietic systems)

Index No	International chemical ID	Oxidation state	Chemical formula	EC No	CAS No	Annex VI of CLP hazard class and category	Hazard statement code
082-011-00-0	lead hydrogen arsenate	(V)	$PbHAsO_4$	232-064-2	7784-40-9	**Carc. 1A** **Repr. 1A** Acute Tox. 3 * Acute Tox. 3 * STOT RE 2 * Aquatic Acute 1 Aquatic Chronic 1	H350 H360Df H331 H301 H373 ** H400 H410
028-051-00-4	nickel diarsenide [1] nickel arsenide [2]	(III)	$NiAs_2$ NiAs	235-103-1 [1] 248-169-1 [2]	12068-61-0 [1] 27016-75-7 [2]	**Carc. 1A** STOT RE 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	Carc. 1A STOT RE 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1
028-038-00-3	trinickel bis(arsenate); nickel(II) arsenate	(V)	$Ni_3(AsO_4)_2 . 8H_2O$	236-771-7	13477-70-8	**Carc. 1A** STOT RE 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350 H372 ** H317 H400 H410
028-042-00-5	trinickel bis(arsenite)	(III)	$Ni(H_3AsO_4)_2$	-	74646-29-0	**Carc. 1A** STOT RE 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H372 ** H317 H400 H410
033-006-00-7	arsine	(III)	AsH_3	232-066-3	7784-42-1	Flam. Gas 1 Press. Gas Acute Tox. 2 * STOT RE 2 * Aquatic Acute 1 Aquatic Chronic 1	H220 H330 H373 ** H400 H410
033-007-00-2	tert-butylarsine	(III)		423-320-6	4262-43-5	Pyr. Liq. 1 Acute Tox. 2 *	H250 H330
601-067-00-4	triethyl arsenate	(V)	(H_3AsO_4), triethyl ester	427-700-2	15606-95-8	**Carc. 1A** Acute Tox. 3 * Acute Tox. 3 * Aquatic Acute 1 Aquatic Chronic 1	H350 H331 H301 H400 H410

3. Chemical Agent and Scope of Legislation - Regulated uses of Arsenic acid and its salts in the EU

The uses of arsenic acid and its salts in the workplace are not covered by an indicative or a binding occupational exposure limit (IOEL, BOEL), nor for that matter are arsenic and is compounds whether inorganic or organic.

However, with the exception of arsenic metal, much of their uses as substances are already covered by regulation, albeit with some gaps – a summary is given below, including Classification and Labelling (CLP), REACH Authorisation and Restriction as well as Biocide and Pesticide approvals.

3.1 Directive 98/24/EC and Directive 2004/37/EC

Arsenic acid and its inorganic salts are hazardous chemical agents in accordance with Article 2 (b) of Directive 98/24/EC and fall within the scope of this legislation.

Arsenic acid and its inorganic salts are also carcinogens or mutagens for humans in accordance with Article 2(a) and (b) of Directive 2004/37/EC and falls within the scope of this legislation.

3.2 REACH Registrations (2010 and 2013)

The REACH[10] registrations for all arsenic compounds are listed[11] below

Table 4: REACH Registrations

Substance	Tonnage	Type	Status
Arsenic acid	100-1000	Full	Active
calcium arsenate	-	Intermediate	Inactive
diarsenic trioxide	100-1000	Full	Active (6)
tricopper arsenide	-	Intermediate use only	Inactive
trilead diarsenate	Confidential	NONS	Inactive
triethyl arsenate	Confidential	NONS	Active
arsine	10-100	Full	Active
tert-butyl arsine	Confidential	NONS	Active
gallium arsenide	10-100	Full	Active

Arsenic as a metal is not registered.

The third REACH registration deadline in 2018 applies to quantities of 1 to 100 tonnes. Further registrations of such lower tonnages of salts of arsenic acid as well as other arsenic compounds are quite possible, at which time, further uses may become evident.

Arsenic acid

A full registration in the range of 100-1000 tonnes per annum is contained in a joint submission and listed on the ECHA website as 'active'. This covers manufacture, formulation and industrial uses: in manufacturing another substance, as an intermediate, and in the production of other substances and in the manufacturing of copper foil.

[10] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC (OJ L 396 of 30 December 2006, p. 1; corrected by OJ L 136, 29.5.2007, p. 3)

[11] ECHA https://echa.europa.eu/information-on-chemicals/registered-substances accessed 24 April 2017

Calcium arsenate and lead arsenate[12]

One registration exists for these two salts of arsenic acid. However, it is listed as 'inactive' and no tonnage is given. The use name given is: 'Constituent (Use at industrial sites)'. However, the environmental release categories listed reveal that it is intended for manufacture of substances, inclusion into or onto a matrix, as an intermediate in manufacturing other substances such as basic metals, including alloys.

3.3 Authorised uses under Annex XIV of REACH

Three of the most important As(III) and As(V) compounds are listed on Annex XIV of REACH and subject to Authorisation: arsenic acid (but not its salts), diarsenic pentaoxide and diarsenic trioxide. The sunset dates have already passed for the latter two but not for arsenic acid (August 2017). Companies can only continue to use these substances if they have already received an authorisation or if they have applied for an authorisation and a decision is pending. Such authorisations can impose conditions on both the risk management measures to minimise occupational and indirect human exposure and may also require monitoring in the workplace.

Only five applications for authorisation were received by ECHA, four for diarsenic trioxide covering ca. 850 tonnes per year , all of which have already been granted by the Commission and one for arsenic acid covering ca. 3 tonnes per year which is pending – no applications were received for diarsenic pentaoxide. Table 5 lists the applications, their sunset dates and the review dates granted in the authorisations.

Table 5: Applications for authorisation

Substance	Applicant	Uses applied for	Tonnage/year	RAC and SEAC joint opinion adopted	Sunset date	Commission Implementing Decision	Comment
arsenic acid	Circuit Foil Luxembourg SARL	Industrial use of arsenic acid for the treatment of copper foil used in the manufacture of Printed Circuit Board	3.25	16/03/17	22/08/17	Draft RAC/SEAC opinion for commenting by the applicant	99.9% of the substance is consumed during copper plating
diarsenic pentaoxide	-	None	-	-	21/11/13	21/05/15	-
diarsenic trioxide	Yara France	Industrial use of diarsenic trioxide as a processing aid to activate the absorption and desorption of carbon dioxide by potassium carbonate from synthesis gas formed in the production of ammonia	5.0	09/01/15	21/05/15	29 May 2015 ***Review:*** 21 May 2017	diarsenic trioxide is converted to **diarsenic pentaoxide** (As_2O_5) which is regularly extracted from the system by filtration

[12] https://echa.europa.eu/registration-dossier/-/registered-dossier/12244/3/1/2

Substance	Applicant	Uses applied for	Tonnage/year	RAC and SEAC joint opinion adopted	Sunset date	Commission Implementing Decision	Comment
diarsenic trioxide	Boliden Kokkola Oy	Use of diarsenic trioxide in the purification of metal impurities from the leaching solution in the zinc electrowinning process	700	06/10/14	21/05/15	1 September 2015 ***Review:*** 21 May 2027	Waste co precipitated as **ferric arsenate** with jarosite; disposed under licence to landfill
diarsenic trioxide	Nordenhamer Zinkhutte GmbH	Industrial use of diarsenic trioxide to produce a copper concentrate in the purification of the leaching solution in a zinc electrowinning process	146 (0.4 tonnes / day)	15/10/14	21/05/15	4 September 2015 ***Review:*** 21 May 2027	Waste arsenic disposed of as stabilised jarosite under licence to landfill
diarsenic trioxide	Linxens France SA	Formulation of diarsenic trioxide into a mixture Industrial use of diarsenic trioxide as processing aid in gold electroplating	0.05	10/10/15	21/05/15	1 September 2015 ***Review:*** 21 May 2022	-

3.4 Restricted uses under Annex XVII of REACH

Annex XVII of REACH entry 19 restricts the use of arsenic and its compounds in antifouling, 'treatment of industrial waters' and as wood preservatives.

A total of 144 compounds are listed, including arsenic acid, arsenous acid and their salts, arsines, diarsenic trioxide and diarsenic pentaoxide, as well as organic hexafluoroarsenate salts, (obsolete) organoarsenic medicines, and various other compounds. A total of 39 salts of arsenic acid are listed and a further 9 organic hexafluoroarsenate compounds.

Derogated uses under this restriction are related to: wood preservation for professional and industrial use 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.

3.5 Plant Protection Products Regulation (EC)1107/2009

The following arsenic compounds are included in the EU Pesticides database but are "Not Approved" and they are not included as active substances in Annex I to Directive 91/414/EEC, :

- Methylarsonic acid, CH_5AsO_3, 204-705-6, 124-58-3
- Sodium arsenite $NaAsO_2$ sodium salt of arsenous acid. Sodium arsenite also Na_3AsO_3 , 232-070-5, 7784-46-5
- Sodium dimethylarsinate (Sodium Cacodylate); 204-708-2, 124-65-2;

3.6 Biocidal Products Regulation (EU)528/2012

EU (2013) documented the list of '*existing* [biocidal] *active substances for which a decision of non-inclusion into Annex I or Ia of Directive 98/8/EC has been adopted*': under product type 8, wood preservatives, diarsenic (V) pentaoxide and chromium trioxide and sodium dichromate (components of chromated copper arsenate wood preservatives) are given with phase-out dates of 1 September 2006.

However, it was still possible to import treated wood preserved with CCA's into the EU until the Biocidal Products Regulation entered into force (17 July, 2012) and the regulatory requirements for industry were applied (1 Sept., 2013). Thus, the use of CCA to preserve wood has effectively ceased in the EU, although it may be noted that there is an application pending for a wood preservative with the active substance sodium cacodylate [(CH3)2AsO2H]: this is included in Annex I but is under review.

4. Existing Occupational Exposure Limits

In various EU Member States as well as outside the EU OEL's are established. These OEL's are presented in Table 6: the list should not be considered as exhaustive.

Table 6: Existing Occupational Exposure Limits (OELs) for arsenic and arsenic compounds according to DECOS (2012) and updated according to GESTIS ILV database

Country/ Organisation	Arsenic Compound	Level (mg/m^3)	Time-relation	Remarks
The Netherlands	Arsenic acid salts (insoluble, as As) Arsenic acid and its salts (soluble, as As)	0.05 0.1 0.025 0.05	TWA value (8hr) Short-term value (15min) TWA value (8hr) Short-term value (15min)	C[1]
UK	Arsenic and compounds (as As) (except lead arsenate)	0.1	TWA value (8hr)	C
Denmark	Arsenic and inorganic compounds, (as As) Calcium arsenate	0.01 1	TWA value TWA value	C
Germany	Arsenic and Compounds, except arsine (as As)	0.00083 (inhalable) 0.0083 (inhalable) and 0.066	 corresponding short term value (15 min)	C 4 :10 000 4 : 1 000
Sweden	Arsenic and inorganic compounds, as As	0.03 (total dust)	TWA value (8hr)	C
Austria	Arsenic acids and its salts	0.1 (inhalable) 0.4 (inhalable)	TWA value (8hr) Short term value (15 min)	TRK value

Country/ Organisation	Arsenic Compound	Level (mg/m^3)	Time-relation	Remarks
Finland	Arsenic acids and its salts	0.01 as As	TWA value (8hr)	
France	Arsenic acids and its salts	0.2	TWA value (8hr)	
Latvia	Arsenic acids and its salts	0.01 0.04 mg/m^3	TWA value (8hr) Short term value (15 min)	
Spain	Arsenic acids and its salts	0.1	TWA value (8hr)	
Switzerland	Arsenic acids and its salts	0.1 (inhalable)	TWA value (8hr)	
ACGIH (TLV)	Arsenic and inorganic compounds, as As	0.01	TWA value (8hr)	C
OSHA	Arsenic and inorganic compounds	0.01 (total dust)	TWA value (8hr)	C
NIOSH	Arsenic (inorganic compounds, as As)	0.002 (total dust)	Short-term value (15min ceiling)	C
Japan - JSOH	Arsenic (inorganic and organic compounds, as As)	0.003	TWA value (8hr)	Reference value for an individual excess lifetime risk of 1 : 1 000

Notes:

[1] C: the substance is considered carcinogenic
[2] DECOS originally referred to TRK values, which are no longer used in DE (since 2005)

Biological limit values have been issued by ACGIH (BEI) and MAK Commission for the sum of inorganic arsenic (As3+ and As5+) and methylated metabolites (MMA and DMA). These are 35 and 50 µg/l, respectively. In Finland, a BLV of 70 nmol/l has been set for the inorganic arsenic (sum of As3+ and As5+) in urine. This corresponds the 8 h TWA exposure to arsenic at the level of Finnish OEL of 0.01 mg/m3.

5. Occurrence, Use and Occupational Exposure

5.1 Occurrence

Arsenic is the main constituent of more than 200 mineral species, of which about 60% are arsenate, 20% sulphide and sulpho-salts and the remaining 20% include arsenides, arsenites, oxides and elemental arsenic(Onishi et al, 1969).

Arsenic is rarely found as a pure metal, but is often a component in sulphur-containing minerals, the most common of which is arsenopyrite. Arsenic may be obtained from copper, gold, and lead smelter flue dust (mainly as diarsenic trioxide, As_2O_3), as well as from roasting arsenopyrite. Most, arsenic is not recovered commercially from these sources but is captured as a waste for disposal. Where it is commercially recovered, arsenic is produced as arsenic trioxide or as a pure metal. Limited quantities of arsenic metal have also been recovered from gallium-arsenide semiconductor scrap.

The ability of arsenic to bind to sulphur ligands means that it tends to be associated with sulphide-bearing mineral deposits, either as separate arsenic minerals or as a trace of a minor constituent of the other sulphide minerals. This leads to elevated levels in soils in many mineralised areas where the concentrations of associated arsenic can range from few milligrams to > 100 mg/kg.

It has been estimated that about one-third of the atmospheric flux of arsenic is of natural origin. Volcanic action is the most important natural source of arsenic, followed by low temperature volatilisation (WHO-IPCS 2001/ATSDR 2007).

USGS (2017) estimated the world production of diarsenic trioxide to be 36,500 tonnes in 2015 and 2016. Over two thirds of this is produced in China (25,000) with lesser amounts from Morocco (6,900), Namibia (1960), Russia (1500) and Belgium (1000).

Arsenic is presently obtained as a by-product of the smelting of copper, lead, cobalt and gold ores. Additionally, arsenic and arsenic compounds can be prepared by the reduction of arsenic trioxide with charcoal. Demand for metallic arsenic is limited and thus most arsenic is marketed and consumed in combined form, principally as arsenic trioxide which is subsequently converted to arsenic acid (WHO-IPCS 2001/ATSDR 2007).

High arsenic concentrations in groundwater have been noted especially in parts of India and Bangladesh, with groundwater levels of up to 200 µg/L (Guha Mazumder et al, 2011)and to the floodplain areas along the Mekong river (Laos, Cambodia, Vietnam). In some regions of China burning of arsenic-rich coal has been identified as a source of environmental and consumer exposure(Yajima et al, 2012). A textbook case of arsenic-related peripheral vascular disease was found in the early twentieth century, being endemic along the southwestern coast of Taiwan. The disease involved the lower extremities and it was called 'Blackfoot disease' because of the gangrenous appearance of the feet of patients. Epidemiological studies revealed that it was associated with the consumption of fossil artesian well water containing high levels of arsenic9Tseng et al, 2002). The source of elevated arsenic concentrations in groundwater is considered to be the release of arsenic from river sediments. It is estimated that about 10 million residents in Southeast Asia are at risk from consuming arsenic-contaminated groundwater (Kim et al,2011). The same problem also appears in some countries of Latin America. It has been estimated that some 4.5 million people in Latin America are chronically exposed to high levels of arsenic (> 50 µg/L drinking water), with extremes up to 2000 µg/L. WHO has recommended a provisional guideline value of 10 µg arsenic/L drinking water, based on the water treatment performance and analytical achievability(WHO 1996).

5.2 Production and Use Information

This section initially considers ‘use’ in the sense of a substance, then focusses on the occurrence of arsenic acid and its salts in process wastes of which a number of importance are identified. Given the complexity of the chemistry and the occurrence of both As (III) and AS (V) metabolites in nearly all human biomonitoring studies which were able to separate the main species, the uses considered here are wider than just those of arsenic acid and its salts alone.

Arsenic and arsenic compounds have been produced and used commercially for centuries. Current and historical uses of arsenic include pharmaceuticals, wood preservatives, agricultural chemicals (e.g. 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 (e.g. as a decolouriser and fining agent in the production of bottle glass) and the manufacture of speciality glass (ECHA 2012; ECHA 2010)) in the semiconductor industry, and in the production of copper foil for printed circuit boards (ECHA 2012).

Processing of non-ferrous metals leads to significant arsenic containing waste streams, including **metal arsenates**. In the metallurgical industry, arsenic is used to harden copper and lead-antimony alloys; applications include ammunitions, solders, battery posts, bearings, and lead shot. In the past, the principal use for diarsenic trioxide was for the production of **arsenic acid** in chromated copper arsenide (CCA) wood preservatives. In glassmaking, arsenic is used to disperse bubbles or for colour. In the semiconductor industry, high-purity arsenic is used in applications such as solar cells, light emitting diodes, lasers, and integrated circuits. Historically, arsenic has been included in agricultural chemicals (see Annex I), either directly or after conversion to arsenic acid, and was widely used as a pesticide and fertilizer.

The regulatory conditions in Europe with regards to arsenic and is compounds in general (See Section 3 and Appendix 3 for further details) are such that many uses have become subject to regulation since the mid 1990's and most recently through Authorisation under REACH. Triggered mainly by their toxicity and the classification of some compounds as Carc. 1A (known human carcinogen) first under the DSD and later the CLP regulation, other measures have been taken over time which have significantly reduced the use of arsenic and compounds in Europe.

In the agricultural industry, arsenic has historically been used in a range of applications, including pesticides, herbicides, insecticides, cotton desiccants, defoliants, and soil sterilants. These are no longer approved as active substances under the Biocidal Products Regulation or Plant Protection Products Regulation (see sections 3.3 and 3.4 above). This includes the use of diarsenic pentaoxide/ arsenic acid to produce CCA wood preservatives, once the major use of arsenic (see above).

Until the 1970s, arsenic was used in the treatment of cancer, psoriasis, and chronic bronchial asthma, and organic arsenic was used in antibiotics for the treatment of spirochetal and protozoal disease (ATSDR 2007). Recently, arsenic trioxide has been approved to be used in the treatment of patients with acute promyelocytic leukaemia by the US Food and Drug Administration in 2000 (Lo-Coco et al 2013) and in 2013 in Europe by the European Medicines Agency (EMA) (EMA 2013).

Until recently arsenic-containing dental pastes were authorized in France, Estonia, Latvia and Lithuania and have been used to remove damaged nerves in the dental pulp. Following a review in 2014, the EMA's CHMP (Committee for Medicinal Products for Human Use) has concluded that the benefits of the dental pastes containing arsenic do not outweigh their risks and has recommended revoking the marketing authorisations for these dental pastes in the EU (EMA 2014).

Summary data on the quantities of arsenic compounds used in the EU is not readily available. Only when the third REACH registration deadline due in mid-2018 has passed, for substances produced in quantities of 1 to 100 tonnes per year, will the picture be more complete. Globally, an estimated 50% of arsenic produced continues to be used to make arsenic-based insecticides and herbicides, and another 30% is used to make chromated copper arsenate (CCA) wood preservatives; the electronics industry uses 5% of the arsenic produced to make gallium-arsenic semiconductors and the remaining 15% is used in glassmaking, and to harden metal alloys (Carex Canada, 2012).

Use of arsenic acid in chromated copper arsenide (CCA) wood preservatives.

Wood preservation in general is a major industry in the EU, with 11.5 million m^3 of wood treated yearly. The sector is characterised by a large number of relatively small plants. It has been estimated that 1000 installations were involved in the treatment of wood in the EU-15. It is reported that 68 % of the plants use less than 25 t/yr of solvents (JRC, 2009).

Chromated, Copper arsenate (CCA) has been widely used in wood impregnation. Following an opinion by the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) (CSTEE 1998) several uses of CCA were banned in 2003 (REACH

Annex XVII Entry 19), mainly in residential or domestic constructions(Commission Directive 3003/2/EC[13]; REACH[14], .

Prior to restriction in 2003, wood preservation was the main use of arsenic acid and indeed arsenic as a whole. However a derogation for professional and industrial use, e.g. in farm fencing, railway sleepers and construction materials not intended for the home was included. Since the introduction of the above restriction in 2003 and even though the EME/EEA guidebook (2013) lists CCA types as the most widely used water-borne wood preservative, other European legislation has had a further impact. EU (2013) documented the list of '*existing [biocidal] active substances for which a decision of non-inclusion into Annex I or Ia of Directive 98/8/EC has been adopted*': under product type 8, wood preservatives, diarsenic (V) pentaoxide and chromium trioxide and sodium dichromate are given with phase-out dates of 1 September 2006. However, until the Biocidal Products Regulation entered into force (17 July, 2012) and the regulatory requirements for industry were applied (1 Sept., 2013), it was still possible to import treated wood preserved with CCA's into the EU.

EEA (2016) noted an increase in recycling activities, which has involved better sorting as well as the collection of treated wood and some chemical waste, which in turn has led to the identification of increased amounts of hazardous waste. As examples of the volumes, Germany reported 1,308, Portugal 32, Sweden 101 kilo tonnes of wood waste in 2012. The quantity of CCA treated wood waste is not quantified but is still expected to be significant.

Thus, the use of CCA to preserve wood has effectively ceased in the EU, as has the import of CCA treated timber. However this leaves a considerable legacy of treated timber still in use with implications for occupational exposure in relation to waste treatment and recycling for the future.

Production of metal arsenates as a waste in non-ferrous metals refining (see JRC, 2014).

Zinc refining

As indicated in two recent authorisations granted by the Commission, for the use of diarsenic trioxide to produce a copper concentrate in the purification of metal impurities from the leaching solution in the zinc electrowinning process, the final waste product is **Ferric arsena**te, a salt of arsenic acid.

Arsenic constituents from the zinc process are bound to inorganic waste materials as ferric arsenate. Ferric arsenate is precipitated simultaneously with jarosite, (potassium iron sulphate hydroxide; $KFe^{3+}{}_3(SO_4)_2(OH)_6$) which is the main waste component from the zinc process The solid wastes are filtered, washed, and landfilled under licence in an area approved for hazardous waste. Prior to disposal, the dissolution properties of As from the waste are adjusted (stabilised by neutralisation and sulphidation) to ensure that leaching from the jarosite stays within permitted limits. There are reportedly ca. 20 zinc refining plants in the EU.

[13] Commission Directive 2003/2/EC of 6 January 2003 relating to restrictions on the marketing and use of arsenic (10th ATP to Council Directive 76/769/EEC). 2003

[14] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC (OJ L 396 of 30 December 2006, p. 1; corrected by OJ L 136, 29.5.2007)

Copper refining

Primary recovery of copper can be achieved by pyrometallurgical or hydrometallurgical processes. Approximately 20 % of primary copper is produced by the direct leaching of ores (hydrometallurgical route). Nowadays, sulphidic concentrates (15 – 45 % Cu) are the most important raw materials for the pyrometallurgical primary copper route, with a share of more than 85 %. Arsenic has to be removed from both pyro-metallurgical and hydro-metallurgical processes.

Fluidised roaster furnaces are increasingly used for the processing of As-rich copper concentrates, since there is a trend towards higher As grades in several major copper mines at increased depth and some newer mines also possess a higher arsenic content. After initial cyclone separation, cooling and filtration to remove copper and valuable metals, the furnace gasses are further cooled; the roasted arsenic dust and mercury are separated in a fabric bag filter. This 'roaster dust', is collected and transported in a closed system for waste storage in a concrete silo.

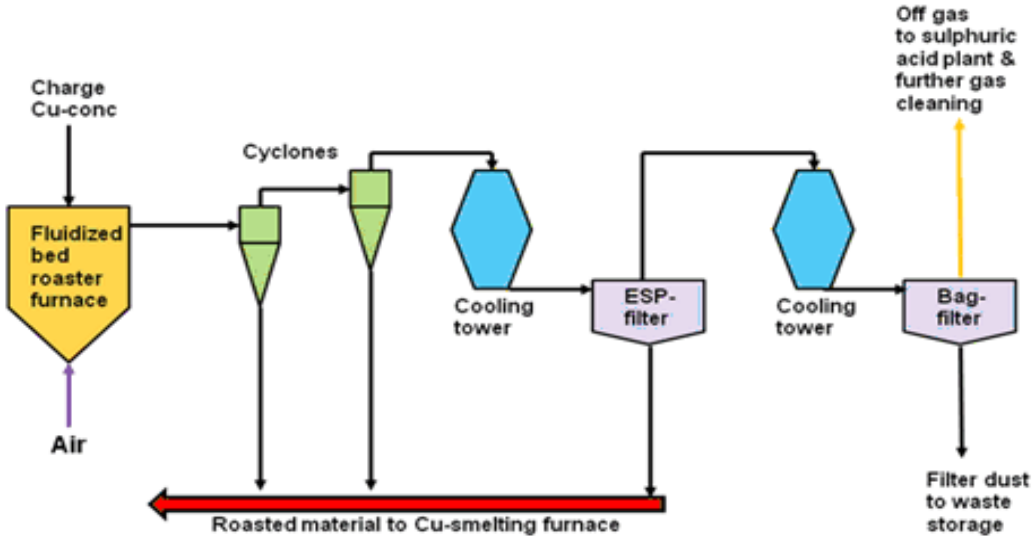

Figure 1: A flowsheet of a fluidised bed roaster furnace and gas treatment system is given (JRC, 2014[15]).

In the non-ferrous metals industry, trace metals can be effectively removed from aqueous effluents by the addition of ferric salts. Arsenic is removed from various stages of metals refining as either calcium or ferric arsenate by precipitation. Effluent that contains arsenite is generally oxidised prior to precipitation to ensure that the arsenate predominates. The precipitation of insoluble ferric arsenates is accompanied by the co-precipitation of other metals, such as selenium, that involves interactions between the various metals species and the ferric hydroxide precipitate. This makes ferric salts a very effective scavenger for the removal of trace contaminants.

[15] JRC 2014: ECI Copper Installations 2008 - Copper Smelters and Refineries in the EU - 2012

The two aforementioned applications for Authorisation for zinc refining provide the best insight into the potential for worker exposure to metal arsenates in dealing with arsenic rich hydro-metallurgical wastes. Little or no specific information on the potential for occupational exposure during the refining of non-ferrous metals in general and in particular the handling of arsenic-rich wastes and tailings is available.

Uses of arsenic metal (As 0)

Elemental arsenic is used in the manufacture of alloys, particularly with lead (e.g. in lead acid batteries) and copper. Gallium arsenide is widely used in the semiconductor and electronics industries. Because of its high electron mobility, as well as light-emitting, electromagnetic and photovoltaic properties, gallium arsenide is used in high-speed semiconductor devices, high-power microwave and millimetre-wave devices, and opto-electronic devices, including fibre-optic sources and detectors (IARC, 2006).

High-purity arsenic (99.9999%) is used by the electronics industry for GaAs semiconductors. Semiconductor technology devices based on GaAs circuitry are a key element of many wireless and wi-fi consumer electronic products such as digital mobile phones, personal communication systems, GPS navigation, satellite and fibre optic communications and wireless networks (EISA, 2007). Arsenic metal also is used for germanium-arsenide-selenide specialty optical materials, while indium-gallium-arsenide is used for short-wave infrared technology. Other uses for Arsenic metal are in: the hardening of ammunition (<1% arsenic metal), lead shot, and clip-on wheel weights; the grids in lead-acid storage batteries are strengthened by the addition of arsenic metal; the reduction of friction in bearings.

Uses of arsine As (III^-)

Arsine is used as a doping agent to manufacture crystals for computer chips and fibre optics. EISA (2007) reported that in its intrinsic state, silicon does not carry an electrical current very well (high resistivity). Its molecular and electrical properties must be changed in order to increase its conductivity. the use of arsenic doping (either as gaseous arsine or solid arsenic) in the production process for semiconductor devices in tiny (atomic) amounts is thus essential. They claim that due to the unique characteristics of arsenic doping chemistry there are no replacement elements for arsenic.

5.3 Occupational exposure

5.3.1 General exposure

Exposure to airborne particles

Human exposure is primarily through inhalation of arsenic-containing particulates, but ingestion and dermal (skin-to-mouth) exposure may be significant in particular situations (e.g. chromium copper arsenate (CCA)-treated timber). It is extremely rare for workers to be exposed to arsenic alone; the exposure is usually to arsenic in combination with other elements (WHO-IPCS, 2001).

DECOS (2012) who provided the most recent review of the carcinogenicity of 'arsenic and inorganic arsenic compounds', relied on WHO-IPCS (2001) and ATSDR (2007) data with regards to exposure in the working population. A more recent update to reflect the situation in the EU following the implementation of OSH, REACH and BPD/R legislation is unfortunately not available. Relevant, recent references have been added here to update the situation; while generally representative and focussed on the EU, , this is not exhaustive.

Lewis et al, (2012) considered that although there is extensive information available on total arsenic in air, less is known on the relative contribution of each arsenic species. Despite sampling and analytical limitations, the available data is adequate to show that arsenic in air is mainly in the inorganic form. Reported average concentrations of As(III)

and As(V) ranged up to 7.4 and 10.4 ng/m^3, respectively, with As(V) being more prevalent than As(III) in most studies. Concentrations of the organic methylated arsenic compounds are negligible (in the pg/m^3 range).

5.3.2 Occupational exposure from uses and processes relevant to arsenic acid and its compounds

CAREX Canada (2017) estimates that approximately 25,000 Canadians are exposed to arsenic at work; about half are exposed due to the use of arsenic in CCA wood preservatives, i.e. to ferric arsenate (in Canada, CCA is still allowed to be used as wood preservative). The largest industrial groups exposed to arsenic through CCA are sawmills and wood preservation, as well as foundation, structure, and building exterior contractor work, and non-residential building construction. The remaining workers exposed are employed in metal processing and manufacturing, oil and gas extraction, metal and ore mining, and water, sewage and other systems industries. A total of 8% of workers in the non-ferrous metal production and processing industry are exposed to arsenic. In iron and steel mills, arsenic is produced as a by-product during processing of other metals. Farmer and Johnson (1990) quantified inorganic arsenic and its methylated metabolites to investigate the occupational exposure of timber-treaters as well as workers in other industries. Although nearly 30 years old, this data provides a useful benchmark of exposure in UK industries prior to the implementation of the current EU OSH legislation and prior to the implementation of specific regulation of wood preservatives in the EU.

Table 7: Maximum concentration (and frequency of detection) of individual arsenic species in urine from various groups of workers (Detection limit 0 5 µg/l) - from Farmer & Johnson (1990)

Group	No of sampled workers	As(V) µg/g	As(III) µg/g	MMAA µg/g	DMAA	Geometric mean – tot. As µg/g
Glasgow controls	40	<0.5 (0)	1.0 (5)	0.6 (4)	39.0 (40)	**4.4**
Semiconductor manufacture	14	2.8 (1)	2.0 (1)	1.4 (2)	22.2 (14)	**5.9**
Electronics research	7	2.0 (3)	3.4 (4)	2.4 (4)	13.1 (7)	**9.7**
Glass manufacture	30	3.8 (2)	12.1 (26)	6.2 (24)	27.1 (30)	**10.2**
Timber treatment	5	6.7 (3)	20.9 (5)	21.3 (4)	80.7 (5)	**47.9**
Glass manufacture	28	12.2 (21)	54.7 (26)	146 (28)	304 (28)	**79.4**
Arsenical manufacture	24	185 (22)	187 (24)	190 (24)	540 (24)	**245**

CCA treated timber

Where occupational exposure is concerned, the repair, recycling and eventual removal to waste of CCA treated timber (as copper chromate), as well as the remediation of contaminated timber impregnation sites are potential sources of occupational exposure to copper chromate in the EU and fall within this evaluation.

Timber is usually treated in industrial installations using vacuum or pressure to impregnate it with solutions of chromium, copper and arsenic; the preservative effect is mainly from Copper(II) arsenate, while the chromate was intended to fix it in the timber binding through chemical complexes to the wood's cellulose and lignin. The starting reagents are: arsenic acid or sodium arsenate, potassium or sodium dichromate, copper sulfate or basic copper carbonate or copper hydroxide.

Katz and Salem (2005) quoting Nygren and Nilsson (1992), found only pentavalent arsenic in ten samples of CCA impregnated timber.

Farmer and Johnson (1990) investigated occupational exposures to arsenic in various industries, including wood impregnation with CCA in the UK. For the timber-treaters, the mean total (arsenite, arsenate, monomethylarsonic acid MMA and dimethylarsinic acid - DMA) arsenic concentration was 79.4 µg/g creatinine, while for the controls it was 4.4 µg/g creatinine. The authors considered that exposure was to airborne pentavalently inorganic arsenic during the mixing of the chemicals and via possible skin contact in handling the dried wood after treatment and removal from the solution. Decker et al. (2002) examined the airborne concentration and particle size distribution of wood particles from CCA pressure-treated timber at outdoor (measured over the whole work day) and indoor (measured during the performance of specific tasks) work sites in the USA. At the outdoor (residential deck construction) sites, the arithmetic mean total dust concentration, measured using personal filter cassette samplers, was 0.57 mg/m^3 (MMAD >20 µm). Indoor wood dust concentrations were significantly greater and were job category-dependent. The highest mean breathing zone dust concentration, 49.0 mg/m^3, was measured at the indoor sanding operation. Personal impactor sampling demonstrated that the mean total chromium, copper, and arsenic concentrations at the indoor sanding operation were 345, 170 and 342 µg/m^3, respectively.

Cocker et al, 2006 examined exposure to CCA wood preservative from a wide selection of companies treating timber. Sampling kits were provided to all workers and analytical chemistry was done centrally. Some 217, 164, 124 and 93 post-shift urine samples were received following four rounds at six monthly intervals. The results for urinary inorganic As over this 2 year period were elevated above the controls but similar throughout, i.e. ranging from means of 19.4 to 29.4 µmol/mol. A smaller number of workers submitted samples in a time series three times per week over three weeks; these results are shown in Table 8 and are in the same range as the long-term sampling. Workers exposed to CCA wood preservatives have concentrations of inorganic arsenic and chromium in urine that are significantly higher than those from non-occupationally exposed people but below the UK BMGV (at least for Cr) that would indicate inhalation exposure at UK occupational exposure limits for hexavalent chromium and arsenic.

Table 8: Urinary inorganic arsenic and Cr in workers and controls form 3 samples per week for 4 weeks (from Cocker et al. 2006).

	Workers	Controls	Workers	Controls
	Arsenic µmol/mol	Arsenic µmol/mol	Chromium µmol/mol	Chromium µmol/mol
Mean	22.0	11.7	2.8	0.6
Geo. Mean	16.7	8.9	1.5	0.3
SD	18.2	10.4	3.2	1.0
GSD	2.1	2.1	3.5	2.7
90th %	40.2	22.9	6.5	1.0
No. of samples	150	241	150	241
% < LOD	0	0	10	60

Nygren et al. (1992) examined six wood joinery shops.

Table 9: Personal sampling during work with impregnated timber with the use of three types of machines. The results are given as geometric means (GM) of 8 h time-weighted averages. N = number of samples, NP = number of plants (sites) and Nm = number of machines (from Nygren et al. 1992).

Type of machine	Dust	As	Cr	Cu			
	mg/m^3	µg/m^3	µg/m^3	µg/m^3	*N,*	*NP*	*Nm*
Cutting	0.32	0.54	0.38	0.38	20	4	7
Sanding	1.2	2.4	2.3	1.9	15	3	6
Circular saw	0.54	3.1	2.1	1.8	13	3	4

The mean exposure to wood dust was found to be below 1 mg/m^3 and the mean airborne concentration of arsenic around various types of joinery machines was in the range from 0.54 to 3.1 µg/m^3. No hexavalent chromium was detected in any samples. To investigate possible increased urinary excretion of arsenic among joinery workers, urine samples from five workers were collected each morning and afternoon during one working week. None of the workers showed any arsenic concentrations outside the normal range and the highest was less than 27µg/g creatinine. Within the normal urinary arsenic concentration range, there was no tendency for the urinary arsenic concentrations to increase during the working week.

Subra et al., 1999 found levels of As in personal air samples from two workshops machining wood impregnated with CCA preservatives, to be 30-67 µg/m^3 in one plant (8 workers) and 10-62 µg/m^3 in another plant (8 workers). In a study performed in Denmark to evaluate arsenic exposure in workers impregnating wood with CCA solutions (Jensen and Olsen, 1995), the maximum air exposure concentration was 17.3 µg/m^3, found for a single worker who was filling an impregnation container with CCA paste.

Thus, significant exposure to airborne heavy metals, including arsenic in the form of copper arsenate can occur not only during the impregnation of wood with CCA but also when CCA treated wood is processed, treated as waste or recycled.

Arsenic exposure from copper and other non-ferrous metal refining

Mining waste

Martin et al. (2014) reviewed the health effects associated with inhalation of arsenic containing particulate matter arising from mining operations. High temperature processes, such as smelting and coal combustion, are typically associated with fine particulates, accumulation-mode particulates, and vapors (Csavina et al 2012). Fugitive dust emissions from mine wastes and mechanical processes associated with the hard rock mining industry such as crushing of sulphide ore and concentrates, and mechanical disturbance and wind erosion of uncontained mine tailings are also associated with elevated levels of arsenic. Airborne arsenic-contaminated particulates generated by mining operations may often be small enough to be inhaled, and have the potential to directly reach the tracheobronchial and/or alveolar regions of the respiratory tract of populations living within the reach of the industrial plume or raised dust material (Moreno et al. 2007; Querol et al. 2000). However, particles that have been deposited on the ground or other surfaces may be either ingested due to physical contact, or re-suspended as dust, and then inhaled; the ingestion and inhalation exposure pathways may contribute equally to the arsenic-associated risks in such populations (Cao et al.; 2014; Moreno et al. 2007).

Arsenic associated with the fine fraction may remain in the atmosphere between seven and up to 10 days (Rahn, 1976; Matschullat, 2000), and can travel long distances (ATSDR, 2007).

Martin et al. (2014) summarised the recent literature on air emissions from mining operations, smelting and mine tailings (see Table 11 below). The average total arsenic concentrations in the air, recorded in particulate matter (PM) sampled within <1 km to ca. 3km of various mining operations, including smelting, coal combustion and mine waste are given for European sites. Values in the low hundreds of ng/m^3 were reported for copper smelter sites in Belgium and the UK but the data is rather old (Lee et al., 1994; Buchet et al., 1980). More recent copper smelter data from Spain indicates average PM values over representative time-spans (years) of ca. 10 ng/m^3 (max 80 ng/m^3; Oliviera et al., 2005; Sanchez-Rodas et al., 2007; De la Campa et al., 2008). However, where mine tailings are concerned, the average air values reported can vary from 1 to over 1000 ng/m^3 (Querol et al., 2000; Protonotarios et al., 2002; Castillo et al., 2013; Tsopelas et al., 2008). The lower values were from more recent surveys but the sample size (4 sites) is too small to draw firm conclusions as to a trend. Where As species were measured, inorganic As(V) predominated in particulate matter in air, i.e. at concentrations 3 to 6 times higher than As(III) (Oliviera et al., 2005; Sanchez-Rodas et al., 2007; De la Campa et al., 2008; Tsopelas et al., 2008).

Table 10: A summary of recent literature on air emissions from mining operations, smelting and mine tailings; from Martin et al (2014), all in ng/m^3 as total arsenic unless otherwise stated.

Source	Location	Sampled and size fraction	Distance from source (km)	Total As (Min-Max)	As(III) (Min-Max)	As(V) (Min-Max)	Reference
Pb, Cu smelter	Belgium	1978, TSP	<1	330	-	-	Buchet, et al. (1980)
Cu smelter	UK	-	<1	93.9 ± 89.7 (10.6–572.3)	-	-	Lee, et al. (1994)
Cu smelter	Huelva, SW Spain	2000	2	12.3 ± 1.6 (3.0–33.8)	1.2 ± 0.3 (0.3–1.8)	10.4 ± 1.8 (2.1–30.6)	Oliviera et al. (2005)
Cu smelter	Huelva, SW Spain	2001 pm10 2002 pm10	2	7.7 (1.6–29.4) 9.9 (1.3–79.8)	1.2 (0.6–2.2) 2.1 (0.4–3.4)	6.5 (0.01–25.7) 7.8 (0.01–56.2)	Sanchez-Rodas et al. (2007)
Cu smelter	Huelva, SW Spain	2001 pm2.5 2002 pm2.5	2	6.4 (0.8–30.2) 7.9 (1.0–56.6)	0.9 (0.01–1.6) 1.4 (0.1–2.7)	5.0 (0.01–25.3) 6.6 (0.01–56.2)	De la Campa et al. (2008)
Cu smelter	Huelva, SW Spain	2004 pm10 2004, pm2.5 2005, pm10 2005, pm2.5	3.5	4.67 (max: 22.4) 3.04 (max: 19.0) 10.6 (max: 62.1) 9.18 (max: 60.3)	-	-	Fernandez-Camacho et al. (2010)
Cu smelter	Huelva, SW Spain	2009 pm2.5	5	2.1 ± 4.2 (0–20)	-	-	Chen et al. (2012)
Cu mining & smelter	Bor, E Serbia	1994-2008 Ave.	0.8 1.9 2.5	131.4 (<2–669) 51.3 (<2–356) 93.7 (<2–670)	-	-	Serbula et al. (2010)
Cu mining & smelter	Bor, E Serbia	2009, PM10	0.65	32.97 ± 53.63 (2.4–149)	-	-	Kovacevic et al. (2010)
Ferro-manganese plant	Dunkirk, France	2003-2005, pm10	2	5.1 ± 5.4 (0.5–35.1)	-	-	Alleman et al. (2010)
Cu-Pb-Zn mine tailings	Aznalcazar, S. Spain	1998, TSP	0 0.5	221 (4.9–2681) 69 (2–921)	-	-	Querol et al. (2000)
Historical Ag-Pb mine tailings	City of Lavrion, Greece	PM10 - Overall ave. - Winter - Summer	1	 520 (1–3031) 115 (1–791) 909 (121–3031)	-	-	Protomotarios et al. (2002)
Cu-Au-Ag mine waste. Total bulk deposition (mg/m2)	Rio Tinto mines, Spain	2009-2010/ 2010-2011	0 0.5 1	4.4/2.1 0.7/0.5 0.7/1.0	-	-	Castillo et al. (2013)
Smelter and other industries	Aspro-prygyros, Greece	2004-2006 - TSP - pm10-2.5 - pm 2.5		 3.4 ± 0.3 1.9 ± 0.3 1.1 ± 0.3	 <0.2 <0.2 <0.2	 3.2 ± 0.4 1.7 ± 0.4 1.0 ± 0.4	Tsopelas et al. (2008)

Due to the projected increase in global copper production over the next 20 years (Northey et al. 2014), it is also likely that smelter emissions, and the generation of flue dust and other associated waste products, will also increase (Montenegro et al 2013).

Copper and other non-ferrous metal smelting

The data evaluated by WHO-IPCS (2001), ATSDR (2007) and DECOS (2012) relevant to this sector is largely from smelting and refining of copper and largely predates the year 2000.

Exposure investigations indicated that the arsenic exposure concentrations (8-hour TWA) in **copper smelters** ranged from 0.8-746 µg/m^3 (Vahter et al., 1986; Hakala and Pyy, 1995; Jakubowski et al., 1998; Ferreccio et al., 1996; Offergelt et al., 1992; Liu and Chen, 1996). Much higher arsenic exposure concentrations were reported in older exposure investigations (e.g. pre. 1990's?).

Two of the authorised uses of diarsenic trioxide that have been granted by the Commission involve the purification of zinc. The waste product from this process is jarosite containing ferric arsenate[16] and is thus relevant to the current evaluation. For loading/unloading of landfill waste, the dust is deposited and supressed through use of stabilisation and containment methods. Any direct manual handling of waste is not normally needed and contact with skin is incidental. Dust abatement systems are used in loading and unloading of waste in transportation .

Table 11 below presents the exposure and risks estimate for the working contributing scenarios (WCS) taken from the final opinion of RAC and SEAC on the application of Boliden Kokkola Oy (https://echa.europa.eu/documents/10162/d719b55e-3e09-43ae-9299-56c13be92b2f).

Table 11: Risk estimated from exposure of workers at BKO

WCS	Route	PPE/RPE	Exposure	Excess risk	Persons exposed[17]
1, 3, 5 high exposed	Inhalation	RPE	1.85 µg/m^3	2.59 x 10^{-4}	10
	Inhalation	No RPE	18.5 µg/m^3	2.59 x 10^{-3}	10
2, 4 low exposed	Inhalation	RPE	0.25 µg/m^3	-	-
	Inhalation	-no RPE	2.5 µg/m^3	3.5 x 10^{-4}	40

In a similar manner the exposure and risks estimate for the working contributing scenarios (WCS) taken from the final opinion of RAC and SEAC on the application of Nordenhamer Zinkhütte GmbH (https://echa.europa.eu/documents/10162/3aa8d418-275c-4732-ab80-80e8462a1be2) are given below.

[17] 10 + 40 persons, in sum 50, with or without PPE

Table 12: Risk estimated from exposure of workers at NZH

WCS	Route	PPE/RPE	Exposure	Excess risk	Persons exposed[18]
1, 4, 5 high exposed	Inhalation	RPE	0.12 µg/m^3	1.68 x 10^{-5}	10
	Inhalation	No RPE	1.2 µg/m^3	1.68 x 10^{-4}	10
2, 3 low exposed	Inhalation	RPE	0.02 µg/m^3	-	-
	Inhalation	No RPE	0.22 µg/m^3	3.08 x 10^{-5}	30

Gaweda (2005b) measured cadmium, nickel and arsenic concentrations in the workplace air at a large Polish copper smelter (Plant I) and a non-ferrous metals smelter (Plant II). Personal air samples (15 minutes, sampled once or twice and extrapolated to full shift) were taken at 'several dozen' workstations, each with 2-6 workers involved in copper, zinc, cadmium, lead, silver refining, sulphate of Ni(I), and selenium production. In Plant I, exposure to arsenic ranged from very low in copper electro-refining processes (mean ca. 0.5 µg/m^3), 5.5 µg/m^3 in the silver refining process and ca. 10µg/m^3 in copper refining. In Plant II, the amounts of arsenic determined in the air were smaller, i.e. all below 3.3 µg/m^3 for production of raw zinc. Exposure to Cd was also measured.

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). The workers were investigated using personal air sampling, post shift urine sampling and clinical examination for signs of As exposure related neurotoxic effects. A mean of 25.2 (0.2 – 92.3) µg/m^3 total As in air was measured, while a mean of 86.82 (17.4 - 434.7) µg/L total As in urine was recorded. Mean inorganic As(III) and As(V) in urine was respectively 9.9 (0.3-22.8) and 5.38 (0.7-14.5) µg/L.

To examine the differences in urinary arsenic metabolism patterns in men affected by occupational exposure, Janasik & Reszka (2015) performed a study on 149 **copper mill** workers and 52 healthy controls without occupational exposure. The purpose of the study was to elucidate the role of genetic factors in arsenic (As) metabolism - only the exposure data is reported here (see Figure 2). Air samples were collected using individual samplers during work shifts. Urine samples were analysed for total arsenic, As(III); As(V), MMA, DMA and arsenobetaine. The geometric mean arsenic concentrations in the air were 27.6 ± 4.9 (0.2 to 275.6) µg/m^3. Concentrations above the MAC value were found in 82 cases among the 149 investigated subjects. A significant correlation ($p < 0.05$) was observed between arsenic in air and inorganic arsenic, as well as the sum of MMA and inorganic arsenic.

[18] 10 + 30 persons, totally 40 persons, with or without PPE.

Table 3 Geometric mean values of arsenic and chemical species in urine of copper mill workers and control group

Parameter	*N*	Total As		AsB		As^{III}		DMA		MMA		As^{V}	
GM ± GSD (range)		µg/l As	µg/g creat.	µg/l As	µg/g creat.	µg/l As	µg/g creat.	µg/l As	µg/g creat.	µg/l As	µg/g creat.	µg/l As	µg/g creat.
Copper mill workers	149	37.8 ± 2.5 (2.8–511.6)	34.8 ± 2.1 (5.2–319.6)	5.5 ± 4.2 (0.2–370.6)	5.0 ± 3.6 (0.1–241.3)	4.0 ± 3.1 (0.1–37.7)	3.6 ± 2.8 (0.1–32.3)	15.6 ± 2.7 (0.4–112.3)	14.4 ± 2.3 (1.0–85.2)	3.7 ± 2.2 (0.4–26.0)	3.4 ± 2.1 0.3–17.3)	2.0 ± 3.4 (0.1–23.8)	1.8 ± 2.9 (0.1–50.4)
Control group	52	6.7 ± 3.4 (1.2–124.2)	5.4 ± 3.3 (0.7–73.9)	1.3 ± 5.6 (0.15–86.8)	1.0 ± 5.1 (0.4–73.1)	0.3 ± 2.7 (<LOD–1.7)	0.3 ± 2.8 (<LOD–1.09)	4.1 ± 2.8 (1.0–34.8)	3.4 ± 2.5 (1.5–23.5)	0.3 ± 2.3 (0.05–1.3)	0.3 ± 2.5 (0.11–1.2)	0.2 ± 2.4 (<LOD–0.8)	0.2 ± 2.5 (<LOD–0.6)
p		$p < 0.05$*	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$

* Statistical significance as compared to the controls

Figure 2: reproduced from Janasik and Reszka (2015).

Concentrations of arsenic in the breathing zone of **underground gold-miners** in Ontario (Canada) were reported to range between 2.4 and 5.6 µg/m^3 (geometric mean) (Kabir and Bilgi, 1993). In a study relating arsenic exposures to lung cancer among tin-miners in Yunnan province (China), Taylor et al. (1989) reported mean concentrations of airborne arsenic to range from 0.42 mg/m^3 in 1951 to 0.01 mg/m^3 in 1980.

According to the Finnish biomonitoring statistics from 2012, the highest exposures to arsenic were detected in the different tasks of copper and nickel production. From all the samples analysed during year 2012 (n=612), the Finnish BLV (70 nmol/l as inorganic As) was exceeded in 4% of the samples, the highest levels exceeding 200 nmol/l. These samples exceeding the BLV were mainly from copper and nickel production, especially from cleaning and smelting activities (Kiilunen, 2013).

Arsenic exposure from glassmaking

No specific references to occupational exposure for the use of arsenic acid in glassmaking were found but it appears to be interchangeable with diarsenic trioxide in fining glass, i.e. aids in removing bubbles and colour from the glass. No applications for authorisation under REACH for either substance were received for this use. It is understood, e.g. from Ishiguro et al. (1992) that alternatives such as Selenium and Cerium may be available.

Apostoli et al, (1999) investigated exposure to diarsenic trioxide among 51 Glass workers in Italy who were monitored by measuring dust in the breathing zone with personal air samplers and who provided urine samples at the end of their work shift. A control group of 39 subjects not exposed to As were also examined. Environmental concentrations of As in air were 59 (10-154) for batch mixers, 127 (10-312) for oven chargers and 13 (1.5-15) µg/m^3 for moulders finishers. Urinary concentrations in the exposed group as a whole were: 15 (1-57) µg/l for As(III), 6 (1-17) for As(V), 29 (1-95) for MMA and 58 (10-232) for DMA. The mean concentration of total inorganic As plus MMA and DMA totalled 106 (15-312)µg/l, whereas the control group showed 8.6 (2.5-22). For 41 samples the values of inorganic As in air were higher than the current limit values (TLV-TWA) proposed by (ACGIH, 2016) of 10 µg/m^3. Such values for total arsenic in urine from workers exposed to As in the glassmaking industry tend to agree with the ranges reported by Farmer and Johnson (1990) at two plants in the UK a decade earlier.

A study of 35 crystal glassworkers within the mix-and-melt and batch-house areas also indicated the potential for arsenic exposure. Potential air monitoring of 8 workers found airborne concentrations of 2-11 mg/m^3(Chrostek et al, 1980). Biological monitoring of workers in glass manufactories in the Murano district of Venice, carried out by Montagnani et al, (2006) through urinary arsenic measurement, revealed that workers employed in the mixture preparation and in the furnace work are still significantly exposed to arsenic (the dustiness of As2O3) despite the technical preventive measures adopted (mean concentrations of different arsenic species in the urine samples of workers are 2-3 times higher than the upper limit of reference for the non-exposed population).

Other industries with reported arsenic exposure.

Horng et al, (2002) reported on beryllium, arsenic, and selenium in the urine of steel production and steel quality control (QC) workers, in comparison to healthy control subjects. The urinary levels of these elements in steel production (As, 38.1 +/- 28.7 microg/L; Be, 1.58 +/- 0.46 microg/L, and Se, 69.2 +/- 28.8 +/- g/L) and in quality control workers (As, 23.9 +/- 18.1 microg/L; Be, 1.58 +/- 0.46 microg/L, and Se, 54.8 +/- 25.1 microg/L) are significantly higher than in the controls (As, 10.3 +/- 8.7 microg/L; Be, 0.83 +/- 0.46 microg/L; and Se, 32.3 +/- 13.5 microg/L). The authors noted that one quality control worker and three production workers showed total urinary As values above 100µg/l.

During coal combustion, arsenic readily oxidizes to form arsenic oxide vapor (Huggins et al, 1993) which combines with calcium oxide and condenses on the surface of fly ash

particles in the form of calcium arsenate (Bolanz et al, 2012; Furimsky, 2000; Zhao et al, 2008). Solid by-products of the combustion process, including fly ash and bottom ash, are major sinks for arsenic. Workers in coal-fired power plants may also be exposed to arsenic found in the coal, or more likely that found in the fly ash during cleaning. Yager et al, (1997) reported arsenic concentrations (8-h TWA) between 0.17 and 375.2 µg/m^3 (mean 48.3) in the breathing zone of maintenance workers in a coal-fired power plant in Slovakia.

Yager et al, (1997) reported arsenic concentrations (8-h TWA) between 0.17 and 375.2 µg/m3 (mean 48.3) in the breathing zone of maintenance workers in a coal-fired power plant in Slovakia. According to Shuhua X et al, (2014), the urinary arsenic level in steel smelter workers exceeded the biological exposure index (BEI) limit for urinary arsenic of 35 µg/l by 65.52%. Xi et al, (2011) investigated occupational exposures to arsenic in copper- and steel-smelting workers in China, and found that the workers in copper smelter had significantly higher concentrations of iAs, MMA, DMA in urine with creatinine adjustment but a lower value of primary methylation index (PMI) than that of steel-smelting plants workers. In addition, in some workers, a hyperkeratosis and/or hyperpigmentation were found. Occupational exposure related to arsine and gallium arsenic in the semiconductor and microchip industry.

Arsine or substitutes such as tertbulyl arsine and gallium arsenide are not covered by the current mandate – if time allows, this section can be expanded during RAC consultation depending on COM's response. Most of the reviews are from outside the EU, e.g. China, Taiwan, Japan and Korea.

NIOSH conducted a study of arsenic exposures and control systems for gallium arsenide operations at three microelectronics facilities during 1986 – 1987. Results at one plant showed that in all processes evaluated but one, the average arsenic exposures were at or above 5 µg/m^3, with a maximum exposure of 8.2 µg/m^3. While cleaning the liquid encapsulated Czohralski (LEC) pullers, the average potential arsenic exposure of the cleaning operator was about 500 µg/m^3. Area arsenic samples collected at the plant in break-rooms and offices, 6 – 20 meters from the process rooms, had average arsenic concentrations of 1.4 µg/m^3 (Sheehy et al, 1993) . Kiwhan Byun et al,(2013) evaluated the exposure to arsenic in preventive maintenance (PM) engineers in a semiconductor industry by detecting speciated inorganic arsenic metabolites in the urine. Levels of urinary arsenic metabolites in PM engineers from the clean process and ion implantation process areas were higher than that in office workers. For a complete assessment of arsenic exposure in the semiconductor industry, the study suggested that further research is needed.

5.4 Routes of exposure and uptake

5.4.1 Worker exposure

The primary route of exposure for the worker population is by inhalation, but ingestion and dermal exposure due to hand to mouth transfer, may be significant in particular situations; dermal absorption is considered to be limited.

5.4.2 General population

The general population is exposed to arsenic mainly by the oral route through dietary intake including drinking water, but contaminated air is also a potential source of exposure through the inhalation route although inhalation of arsenic from ambient air is generally a minor route of exposure for the general population.

6. Monitoring Exposure

WHO (2001) and ATSDR (2007) summarised reference methods for monitoring arsenic and arsenic compounds in air and biological samples.

6.1 External exposure

Arsenic in air is usually associated with particulate matter and therefore standard methods involve collection of air samples on glass fibre or membrane filters, acid extraction of the filters and arsine generation. Atomic absorption spectrophotometry (AAS) is the major technique used to analyse arsenic and arsenic compounds in air.

Total arsenic (AsT) is measured by applying digestion techniques to the samples and atomic absorption spectroscopy (AAS) for the analytical part. The inorganic arsenic fraction is measured by applying a hydrogenation method. With this method only inorganic arsenic compounds and their methylated metabolites (monomethylarsonic acid - MMA and dimethylarsinic acid - DMA) are transformed into volatile hydrides and quantified.

Other available methods for determining arsenic and arsenic compounds in air are presented in Table 13.

Table 13: Analytical methods for determining arsenic and its compounds in air samples

Sample Matrix	Assay procedure	Limits of Quantification/Detection	References
Air (arsenic and its compounds) MAK Collection for Occupational Health and Safety	GFAAS*	Limit of Quantification: 0.15 ng of arsenic (absolute) 0.25 µg/m³ for an air sample of 1.2 m³ (flow rate 10 l/min-2 hours sampling time).	DGUV Information 213-503 Method 04, July 2014
Air (As(0) and compounds, as As, except AsH_3 and As_2O_3) (NIOSH method 7900)	HGAAS	Limit of detection: 0.02 µg/sample Limit of quantification (Air) 0.0002 mg/m³ for 480 l sample (less than 3 hours) (flow rate 1-3 l/min)*	NIOSH (16)
Air (arsenic trioxide, as As) (NIOSH method 7901)	GFAAS*	Limit of detection: 0.06 µg/sample Limit of quantification (Air) 0.0004 mg/m³ for 480 l sample (less than 3 hours) (flow rate 1-3 l/min)	NIOSH (17)
Air (arsenic) (NIOSH method 7300)	ICP-AES	Limit of detection: 0.14 µg/sample Limit of quantification (Air) 0.001 mg/m³ for 480 l sample (2 hours) (flow rate 1-4 l/min)*	NIOSH (18)

Sample Matrix	Assay procedure	Limits of Quantification/Detection	References
Air (particulate organoarsenal) (NIOSH method 5022)	Ion chromatography, HGAAS	Limit of detection: 0.02 µg As/sample Limit of quantification (Air): Limit of quantification (Air) 0.0002 mg/m^3 for 480 l sample (less than 3 hours) Flow rate (1-3 l/ minute)*	NIOSH (19)
Air, wipes (smear tabs) or bulks (OSHA method ID-105)	GFAAS	Limit of quantification: 0.25 µg/sample Air 0.0005 mg/m3 for 480 l sample (4 hours) Flow rate (1-2 l/min per minute)*	OSHA (20)

Notes:
GFAAS: Graphite furnace atomic absorption spectrometry,
HGAAS: Hydride generation atomic absorption spectrometry,
ICP-AES: Inductively-coupled plasma, atomic emission spectroscopy.
* Sampling time calculations have been performed using the maximum flow rate

6.2 Biomonitoring of exposure (internal exposure)

Biomonitoring of arsenic exposure in the workplace can be done by measuring arsenic in urine.

Monitoring of total urinary arsenic (AsT) results in data that include the non-toxic organic arsenic fraction mainly ingested from seafood. This data are difficult to be interpreted in the context of risk assessment. For this reason, in occupational biomonitoring, the most commonly used method has been to measure the sum of arsenic species (iAs + DMA + MMA) of inorganic origin, which excludes all non-toxic organic arsenic species. However, methylated metabolites of inorganic arsenic (DMA and +MMA) are also received from dietary sources, especially from seafood. Therefore, workers should be instructed to refrain from eating marine organisms for at least 48 hours before urine collection for the assessment of exposure to inorganic arsenic(Buchet et al 1994).

AAS has been a common analytical procedure for measuring total arsenic in biological samples, including blood, serum, urine, hair, nails and soft tissue (ATSDR, 2007) . It allows the simultaneous determination of iAs (inorganic arsenic), MMA and DMA, eliminating the possible influence of organoarsenicals, such as arsenobetataine, of dietary origin(Buchet et al, 1996). However, because of the confounding effect of dietary DMA, methods to allow speciation of different arsenic species has been developed.

Morton et al (2006) describes a liquid chromatography-inductively coupled plasma-mass spectrometry (LC-ICP-MS) speciation method for five arsenic compounds [arsenobetaine (AB), arsenite, arsenate, monomethylarsonic acid (MMA), and dimethylarsinic acid (DMA)] in urine. Concentrations of these arsenic species in urine samples are reported in two sets of non-occupationally exposed controls with one set having consumed fish

within 24 h (n = 31) and the other not having consumed fish for 48 h (n = 34). Arsenic species in urine samples from workers in both the timber treatment industry (n = 49) and semiconductor industry (n = 46) are also reported. The arsenic content in all of the samples was also determined using hydride-generation coupled with ICP-MS. The results show that urine samples from people not occupationally exposed to arsenic contain low levels of DMA, MMA, and AB and that only urine from smokers contained any inorganic arsenic. Consumption of seafood was seen to significantly increase the levels of AB and DMA in the unexposed persons. Urine samples from the semiconductor workers exhibited significantly higher levels of arsenite, arsenate, and DMA than the unexposed samples. The urine samples from timber treatment workers exhibited significantly higher levels of four arsenic species (not AB) than those observed in both the control groups and the semi-conductor workers.

Morton et al (2006) emphasized the importance of the speciation of different arsenic species in order to avoid misinterpretations due to the dietary sources of DMA. Speciation of different urinary arsenic species can provide a more comprehensive picture on occupational exposure. However, the challenge is a lack of proper reference values for individual arsenic species. In population studies, the levels of inorganic As3+ and As5+ in urine have remained in the majority of samples below the LODs, which has resulted in an inability to set a reference level for these individual species.

Recently, the same laboratory published a novel, sensitive µLC-ICP-MS based method for the speciation of different arsenic species, which is able to detect As3+ and As5+ levels as low levels as 0.02-0.04 µg/l (LOQ), respectively (Leese et al., 2014). On the basis of 95 samples, collected from working aged, occupationally non-exposed workers they were also able to establish a reference values for different arsenic species, including As3+ and As5+ in urine. These were 0.54 and 0.23 µg/l for As3+ and As5+, respectively. The authors concluded that the existence of methylated metabolites in a urine sample does not necessarily equate to evidence of inorganic arsenic exposure and its subsequent methylation. Therefore, the traditional methods where an amalgamated value (total less AB, e.g. ACGIH BEI and German BAT approach) is determined is not an accurate measurement of exposure.

Other available methods for determining arsenic and arsenic compounds in biological samples are presented in Table 14.

Table 14: Analytical methods for determining arsenic and its compounds in biological samples

Sample Matrix	Assay procedure	Limit of Detection	References
Urine	GFAAS	0.03 µg/l	Horng *et al*
Urine (inorganic acid plus monomethylarsonic acid and dimethylarsinic acid)	HGAAS	1 µg/l	ACGIH
Urine	HGAAS	Inorganic As^{III}: 1.1 µg As/l Methyl As^{III}: 1.2 µg As/l Dimethyl As^{III}: 6.5 µg As/l	Del Razo *et al*
Urine (As^{III}, As^{V}, mono-methylarsonic acid, di-methylarsinic acid and monomethylarsonous acid)	Ion-pair chromatographic separation/HGAAS	4 µg/l	Le *et al*
Urine (As^{III}, As^{V},	HPLC with anion-	0.4–1.7 µg As/l for	Verdon *et a*l

monomethylarsonate, dimethylarsinate)	exchange column ICP-MS* with dynamic reaction cell (DRC)	various species	
Urine (As^{III}, As^{V}, MMA, DMA)	HPLC with anion and cation- exchange column ICP-MS	As^{III} 0.3/0.3 µg As/l As^{V} 0.2/0.4 µg As/l MMA 0.2/0.3 µg As/l DMA 0.3/0.2 µg As/l	Suzuki *et al*
Urine (AsIII, AsV, MMA, DMA)	µLC-ICP-MS	(LOD/LOQ) AsIII 0.004/0.02 µg As/l AsV 0.051/0.04 µg As/l MMA 0.03/0.04 µg As/l DMA 0.003/0.04 µg As/l	Leese et al. 2014

Notes:

ICP-MS: Inductively-coupled plasma mass spectrometry,
HPLC: High-performance liquid chromatography.

7. Health Effects

The evaluation of health effects is made on the available toxicological data which does not discriminate between arsenic species and therefore this evaluation is not exclusive to arsenic acid and its inorganic salts. Diarsenic trioxide is a trivalent arsenic substance, diarsenic pentoxide and arsenic acid are pentavalent arsenic substances.

7.1 Toxicokinetics (Absorption, distribution, metabolism and excretion - ADME)

7.1.1 Human data

Arsenic absorption depends on its chemical form. The rate of absorption of arsenic in highly insoluble forms (e.g., 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 (~9 µg/L) of mother-infant pairs exposed to drinking water containing high levels of arsenic (~200 µg/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.

A simplified scheme of arsenic metabolism in many mammals, including humans, is shown in Figure 3 .

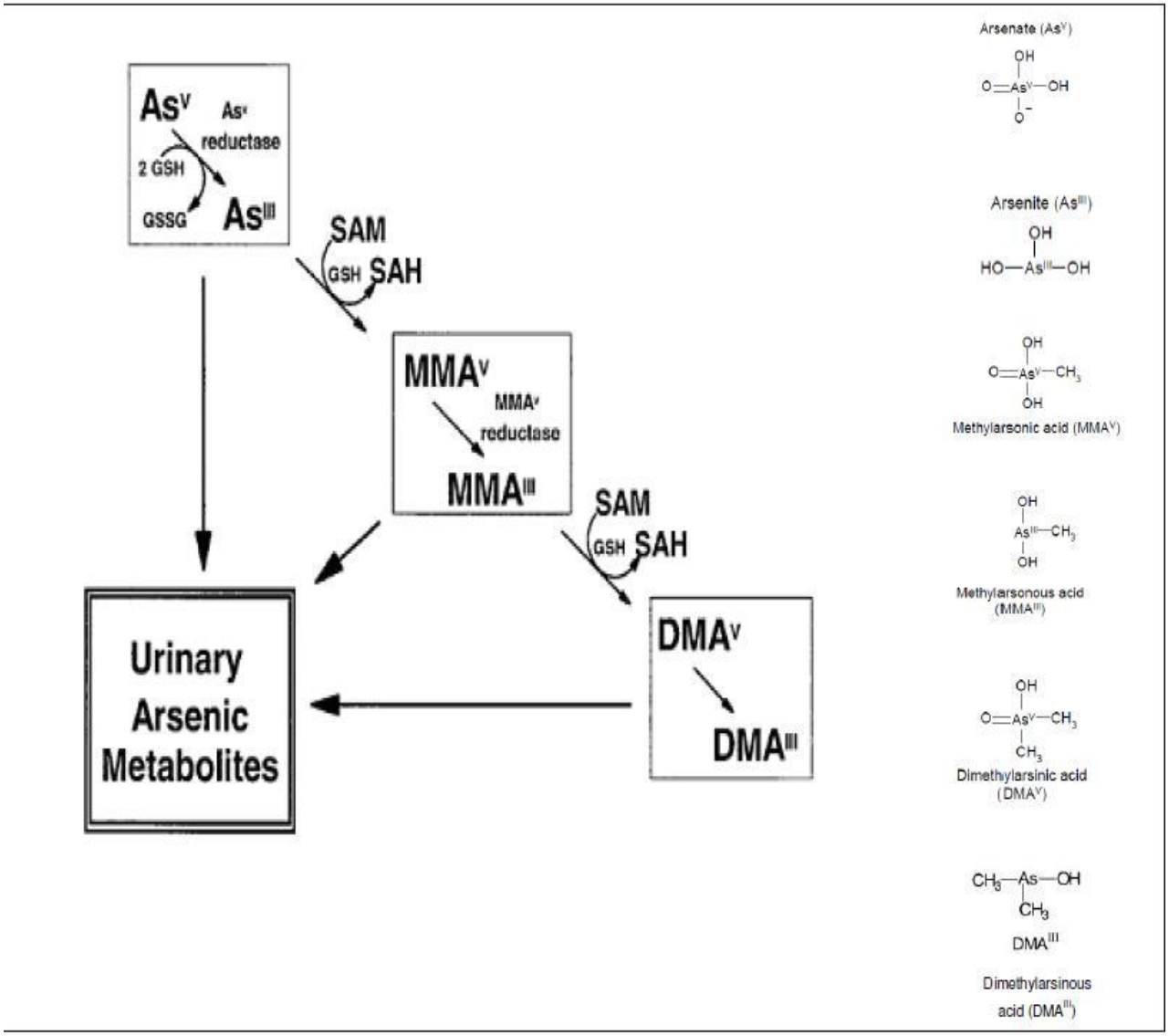

Figure 3: Metabolism of arsenic in the liver (DECOS, (2012))

Reduction from pentavalent to trivalent arsenic states may occur nonenzymatically via glutathione or enzymatically. Oxidation and methylation are coupled in arsenic metabolism with the trivalent arsenic form as substrate and a methylated pentavalent form as the product. As^{V}, As^{III}, monomethylarsonic acid (MMA^{V}) (humans excrete a relatively high amount of monomethylarsonic acid in their urine), monomethylarsonous acid (MMA^{III}), dimethylarsinic acid (DMA^{V}) (the major form in many mammals; 60-80% in humans), and dimethylarsinous acid (DMA^{III}) are found in human urine. In rats, some arsenic is further metabolised to a form with three methyl groups, TMAO. Some forms of arsenic can reversibly change valence state from pentavalent to trivalent and back again (e.g. arsenate ^ arsenite). SAM (S-adenosyl methionine): serves as the methyl donor; SAH (S-adenosylhomocysteine); GSH (glutathione reduced); GSSG (glutathione oxidised) ((Kitchin, 2001) and Tchounwou et al, 2003). There is a considerable variation in the methylation of inorganic arsenic among mammalian species. Compared to human subjects most experimental animals (mouse, rat, rabbit, hamster, dog) excrete very little MMA, while the methylation to DMA is more efficient than in humans. There is an overall higher excretion of arsenic in urine of experimental animals than in humans except for the rat since most of the produced DMA is retained in the erythrocytes. The chimpanzee and the marmoset monkey however lack the ability to methylate arsenic (EPER, 2012).

7.1.2 Animal data

Beck et al (2002) investigated the relationship between airborne arsenic exposures and systemic uptake in rabbits. New Zealand white rabbits were chosen as test animals because metabolism of arsenic in rabbits and humans is fairly similar, with the exception that humans excrete more monomethylarsonic acid than rabbits.

Hughes et al (2003) examined that the accumulation of arsenic in tissues after repeated oral administration of arsenate in mice was highest in bladder, kidney and skin.

Animal experiments (Stevens et al, 1977) support the trends of arsenic to cross the placenta which has been observed in humans (see Section 7.1.1).

7.1.3 In vitro data

An in vitro investigation using human skin indicated that absorption is likely to be relatively low compared with the oral and inhalation routes (Wester et al, 1993). After 24 h, 0.93% of a dose of (73As) as arsenic acid passed through the skin, with 0.98% remaining in the skin after washing. Absorption was lower when (73As) was mixed with soil.

7.1.4 Toxicokinetic modelling

EFSA (2009) reported in its Scientific Opinion on Arsenic in Food that several physiologically based models were developed to describe the absorption, distribution, metabolism, and elimination of arsenic in target organs.

Mann et al. (1996a; 1996b) extended an inorganic arsenic physiologically based pharmacokinetic (PBPK) model developed for hamsters and rabbits to humans. Their model described the pharmacokinetics of arsenite, arsenate, methylarsonate and dimethylarsinate. The routes of intake considered were inhalation of arsenic dust and fumes, and oral intake of arsenic via drinking water and food. The model consisted of lungs, blood (plasma and red blood cells), the liver, skin, kidneys and remaining tissues. Distribution of arsenic into tissues was described using a diffusion-limited model based on the fact that non-ionised compounds such as arsenite freely diffuse through the capillary membrane whereas ionised compounds such as arsenate, methylarsonate and dimethylarsinate diffuse only through the pores of the membranes. Partition coefficients were originally estimated from rabbit and hamster data and assumed to be the same for humans. Metabolic rates for reduction and methylation (V_{max} and K_m), in addition to oral absorption rate constants, were all optimised using data obtained from the cumulative excretion of arsenic and its metabolites in urine from human volunteers. The model gives satisfactory results for comparing the urinary excretion of arsenic metabolites under different exposure conditions, especially different routes of absorption and different oxidation states of the absorbed inorganic arsenic.

Yu (1999a; 1999b) developed a PBPK model for short-term oral exposure to inorganic arsenic in humans. The model described four circulating species (arsenite, arsenate, methylarsonate and dimethylarsinate) in various tissue groups and considered both reductive metabolism and methylation. Transport into tissues was modelled as a flow-limited process. Partition coefficients determined in the Yu model were based on a single study using a child poisoning case. Using this model, the input parameters that most significantly affected the output of the model were the maximum methylation reaction rate, the level of GSH for determination of the reaction rate of arsenate to arsenite, and the urinary excretion constants.

Recently, El-Masri and Kenyon (2008) published a model consisting of interconnected individual PBPK sub-models for arsenite, arsenate, methylarsonate, and dimethylarsinate in humans. Each submodel was constructed using flow-limited compartments describing the mass balance of the chemicals in the gastrointestinal (GI) tract, the lungs, liver, kidneys, muscles, skin, heart, and brain. The metabolism of inorganic arsenic in the liver was described as a series of reduction and oxidative methylation steps incorporating the

inhibitory influence of metabolites on methylation. The inhibitory effects of arsenite on the methylation of methylarsonite to dimethylarsinate, and methylarsonite on the methylation of arsenite to methylarsonate were modelled as non-competitive. To avoid the uncertainty inherent in the estimation of many parameters from limited human data, *a priori* independent parameter estimates were derived using data from diverse experimental systems including human cells and tissues.

Liao et al, (2009) refined the basic compartmental structure that was previously employed in PBPK models for arsenic exposure in humans, taking into account variations of physiological parameters such as blood flow rates, organ volumes and water elimination according to age.

7.1.5 Biological monitoring

There are several potential biomarkers for monitoring arsenic exposure in biological specimens such as blood, urine, hair and/or nails, but is most readily measured in urine.

According to DECOS (2012) and the German Research Foundation (DFG) (1995; 2002), the determination of arsenic in blood, hair and finger nails have not acquired any importance in the biomonitoring of occupationally exposed persons. This is mainly due to the existing analytical difficulties for carrying out chemical speciation for the different arsenic forms in blood, hair and finger nails, which hinder the distinction of the contributions of inorganic and organic arsenic intake sources. In addition, regarding blood, the biological half-life for both inorganic and organic arsenic is relatively short. This means that the blood concentration is only at an increased level for a short time after absorption. Therefore, blood arsenic analysis is only used as an indicator of very recent or relatively very high exposures. Hair and nails, although they offer advantages of being readily and non-invasively sampled, they are associated with additional limitations, such as risk of significant external contamination, lack of standardized sampling procedures and of relevant studies for the evaluation of threshold limit values.

There is wide agreement that urine biomarkers are the preferred approach and have been accepted as a convenient biomarker of dose by WHO-IPCS (2001). Key advantages over blood, hair and nails are the following:

- relative ease of sample collection,
- the majority of absorbed inorganic arsenic (iAs) is eliminated via urine, including various metabolites,
- availability of analytical techniques allowing arsenic speciation in urine.

The arsenic concentration in urine increases slowly and remains at a relatively constant level during the first three days of exposure. During the working day and from the end of work to the beginning of the next shift there are no notable changes in the concentration. The elimination kinetics show that during the working week, there is significant accumulation of arsenic and its metabolites. Sampling should therefore take place at the end of the working week(DFG, 1995; 2002).

In arsenic biomonitoring it is possible to measure:

- the total As (AsT), and
- the sum of inorganic arsenic compounds (iAs + DMA + MMA), including iAs 40 (arsenate + arsenite) and the methylated metabolites (DMA + MMA).
- As3+, As5+, DMA and MMA separately

Methods for the measurement of total arsenic (AsT) and iAs+MMA+DMA are described in Section 6.

Monitoring of total urinary arsenic (AsT) is not recommended since it results in data that include the non-toxic organic arsenic fraction mainly ingested from seafood. In

occupational biomonitoring, the most commonly used method is to measure the sum of arsenic species (iAs + DMA + MMA) of inorganic origin. However, the diet, especially seafood may significantly contribute especially to the levels of DMA in urine.

In persons not occupationally exposed to arsenic, the diet and drinking water are the main source of inorganic arsenic compounds (see Section 5.1). Food, with exception of seafood, generally contains less than 0.25 mg As/kg. The daily uptake with food is estimated to be between 0.04 (without fish) and 0.19 mg arsenic (with fish). The effect of the diet history on urinary arsenic species of inorganic origin (iAs + MMA + DMA) in the general populations in France and Germany is illustrated in Table 15.

Table 15: Effect of the diet history on urinary arsenic species of inorganic origin (iAs + MMA + DMA) in the general populations in France and Germany.

Country	Sum of inorganic arsenic and methylated metabolites (iAs + MMA + DMA) (µg/g creatinine); P95		
	Fish consumption ≤ once a month (P95/GM)	Fish consumption - once a week to twice a month (P95/GM)	Fish consumption -> once a week (P95/GM)
FRANCE (ENNS 2006–2007)a	5.38/2.66 [2.37–2.97]	8.28/3.39 [3.25–3.53]	8.93/3.76 [3.52–4.02]
GERMANY (GerES III, 1998) b	10.0/2.65 [2.49–2.82]	13.2/2.86 [2.72–3.02]	27.0/4.37 [4.02–4.74]

Notes: [a] Saoudi et al 2012; [b] Wilhelm et al 2004.

The frequency of fish consumption clearly causes substantially higher values of iAs + MMA + DMA, as illustrated in Table 15. This is due to a direct intake of MMA and DMA through diet, which does not represent an intake of toxic inorganic arsenic. For this reason, the intake of non-inorganic MMA and DMA must be excluded from sampling by appropriate procedures and protocols. This is achieved by prohibiting fish consumption during 48 hours before sampling. Only in this way, the sum of arsenic compounds of iAs + DMA + MMA, can be interpreted as a measure of the sum of inorganic arsenic intake to be further used in risk assessment. However, since even by this way, the potential confounding effect of dietary sources cannot to be fully excluded, recent research have concentrated to the development of more sensitive methods for the speciation of different arsenic species.

In population studies, the levels of inorganic As3+ and As5+ in urine have often remained in the majority of samples below the LODs, which has resulted in an inability to set a reference values for these individual species.

Regarding the composition of urinary arsenic species of inorganic origin in the general population, Heinrich-Ramm (2001) found in Germany: inorganic AsIII (11.9%), inorganic AsV (0.0%), DMA (88.1%), and MMA (0.0%) by applying anion exchange chromatographic species separation with on-line hydride-technique atomic absorption spectrometry. Pentavalent inorganic arsenic iAs(V) was not detected in non-occupationally exposed persons by this method.

Recently, Leese et al, (2014) published novel, sensitive µLC-ICP-MS based method for the speciation of different arsenic species, which is able to detect As3+ and As5+ levels as low levels as 0.02-0.04 µg/l (LOQ), respectively (Leese et al, 2014). On the basis of 95 samples, collected from working aged, occupationally non-exposed workers they were also able to establish a reference values for different arsenic species, including As3+ and As5+ in urine. These were 0.54 and 0.23 µg/l for As3+ and As5+, respectively.

WHO (2015) human biomonitoring reported that toxicologically relevant arsenic (TRA) species include arsenious acid (As[III]), arsenic acid (As[V]), monomethylarsonic acid

(MMA), dimethylarsinic acid (DMA) and trimethylarsine oxide (TMAO). Exposure to toxic arsenic species (through food, water or dust particles) is reflected in measurement of arsenic in urine, where DMA predominates (Šlejkovec et al., 2008). Therefore, the most common biomarker of exposure to inorganic arsenic is urinary DMA, and also MMA (Alyward et al., 2014). Blood levels of arsenic do not appear to be a reliable indicator of chronic exposure to low levels of arsenic, due to the fast clearance of arsenic in blood (ASTDR, 2007)., Arsenic is mostly present in non-toxic organic forms in fish and shell fish, which are much less harmful to humans than inorganic arsenic(Horvat, Šlejkovec and Falnoga, 2012). The ReV (reference value) for total arsenic in urine, according to the findings of the German HBM survey, is 15 µg/L for children and adults who did not eat fish during 48 hours prior to sample collection (Schulz et al., 2011).

Table 9. Summary of available HBM data on arsenic (toxicologically relevant species including inorganic arsenic and its metabolites)

Country	Study	Population (N)	Total arsenic			TRA species	Reference
			Blood (ng/mL)	Urine (µg/g creat.)	Urine (µg/L)	Urine (µg/g creat.)	
Belgium (Flanders)	FLEHS first survey (2007-2011)	Neonates (241)	0.54 GM 2.18 P90				Schoeters et al., 2012a
		Mothers 20–40 y.o. (235)	0.64 GM 2.04 P90	15.9 GM 71.4 P90		3.7 GM 10.7 P90	
		Adolescents 14–15 y.o. (207)	0.62 GM 2.12 P90	9.3 GM 49.0 P90		3.6 GM 8.0 P90	
Germany	GerES I (1985–1986)	Adults 25–69 y.o. (2542)			9.02 GM 37.5 P95		Kolossa-Gehring et al., 2012; Schulz et al., 2007b
	GerES II (1990–1992)	Adults 18–79 y.o. (4001)	0.5 GM 2.0 P95		6.33 GM 30.2 P95		
		Children 6–17 y.o. (731)	0.33 GM 1.4 P95		6.01 GM 27.5 P95		
	GerES III (1998)	Adults 18–69 y.o. (4052)	0.61 GM 2.4 P95		3.87 GM 19.3 P95		
	GerES IV (2003–2006)	Children 3–14 y.o. (1734)	0.23 GM 0.3 P90		4.4 GM 11.0 P90		
France	ENNS (2006–2007)	Adults 18–74 y.o. (1515)		11.96 GM 61.29 P95		3.34 GM 8.9 P95	Frery et al., 2012
Italy	PROBE (2008–2010)	Adolescents 13–15 y.o. (252)	0.82 GM 3.69 P95				Pino et al., 2012
Slovenia	Pilot HBM (2007–2009)	Adults 20–40 y.o. (274)	0.74 GM 2.98 P95				Snoj Tratnik, Mazej & Horvat, 2012

Figure 4: Table 9 Summary of Human Biomonitoring data (WHO, 2015)

As regards occupational monitoring, studies of small groups of metal and sulphuric acid smelter workers with varying industrial hygiene conditions have reported urinary inorganic arsenic levels ranging as high as several hundreds of µg/L during or after work exposure (Jakubowski et al,1998; Offergelt et al, 1992; Vahter et al, 1986; WHO, 2001) As explained above, sampling should take place at the end of the working week (Commission, 2003).

A survey of occupational exposure (Cocker et al, 2006) to copper chrome arsenic (CCA) based wood preservatives during vacuum pressure timber impregnation, involved

biological monitoring based on analysis of chromium and arsenic in urine samples collected from UK workers; see section 5.3.4 for further details of study..

At European level, a value representing the background exposure to inorganic arsenic in the general population could be used as a basis for setting a BGV. Since dietary sources, especially seafood may have a significant impact on total MMA and DMA levels, speciation of arsenic species and separate determination of As3+ and As5+ would be the preferred method for assessing occupational exposure. However, due to the limited database no BGV for As3+ and As5+ can be currently set.

To this end, the following reference values for inorganic arsenic in urine of the general population are available from Germany, France and the UK:

a) Germany: the data were derived by the German Environmental Survey 1998 (GerES III) (Becker et al, 2003), which included a total of 4822 persons aged between 18 and 69 years from 120 localities. The study took into account parameters such as gender, age, community size and place of residence (West- or East-Germany) as well as the frequency of fish consumption. This survey comprised three main instruments of investigation. First, human biomonitoring was done on blood and urine samples to determine levels of internal exposure. Second, the contribution of the domestic environment to exposure was assessed by analysing domestic tap water and house dust. Finally, information on exposure conditions was collected by way of questionnaire-based interviews; questions related to, inter alia, food selection. Characteristics of the frequency distribution (percentiles) including 50th percentile (median) were calculated for the weighted data of the compound. In addition, the geometric means, their confidence intervals, and the arithmetic means were calculated. The study results are given related to both volume of urine (in µg/L) and amount of creatinine (µg/g).

Overall, the value of 15 µg/L (no fish consumption within 2 days before sampling; P95) was recommended as a reference value representative for the German adult population and is only valid if a consumption of fish or seafood during the last 48 hours before sample collection is excluded (Wilhelm et al, 2004). When comparing the results of this survey with the previous one (GerES II, 1990/92), it becomes obvious that the mean concentrations of arsenic have decreased considerably for the 25 to 69 year old population (in 1990/92 mean values were 6.3 µg/L while in 1998 they were 3.9 µg/L).

The DFG has estimated that an 8 h TWA exposure to 0.01 mg/m3 results in urinary arsenic levels (sum of As3+, As5+, MMA and DMA) of 50 µg/L, 0.05 mg/m3 in 90 µg/L and 0.1 mg/m3 in 130 µg/L.

b) France: the data were obtained by the French National Nutrition and Health Study (ENNS) which was carried out between 2006 and 2007 and involved adults aged 18 – 74 years (in total 5217 participants). The study took into account, among other parameters, fish/seafood consumption (the participants were asked to avoid this kind of food 3 days preceding urine collection). Results were presented as geometric means and selected percentiles of urinary arsenic concentrations (µg/L) and creatinine-adjusted urinary arsenic (µg/g creatinine) for the sum of inorganic arsenic and metabolites (iAs + MMA + DMA). The study resulted in setting up for the French adult population, a reference value of 10 µg/g creatinine (no fish consumption within 3 days before sampling; P95) Saoudi et al, 2012).

Data are also available from the USA (CDF, 2013; Caldwell et al, 2009) . The levels of total and speciated urinary arsenic were examined in the urine of 2557 participants of the 2003 - 2004 National Health and Nutrition Examination Survey (NHANES). Data were compiled as geometric means (GM) and selected percentiles of urinary arsenic concentrations (µg/L) and creatinine-corrected (µg/g creatinine) for total arsenic (AsT), dimethylarsinic acid, arsenobetaine, and a sum of the inorganic related species. The 95th percentile for the sum of inorganic arsenic species (iAs + MMA + DMA) was 19.4 µg/L. However, the dietary history was not specified and this value cannot be directly compared with the European data. Therefore, for the setting of BGV for the sum of iAs

and MMA and DMA, the data from France (95th percentile of 8.9 µg/l) and from Belgium (90th percentile of 10.7 µg/l in 20-40 y o mothers) is preferred, and a BGV of 10 µg/l is proposed.

c) UK: More recently the UK HSL (Leese et al, 2014) has determined 95th percentiles for AS3+ and As5+ species among 95 volunteers (42 females, 53 males) and they are 0.54 µg As/l urine (end of a working week) for As3+ and 0.23 µg As/l urine (end of a working week) for As5+. In this study, 95th percentile for combined iAs+MMA+DMA was 15.1 µg/l.

7.2 Acute toxicity

7.2.1 Human data

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, 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 to 3 mg As/kg bw/day(Armstrong et al, 1984; JW, 1904; Vallee, 1960).

7.2.2 Animal data

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 ≥100 mg/m^3 (76 mg As/m^3). In another study (Gaines, 1960), the acute dermal LD_{50} for the pentavalent arsenicals calcium arsenate and lead arsenate in the rat was ≥2400 mg/kg bw (≥400 mg As/kg bw).

Table 16: LD50 values of different arsenic species in various experimental animal species

Chemical	Species (sex)	Route	LD50 (mg/kg bw as arsenic)	Reference
Arsenic trioxide	Mouse (m)	Oral	26	Kaise, Watanabe & Itoh (1985)
Arsenic trioxide	Mouse (m)	Oral	26-48	Harrison, Packman & Abbott (1958)

Chemical	Species (sex)	Route	LD50 (mg/kg bw as arsenic)	Reference
Arsenic trioxide	Rat (m/f)	Oral	15	Harrison, Packman & Abbott (1958)
Arsenite	Mouse (m)	Intramuscular	8	Bencko et al. (1978)
Arsenite	Hamster (m)	Intraperitoneal	8	Petrick et al. (2001)
Arsenite	Mouse (m)	Intramuscular	22	Bencko et al. (1978)
MMA^{III}	Hamster (m)	Intraperitoneal	2	Petrick et al. (2001)
MMA^{V}	Mouse (m)		916	Kaise, Watanabe & Itoh (1985)
DMA^{V}	Mouse (m)		648	Kaise, Watanabe & Itoh (1985)
TMAO	Mouse (m)		10600	Kaise et al. (1989)
AB	Mouse (m)		>10000	Kaise, Watanabe & Itoh (1985)

otes: f, female; LD50, median lethal dose; m, male

7.2.3 In vitro data

Although inorganic arsenic is more toxic than its major metabolites MMAV and DMAV and other organic arsenic, MMAIII was found to be more cytotoxic than inorganic arsenite in Chang human hepatocytes (WHO 2011: Petrick et al., 2000). In several cell lines, MMAIII was more cytotoxic than inorganic AsIII, whereas DMAIII was at least as toxic as inorganic AsIII for most of the cell types examined, but the pentavalent arsenicals were significantly less cytotoxic (Styblo et al., 1999, 2000). These results show the following order of toxicity: MMAIII > DMAIII ≈ AsIII > AsV > MMAV > DMAV.

7.2.4 Summary

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. It is acutely toxic to humans with ingestion of large doses leading to various adverse effects and eventually death. Generally, trivalent arsenic is more toxic than the pentavalent forms.

7.3 Specific target organ toxicity/Repeated dose toxicity

7.3.1 Human data

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 a,l (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 (35 µg/l; inorganic As plus methylated metabolites in urine) generates neuropathic disorders in the peripheral nervous system.

7.3.2 Animal data

The effects of sodium arsenite fed ad libitum to dogs were examined by Neiger and Osweiler (GD, NRO, 1989). There was a dose-dependent decrease in feed consumption and body weight of the dogs. Weight loss in pair-fed animals was not different from treated animals, so the loss of body weight in the treated animals was not due to sodium arsenite exposure. Two serum enzymes were elevated in dogs examined at the study termination, suggesting arsenite-induced hepatotoxicity. However, no lesions in the liver were observed after gross or light-microscopic examination.

Minor histological alterations in kidney and liver were observed in rats exposed to sodium arsenate (50 µg As/ml) for 320 days in drinking-water (Carmignani et al, 1983). These alterations were characterised by focal changes in the glomerulus and tubules of the kidney, and swollen hepatocytes localised near the centrilobular vein.

There is no recent information on long-term dermal toxicology studies of inorganic arsenic in laboratory animals (WHO, 2001).

Respiratory symptoms were observed in a study of developmental effects in rats. Pregnant female rats exposed to arsenic trioxide dust starting 14 days prior to mating and continuing through mating and gestation exhibited rales at 8 mg As/m3 and laboured breathing and gasping at 20 mg As/m3, with no symptoms at 2 mg As/m3 (Holson et al. 1999). The lungs were examined by gross necropsy and no lesions were found. Intratracheal instillation of arsenic trioxide (13 mg As/kg) or gallium arsenide (1.5– 52 mg As/kg) can cause marked irritation and hyperplasia in the lungs of rats and hamsters (Goering et al, 1988; Ohyama et al, 1988; Webb et al, 1986, 1987). Since this sort of response is produced by a number of respirable particulate materials, it is likely that the inflammatory response is not specifically due to the arsenic. (US-EPA, 2007).

7.3.3 Summary

The major effects of subacute oral exposure are gastrointestinal, haematological cardiovascular, respiratory, effects on the reproductive and nervous systems and dermal (such as skin lesions including hyperkeratinisation and hyperpigmentation of the skin). Chronic lung disease, peripheral neuropathy, hepatomegaly and peripheral vascular disease have frequently been reported in cases of chronic exposure to arsenic.

Effects have been seen in animal studies, although no recent studies are available.

7.4 Irritancy and corrosivity

7.4.1 Human data

Goncalo et al,](1980) reported arsenite-induced irritative contact dermatitis after occupational exposure. Barbaud et al, (1995) reported on the contact hypersensitivity of arsenic in a crystal factory employee based on the patch with arsenate. Several studies of humans exposed to arsenic dusts in the workplace have reported that inorganic arsenic (usually arsenic trioxide) can cause contact dermatitis (Holmqvist, 1951; Pinto and McGill, 1953). Typical responses included erythema and swelling, with papules and vesicles in more severe cases (Holmqvist, 1951). The dermal contact rates that cause these effects in humans have not been quantified.

Inhaled inorganic arsenic dusts containing arsenic trioxide were irritating to the nose, throat, lungs and were reported to lead to bronchitis and rhinitis (LG, 1921; Lundgren et al, 1951; Morton et al, 1989; Pinto et al, 1953). .

Some studies indicate local irritation and dermatitis. Usually the effects (erythema and swelling) were mild but they may progress to papules, vesicles or necrotic lesions in extreme cases(Holmqvist, 1951). There was complete recovery even without treatment when exposure ceased. Such effects have only been observed at workplaces with high levels of arsenic dusts (Pinto et al, 1953; Holmqvist, 1951); not in persons exposed to arsenic in water or soil.

Mohamed (1998) evaluated 11 male workers at a tin smelting factory where arsenic trioxide levels ranged from 5.2 to 14.4 mg/m3. The workers experienced symptoms of generalized itch, dry and hyperpigmented skin, folliculitis, and superficial ulcerations. The authors concluded that arsenic-containing dust collected on the sweat on the workers' skin, causing contact dermatitis.

Local effects on the eyes are often characterised by conjunctivitis, often in combination with facial dermatitis [82], [86] (LG, 1921; Pinto et al, 1953) .

7.4.2 Animal data

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).

7.4.3 Summary

Exposure to arsenic dusts causes irritation to the respiratory system and dermal contact can cause irritation and dermatitis.

7.5 Sensitisation

7.5.1 Human data

Examination of workers exposed to arsenic trioxide dusts in a copper smelter led Holmqvist (1951) to suspect that repeated dermal contact could lead to dermal sensitization. In support of this, Holmqvist (1951) found a positive patch test in 80% of the exposed workers compared to 30% in a control population. These data do suggest that workers may be sensitized to arsenic, but the high response rate in controls seems unusual. A much lower response rate (0.5%) was noted in another patch test study of dermal sensitization (Wahlberg and Boman 1986), and the few positive responses seemed to be due to a cross-reactivity with nickel.

7.5.2 Animal data

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.

7.5.3 Summary

There are some limited data suggesting dermal sensitisation in humans. LLNA with chromated copper arsenate (CCA) showed positive responses, but these cannot be attributed specifically to arsenic. Sodium arsenite and sodium arsenate were not allergenic in the guinea-pig maximisation test.

7.6 Genotoxicity

7.6.1 Human data

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.

7.6.2 Animal data

In one in vivo study (Poddar et al, 2000), sodium arsenite (2.5 mg/kg bw) produced significantly high frequencies of chromosome aberrations in bone marrow cells in mice after 24 h exposure. Similarly, in laboratory animals exposed to sodium and potassium arsenate and to Fowler's solution (arsenic oxide dissolved in potassium carbonate) at doses of 10 mg/kg, the increased frequency of micronuclei (MN) in bone marrow was observed(Tinwell et al, 1991).

In the study of Navarro et al(2004), female CD-1 mice were ip injected with different doses of sodium arsenite every 2 days for a total 7 injections over 14 days. Super-ovulation was induced by injections of equine and human chorionic gonadotrophins overlapping the end of the arsenite treatment. Metaphase II oocytes from these arsenite-treated mice had increased meiotic aberrations. Additionally, zygotes from arsenite-treated mice showed lower rates of cleavage, decreased morula formation and decreased development of blastocysts. More apoptotic nuclei were seen in the blastocysts of arsenite-treated mice. Some of these effects of arsenic on oocytes were observed at 8 mg/kg b.w., a previously established maternal NOAEL.

7.6.3 In vitro data

Inorganic arsenic did not induce point mutations in bacteria or in mammalian cells. However, arsenic can produce chromosomal aberrations in vitro, affect methylation and repair of DNA, induce cell proliferation, transform cells and promote tumours. A significant increase in the number of micronuclei, chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells after exposure to DMA and MMA were observed (WHO-IPCS, 2011/ATSDR, 2007).

In vitro studies with human lymphocytes and fibroblasts showed genotoxic effects of arsenic such as: nicking (unwinding) of DNA, double-stranded DNA breaks, induction of alkaline labile sites, sister chromatid exchanges (SCEs), oxidative damage and

interference with formation and repair of DNA adducts. Methylated trivalent arsenicals were more potent DNA damaging compounds than the other arsenicals (WHO-IPCS, 2011/ATSDR, 2007).

Arsenic was able to induce recombination processes in human peripheral blood lymphocytes (PBL) cultures with a dose-dependent augmentation(WHO, 1996).

Other effects of arsenic on PBL were shown by means of comet assay; particularly sodium arsenite, MMA and DMA induced weak DNA damage(GD, NRO, 1989). In another study, PBL was treated with six arsenic compounds (As3, As5, MMA3, MMA5, DMA5, and TMAO5)(Carmignani et al, 1983). All arsenic metabolites induced micronuclei (MN), except DMA5. MMAs3 showed the highest genotoxic effect, and fluorescence in situ hybridization analysis (FISH) revealed that the MN induction was due to an aneuploidogenic mechanism (Carmignani et al, 1983). The different effects induced by different arsenic compounds in PBL were also showed by Mass et al (2001) . With respect to pentavalent arsenic derivates, trivalent ones produced significant concentration-related increases in DNA damage as shown by the 'comet' tail moment.

In another study(Barrett et al, 1989), in the culture of embryonic cells of Syrian hamster, the frequency of chromosome aberrations (CA) and SCEs was increased in the presence of sodium arsenate and arsenite.

According to Yamanaka et a,l (1989), high concentrations of DMAA (dimethylarsinic acid) (about 1500 mg/kg) induced single DNA breakage in lung cells of male ICR mice.

7.6.4 Summary

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).

7.7 Carcinogenicity

7.7.1 Human data

Studies of populations occupationally exposed (primarily by inhalation) to arsenic, such as smelter workers, pesticide manufacturers and miners in many countries, consistently demonstrated an excess lung cancer risk among the arsenic-exposed. Although all these groups were also exposed to other chemicals in addition to arsenic, it is unlikely that some other factor could explain the findings.

Sufficient quantitative information from human studies on the levels of occupational exposure to ensure reliable assessment of the exposure-response relationship was available for three copper smelter cohorts: Tacoma (USA), Anaconda (USA) and Rönnskär (Sweden).

Regarding the Tacoma copper smelter, the vital status of 2802 men who worked at the smelter for a year or more during the period 1940-1964 was followed for the period 1941-1986, exposure assessment was extended to 1984, the time the smelter closed. The vital status was determined for 98.5% of the cohort, and of the 1583 deaths, deaths certificates were obtained for 96.6%. Exposure to arsenic was estimated from departmental measurements of arsenic in air from the annual report, available since 1938, and from measurements of urinary arsenic since 1948. Before 1971, the airborne arsenic concentrations came from surface sampling, thereafter from personal air sampling. These data were combined to allow for an analysis of the relation between the

concentrations of arsenic in air and various cancers. The conversion of data of urinary arsenic to airborne arsenic was made by the identification of departments and years for which data from both air and urinary arsenic were available and by the determination of the mathematical relation between the two. An increase in lung cancer risk related to cumulative arsenic exposure was observed. The lung cancer standard mortality ratio (SMR) was 188 in the group with <20 years after the first exposure and 217 among those with >20 years since first exposure, indicating a rather short latency period. An earlier publication (Tinwell et al, 1991) contained data on actual daily exposure concentrations, duration of exposure and the risk of lung cancer. In this study, an arsenic exposure category of <400 µg/m^3 (mean 213 µg/m^3) was associated with a statistically significant SMR of 238.7 for copper smelter workers who were exposed to arsenic for 30 or more years.

An elevated risk of lung cancer among workers in the Anaconda copper smelter was originally reported by Lee and Fraumeni (1969). The study population of the latest cohort update(Lubin et al, 2000) consisted of 8,014 white males, who were employed for ≥ 12 months before 1957. Their vital status was followed from 1 January 1938 to 31 December 1987, a total of 4,930 (63%) were deceased, including 446 from respiratory cancer. The vital status at the end of the follow-up period was not known for 1175 workers (15%), and they were assumed to be alive at the end of the study period (except the 81 workers born before 1900 who were assumed to have died). Industrial hygiene data (702 measurements), collected between 1943 and 1958, were used to categorise each work site to an exposure category on a scale 1-10, and work areas were then grouped as representing 'light', 'medium' or 'heavy' exposure. Altogether 446 deaths from respiratory cancer (SMR 155, 95% CI 141-170) were observed. A trend of increasing risk with increasing estimated exposure was seen, the risk increased linearly with time of employment in each exposure category.

The elevated lung cancer incidence among workers of the Rönnskär smelter was originally reported in a population-based case-referent study in Störjan in 1978. Since then, studies using both cohort and case-referent approaches have been published(Jarup et al, 1989). The cohort consisted of 3916 male smelter workers, who had worked for at least 3 months at the smelter between 1928 and 1967. The vital status of all but 15 (0.4%) of them was verified. Mortality of different causes, as defined on death certificates, was compared to local rates. Reference rates were not available for the period before 1951, but the contribution of deaths during this period (89 out of a total of 1275, i.e. 7%) was minor. A positive dose-response relationship was found between cumulative arsenic exposure and lung cancer mortality with an overall SMR of 372 (95% CI 304-450) and a statistically significantly increased risk was observed even in the lowest exposure category, <0.25 (mg/m^3).

Several other investigations examined the correlation between arsenic exposure and probability of lung cancer, including the pesticides manufacture and application, miners and the vicinity of arsenic-emitting industries. However the results of these studies did not allow drawing the specific conclusions (DECOS, 2012).

Studies on exposure in drinking water (Guy, 2003; IARC, 2012) revealed increased risks of cancer in the skin, lungs, bladder and kidney, as well as other skin changes such as hyperkeratosis and pigmentation changes. The effects have been most thoroughly studied in Taiwan, but there is considerable evidence from studies on populations in other countries as well. Increased risks of lung and bladder cancer and of arsenic-associated skin lesions have been reported to be associated with arsenic exposure categories of ≤50 µg/L. Chronic arsenic exposure (via drinking water) in Taiwan has been shown to cause Blackfoot disease, a severe form of peripheral vascular disease which leads to gangrenous changes. This disease has not been documented in other parts of the world, and the findings in Taiwan may depend upon other contributing factors, including dietary, environmental (UV radiation) and genetic (polymorphism of certain enzymes, primarily methyltransferases) factors(Vahter et al, 1995; M, V, 1999).

However, there is good evidence from studies in several countries that arsenic exposure causes other forms of peripheral vascular disease(Guy, 2003). Conclusions on the causality of the relationships between oral arsenic exposure and other health effects are less clear-cut. The evidence is strongest for hypertension and cardiovascular disease, suggestive for diabetes and weak for cerebrovascular disease, long-term neurological effects, and cancer at sites other than lung, bladder, kidney and skin (DECOS, 2012).

WHO assigned a 'provisional guideline value' of 0.01 mg As/L drinking water (10 µg/L) on the basis of both the water treatment performance and analytical achievability. According to WHO, there remains uncertainty over the actual risks at low concentrations.

7.7.2 Animal data

Several animal carcinogenicity studies on arsenicals have been carried out. Limitations of these studies have been discussed by WHO/ATSDR(WHO-IPCS, 2001/ATSDR, 2007).

Smith and Coulahan (2002) investigated effects of mice exposure to arsenic via drinking water containing 500 µg AsV/L over 2 years and found increased incidence in tumours in the lung, liver, gastrointestinal tract and skin.

The arsenic exposure during the perinatal period in rodents was investigated(Waalkes et al, 2003; Waalkes et al, 20040. In these studies, female offspring exposed to arsenic in utero developed dose-related increases in lung adenocarcinoma, benign ovarian tumours and combined benign or malignant ovarian tumours. Females also developed arsenic dose-related uterine and oviduct preneoplasias after foetal arsenic exposure, while male offspring showed dose-related increases in incidence of liver adenoma or carcinoma and additionally dose-related increases in liver tumour multiplicity (tumours/mouse).

IARC (2012) reviewed studies reporting that oral administration of sodium arsenate and DMAV induced lung tumours in mice. The long-term administration of DMAA (Wei et al, 1999) and related arsenicals (Wanibuchi et al, 1999) also induced lung cancer in rats. Calcium arsenate induced lung tumours in hamster 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 arsenite during gestation induced lung, liver, ovary and adrenal tumours in the offspring in several studies, and in the uterus in one study. Therefore, early life transplacental and perinatal exposure to (sodium) arsenite appears to be a time of particular sensitivity in terms of carcinogenesis. Further, oral exposure to DMAV induced urinary bladder tumours in several studies in rats and among studies in mice, only one study showed negative results. Oral trimethylarsine induced liver tumours in rats. Chronic oral exposure to MMAV did not produce tumours in rats and 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.

7.7.3 Summary

Inorganic arsenic compounds produce lung tumours in both animals and humans, following inhalation, oral or parenteral exposures. Exposure to high levels of inorganic arsenic compounds in drinking water has been associated with skin, and urinary tract or bladder cancer or both in humans. Tumours at other sites including the adrenal glands, bladder and liver have also been reported in some animal studies.

Arsenic acid and its salts are classified as Carcinogen 1A under the Classification, Labelling and Packaging Regulation (EC) 1272/2008 (CLP), and 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).

7.8 Reproductive toxicity

7.8.1 Human data

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 (e.g. 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 ≥0.1 mg 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 the frequencies of spontaneous abortions, stillbirths and premature births significantly higher than in the control group(Ahmad et al, 2001).

7.8.2 Animal data

In experimental animals effects on fertility of inorganic arsenic via the inhalatory route were not reported, but exposure to inorganic arsenic (AsIII and AsV) via the oral and intraperitoneal route has shown significant effects on fertility (interference with spermatogenesis, degeneration of follicular cells).

Studies in animals also showed that arsenic caused reduced birth weight, a variety of foetal malformations (both skeletal and soft tissues) and increased foetal mortality. These effects 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.

In the study of Holson et al(1999), the toxic effects on reproduction were investigated in female rats after inhalation exposure to arsenic trioxide for six hours with arsenic concentrations of 0.1 to 20 mg/m^3 (14 days before mating to day 19 of gestation). At

arsenic concentrations of 8 mg/m^3 toxic effects (breathing noises, dry, red exudate around the nose, reduced body weight gains) were observed in dams. At concentrations of 20 mg/m^3 impairments in foetal development (early resorption of the foetuses) were found in addition to marked maternal toxicity.

Reproductive performance was not affected in female rats that received inhalation exposures to concentrations as high as 20 mg As/m^3 or gavage doses as high as 8 mg As/kg bw/day from 14 days prior to mating through gestation day 19. In none of the animal studies maternal toxicity can be unambiguously excluded. However, only the study by Hill et al (2008) administering arsenate to an inbred mouse strain supported the view that foetal malformations can develop in the absence of maternal toxicity. In this study, Hill et al evaluated the developmental toxicity of oral exposure of arsenate during gestation in an inbred mouse strain that does not exhibit spontaneous neural tube malformations. There was no maternal toxicity, as evidenced by losses in maternal body weight following arsenic treatment. However, liver weights were lower in all arsenic-treated groups, suggesting hepatotoxicity due to arsenic exposure. The number of litters affected with a neural tube defect (exencephaly) in each treatment group exhibited a positive linear trend (vertebral and calvarial abnormalities, components of the axial skeleton). Mean foetal weight of all arsenic-treated groups was significantly less than in control. This is the only study proving that foetal malformations can develop in absence of maternal toxicity.

Souza, A.C., et al (2016) reported that arsenic in the form of trivalent arsenite or pentavalent arsenate, is a ubiquitous toxic compound naturally occurring in the environment. This study aimed to evaluate the impact of two different forms of inorganic As on reproductive parameters following oral exposure. Adult Wistar male rats were exposed to *sodium arsenite or arsenate* at concentrations of 0.01 mg/L or 10 mg/L for 56 d in drinking water. Sodium arsenite at both concentrations and sodium arsenate at 10 mg/L produced reduction in daily sperm production, in number of spermatids in the testis, and in sperm in the epididymal caput/corpus regions. Changes in epididymal morphometry were variable and region specific. Total and progressive sperm motility and sperm morphology did not differ markedly between controls and animals exposed to As. The body and reproductive organs weights, as well as testosterone concentration, remained unchanged among all groups. In conclusion, As exposure in drinking water over 56 d produced damage in male reproductive functions in adult rats, suggesting that fertility problems might occur. Therefore, additional studies need to be undertaken to investigate potential mechanisms underlying sodium arsenite- and arsenate-induced disturbances in fertility and reproductive performance.

US-EPA reported that arsenic has been shown to produce developmental effects by inhalation exposure in laboratory animals, although it is unclear whether or not the effects occur only at maternally toxic doses. Mice exposed to 22 mg As/m3 (as As2O3) for 4 hours on days 9–12 of gestation had serious developmental effects (significant increases in the percentage of dead foetuses, skeletal malformations, and the number of foetuses with retarded growth), while those exposed to 2.2 mg As/m3 had only a 10% decrease in average fetal body weight, and those exposed to 0.20 mg As/m3 had no effects (Nagymajtényi et al, 1985). The study was limited by failure to quantify malformations on a litter basis, discuss the nature and severity of the observed malformations, or report on the occurrence of maternal effects. No increases in foetal resorptions, foetal mortality, or malformations, and no decreases in foetal body weight occurred when rats were exposed to 0.2–8 mg As/m3 (as As2O3), 6 hours daily from 14 days prior to mating through gestation day 19 (Holson et al, 1999). At the 8 mg/m3 exposure level, toxicity was observed in the dams, including rales, a dried red exudate at the nose, and lower gains in net body weight than controls. In a preliminary dose-range study, there was a marked significant increase in post-implantation loss (primarily early resorptions) and consequent marked significant decrease in viable foetuses per litter at 20 mg As/m3, a concentration that also produced severe maternal effects including mortality (Holson et al, 1999).

7.8.3 Summary

Recent epidemiological studies and retrospective studies on arsenic exposure from drinking water showed evidence of reproductive toxicity in humans. There is no evidence of effects of arsenic on fertility by inhalatory and/or oral exposure.

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.

7.9 Mode of action (MoA) considerations

7.9.1 Carcinogenicity MoA

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, i.e. 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 1.28 ug/m³. 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/m³. With regards to an estimated exposure of the general population via inhalation in the range of 30 ng/m³, 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.

7.10 Lack of specific scientific information

The cancer mode of action of arsenic and its inorganic compounds has not been established, but it appears not to be related to direct DNA reactive genotoxicity and therefore it is possible that the arsenic carcinogenicity has a threshold exposure level.

It is reported by EFSA (EFSA, 2009) that inorganic arsenic is not directly DNA-reactive and there are a number of proposed mechanisms of carcinogenicity such as oxidative damage, epigenetic effects and interference with DNA damage repair, for each of which a threshold mechanism could be postulated.

The available data (epidemiological and experimental studies) do not allow the identification of threshold exposure levels for key events in the modes of action proposed in the scientific literature and do not allow deriving a numerical threshold value (dose or concentration).

In the absence of new toxicological data or further exploration into the MOA, there are indications that the mechanisms by which inorganic arsenic induces cancers in humans are likely to be mediated by multiple modes of action. There is a lack of data showing what the threshold for these modes of action might be or what the shape of the dose-response curves at low levels of exposure might be.

Therefore it is still prudent to assume a linear dose-response relationship at low doses based on currently available data and carcinogenicity is the critical endpoint and cancer risk assessments have been made (see section 8). It is however acknowledged that for low level environmental exposures the risk estimates derived linearly from the proposed unit risk should be considered as likely to overestimate significantly the real cancer risks.

8. Cancer Risk Assessment

8.1 RAC Reference Dose Response Relationship

See Appendix 1 for full report.

Carcinogenicity

A review was performed of the carcinogenic dose responses of three inorganic arsenic compounds (diarsenic pentoxide, diarsenic trioxide and arsenic acid). Diarsenic trioxide is a trivalent arsenic substance, diarsenic pentoxide and arsenic acid are pentavalent arsenic substances. Arsenic compounds produce lung tumours in both animals and humans, following inhalation, oral or parenteral exposures. Exposure to high levels of arsenic compounds in drinking water has been associated with skin and urinary tract / bladder cancer in humans. Tumours at sites including the adrenal glands, bladder and liver have also been reported in some studies in animals.

The cancer mode of action of arsenic and its inorganic compounds has not been established, but it appears not to be related to direct DNA reactive genotoxicity and therefore it is possible that the arsenic carcinogenicity has a threshold exposure level. However, the available data do not allow the identification of threshold exposure levels for key events in the modes of action proposed in the scientific literature.

Dose response relationships were derived by linear extrapolation. 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.

Carcinogenicity risk assessment

Inhalation exposure (workers)

All of the quantitative cancer risk assessments of inorganic arsenic compounds in the available literature used the same data sets based on death certificates of exposed workers from the Tacoma (USA), Anaconda (USA) and Rönnskar (Sweden) smelting plants.

The risk of lung cancer might be reduced if the particle size of the material in air is such that a proportion cannot enter the lower respiratory tract. However, given the increased lung cancer risk from oral exposures to arsenic (see below), it seems reasonable to associate the risk estimates with all inhalable particles. The epidemiology studies contain insufficient information to discriminate between particle size and likely deposition in the respiratory tract.

Based on the DECOS (2012) risk estimates derived from an epidemiology study in the Anaconda copper smelter plant (as reported by Lubin et al., 2000), the following risk estimates were derived:

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)

Table 17: Excess lifetime (up to age 89) lung cancer risk estimates for workers exposed at different 8h-TWA concentrations of inorganic As (inhalable particulate fraction) for 40 years

Inorganic Arsenic exposure concentration –inhalable fraction (µg/m^3)	Excess lung cancer risk in EU workers (x10-^{3})
10	1.4
5	0.71
2.5	0.36
1	0.14
0.5	0.07
0.25	0.036
0.1	0.014
0.01	0.0014

Dermal exposure

Although there is no evidence that dermal exposure to inorganic arsenic compounds has caused skin or other tumours in humans and dermal penetration of arsenic is likely to be low, RAC has established risk values also for systemic exposure via the skin. The epidemiology studies of the smelter plants included investigations of general health and tumours at a wide range of sites. Hence, it would be anticipated that, had there been any significant increases in skin tumours, these would have been noticed and recorded. No adequate studies investigating the carcinogenicity of inorganic arsenic compounds in experimental animals exposed via the dermal route are available.

For the assessment of systemic cancer risk following dermal exposure, RAC however considered it appropriate to extrapolate risks from the oral risk estimates Hence, dermal risk values are based on human epidemiology data WHO/FAO (2011) that derived a BMLD0.5 (3 µg As/kg/day), for the lung and bladder cancer mortality from the Taiwanese drinking water cohorts (Chen et al 2010a, 2010b). Linearity of the dose-response (further, see Appendix 1) and dermal absorption of 1% was assumed.

The following dose-relationship for the dermal exposure of general population was derived: based on a 70 year lifetime (52 weeks/year, 7 days /week) exposure:

An excess lifetime risk of lung tumours = 1.7 x 10^{-5} per µg As/kg bw/day

(as a dermal exposure)

The worker risk is calculated from risk established for the general population.

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)

8.2 SCOEL Carcinogenicity classification

According to the SCOEL Classification scheme[19] (see Appendix 2), 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 model may be used as a default assumption, based on the scientific uncertainty"* (see Bolt and Huici-Montagud, 2008) Available mechanistic data suggests a non-stochastic mechanism for the carcinogenicity of arsenic. Therefore, an occupational exposure limit could be derived in principle, but the epidemiological and experimental studies, which are available to date, do not allow deriving a numerical threshold value (dose or concentration). Thus, a linear extrapolation procedure is taken as a default.

8.3 DECOS cancer risk assessment

Arsenic was considered by DECOS(DECOS, 2012) to act as a non-stochastic carcinogen.

Since all the 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.

DECOS calculated occupational cancer risk values (HBC-OCRV), taking into consideration the major epidemiological studies on lung and respiratory cancer mortality among workers exposed to arsenic(Jarup et al, 1989; Enterline et al, 1995; Lubin et al, 2000; Lubin et al, 2008); (see Section 7.7.1).

Considering the quality of the publications and the fit of the models, DECOS decided to finally use the outcomes of the Lubin et al study (2000).

DECOS calculated that exposure to:

- 28 µg As/m3 for 40 years will result in 4 additional cancer death cases per 1,000 (4x10-3) deaths:
- 0.28 µg As/m3 for 40 years resulted in 4 additional cancer death cases per 100,000 (4x10-6) deaths.

It is noted that the above calculations are in line with the RAC cancer risk calculations.

8.4 Summary

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.

9. Groups at Extra Risk

DECOS (DECOS, 2012)reported that there were no studies located regarding unusual susceptibility of any human subpopulation to arsenic. However, since the degree of

[19] See Appendix 2 for SCOEL Classification of Carcinogens scheme

arsenic toxicity may be influenced by the rate and extent of its methylation in the liver (see Section 7.9), it seems likely that people may differ in susceptibility because of difference in methylating capacity and the existence of polymorphism has been hypothesised.

While there is some evidence that methylation capacity does vary among individuals (e.g., Buchet et al., 1980; Foa et al., 1984; Tam et al., 1982), the basis of this variation and its impact on human susceptibility have not been established.

Furthermore, smokers may be more susceptible as according to Hertz-Picciotto (1993) arsenic and smoking act in a synergistic manner to produce lung cancer.

EFSA (EFSA, 2009) reported that consumer groups with higher exposure levels include high consumers of rice, such as certain ethnic groups and high consumers of algae-based products.

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Appendix 1. RAC Reference Dose Response Relationship for Carcinogenicity of Inorganic Arsenic Compounds[20]

Table 18: Inorganic arsenic substances included in Annex XIV and the 4th recommendation for inclusion in the authorisation list

Substance name	EC Number	Intrinsic properties specified in Annex XIV/recommendation
Diarsenic pentoxide	215-116-9	Carcinogenic cat 1A
Diarsenic trioxide	215-481-4	Carcinogenic cat 1A
Arsenic acid	231-901-9	Carcinogenic cat 1A

Relevance of endpoints

For applicants applying for authorisation under Article 60(2) (adequate control route), in order to conclude whether the adequate control is demonstrated, only endpoints (i.e. properties of concern) for which the substance is included in Annex XIV need to be addressed in the hazard assessment[21]. However, information on other endpoints might be necessary for comparing the risks with the alternatives.

For applicants aiming at authorisation based on Article 60(4) (socio-economic analysis route) Article 62(4)(d) also applies and the socio-economic analysis (SEA) route will as a consequence focus on the risks that are related to the intrinsic properties specified in Annex XIV. The SEA should in turn consider the impacts related to such risks. In practice the applicant is expected to provide this information in their CSR for which an update may be advisable. However, for an authorisation to be granted, the applicant should also demonstrate that there are no suitable alternatives. In this latter analysis it may be the case that other endpoints than those for which the substance was listed in 'Annex XIV' become relevant in order to demonstrate that no suitable alternative is available.

Diarsenic pentoxide and diarsenic trioxide were included in Annex XIV due to their carcinogenic properties. Arsenic acid was included in the 4th recommendation for inclusion in Annex XIV.

Carcinogenicity

A review was performed of the carcinogenic dose responses of three inorganic arsenic compounds (diarsenic pentoxide, diarsenic trioxide and arsenic acid). Diarsenic trioxide is a trivalent arsenic substance, diarsenic pentoxide and arsenic acid are pentavalent arsenic substances. Arsenic compounds produce lung tumours in both animals and humans, following inhalation, oral or parenteral exposures. Exposure to high levels of arsenic compounds in drinking water has been associated with skin and urinary tract / bladder cancer in humans. Tumours at sites including the adrenal glands, bladder and liver have also been reported in some studies in animals.

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[20] RAC/27/2013/07 Rev. 1, agreed at RAC-27: https://echa.europa.eu/documents/10162/13579/rac_carcinogenicity_dose_response_as_en.pdf/57b6e1ba-51b6-4fbf-b9c5-ca3ba952dd9f

[21] Article 60(2) states "…an authorisation shall be granted if the risk to human health or the environment from the use of the substance arising from **intrinsic properties specified in Annex XIV** is adequately controlled."

The cancer mode of action of arsenic and its inorganic compounds has not been established, but it appears not to be related to direct DNA reactive genotoxicity and therefore it is possible that the arsenic carcinogenicity has a threshold exposure level. However, the available data do not allow the identification of threshold exposure levels for key events in the modes of action proposed in the scientific literature.

Dose response relationships were derived by linear extrapolation. 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.

Bioavailability

Carcinogenic potency of the three arsenic compounds following oral exposures to their solid form is expected to be similar because solubility will not be a limiting factor for human exposure levels[22].

Samples taken from the atmospheres associated with the epidemiology studies do not provide detailed information on the particle sizes contained in the atmospheres. With the systemic nature of arsenic-associated lung carcinogenicity, it is unclear whether particle size is a critical element in inhalation risks as larger particles that are deposited in the upper respiratory tract are cleared by the mucociliary escalator and swallowed present a risk of lung cancer via systemic exposure.

Dermal absorption of inorganic arsenic compounds is reported to be low (<1% – 6). However this has not been thoroughly investigated and the impact of the extensive liver metabolism (first pass-effect) on dermal risk assessment is unclear.

Data on the speciation of arsenic under different exposure conditions are inadequate to permit any differentiation, therefore the risk assessments below are considered to apply to all forms of inorganic arsenic, in the absence of data to the contrary.

Carcinogenicity risk assessment

Inhalation exposure

All of the quantitative cancer risk assessments of inorganic arsenic compounds in the available literature used the same data sets based on death certificates of exposed workers from the Tacoma (USA), Anaconda (USA) and Rönnskar (Sweden) smelting plants.

The risk of lung cancer might be reduced if the particle size of the material in air is such that a proportion cannot enter the lower respiratory tract. However, given the increased lung cancer risk from oral exposures to arsenic (see below), it seems reasonable to associate the risk estimates with all inhalable particles. The epidemiology studies contain insufficient information to discriminate between particle size and likely deposition in the respiratory tract.

Based on the DECOS (2012) risk estimates derived from an epidemiology study in the Anaconda copper smelter plant (as reported by Lubin et al., 2000), the following risk estimates were derived:

Workers

Based on a 40 year working life (8 h/day, 5 days/week):

[22] The solubility of diarsenic trioxide and diarsenic pentoxide are 1.2-3.7 and 65.8 g/100 ml at 20oC, respectively. Arsenic acid is highly soluble in water.

An excess lifetime lung cancer mortality risk = 1.4 x 10^{-4} per µg As/m^3

(derived for the inhalable particulate fraction)

Table 19: Excess lifetime (up to age 89) lung cancer risk estimates for workers exposed at different 8h-TWA concentrations of inorganic As (inhalable particulate fraction) for 40 years

Inorganic Arsenic exposure concentration –inhalable fraction (µg/m^3)	Excess lung cancer risk in EU workers (x10^{-3})
10	1.4
5	0.71
2.5	0.36
1	0.14
0.5	0.07
0.25	0.036
0.1	0.014
0.01	0.0014

General population

Based on an exposure for 70 years (24 h/day every day) and an 89 year life expectancy and extrapolating from the occupational excess risks given in the analyses by DECOS (2012) above the following risk estimates were derived:

An excess lifetime lung cancer mortality risk = 1.0 x 10^{-3} per µg As/m^3

(derived for the inhalable particulate fraction)

Table 20: Excess lifetime lung cancer risk estimates for the general population exposed at different ambient concentrations of As (respirable particulate fraction) for 70 years

Ambient As exposure concentration – inhalable fraction (µg/m^3)	Excess lung cancer risk in the general population (x10-^{3})
10	11
5	5.5
2.5	2.7
1	1.1
0.5	0.55
0.25	0.27
0.1	0.11
0.01	0.01
0.001	0.001
0.0001	0.0001

Dermal exposure

There is no evidence that dermal exposure to inorganic arsenic compounds has caused skin or other tumours in humans. The epidemiology studies of the smelter plants included investigations of general health and tumours at a wide range of sites. Hence, it would be anticipated that, had there been any significant increases in skin tumours, these would have been noticed and recorded. No adequate studies investigating the carcinogenicity of inorganic arsenic compounds in experimental animals exposed via the dermal route are available.

For a dermal assessment of systemic cancer risk it is considered appropriate to extrapolate from the oral risk estimates below.

The following dose-relationship for the dermal route was derived:

Starting point for the assessment: $BMDL_{0.5}$ = 3 µg As/kg/day (0.5% excess risk of cancer)

Excess lifetime risk of lung tumours = 1.7 x 10^{-5} per µg As/kg bw/day

(as a dermal exposure)

For further details on the assessment see 'Oral exposure (general population)' below.

Table 21: Cancer risk estimates for the general population exposed to different dermal daily doses of inorganic arsenic compounds, for an average follow-up period of 11.5 years

Daily dermal exposure of As (µg/kg bw/day)	Excess lung cancer risk (x10^{-5}) (assuming 100% oral absorption and 1% dermal absorption)
10	17
5	8
2.5	4
1	1.7
0.5	0.8
0.25	0.4
0.1	0.17
0.01	0.017

Oral exposure (general population)

Based on human epidemiology data WHO/FAO (2011) derived a $BMLD_{0.5}$, by applying a number of models to lung and bladder cancer mortality data from the Taiwanese drinking water cohorts, using data from the most recent publications of Chen et al (2010a, 2010b). The four models with a good fit to the data were gamma, log-logistic, multistage and quantal linear. The $BMLD_{0.5}$ does not describe the shape of the dose response curve, but because a quantal linear model has a good fit to the data, a linear dose response relationship can be assumed.

The WHO/FAO risk estimates for the oral route are recommended over the other published cancer risk estimates for several reasons. The assessment was well described and used a variety models to find the best fit to the data from a number of studies, in order to find the most conservative cancer risk estimates using the defined approach. This assessment used the most up-to-date data from the Taiwanese drinking water cohort. Although this does not produce the greatest excess risk per unit exposure, it is

considered to be the most robust assessment for oral arsenic exposure available at the present time.

The following relationship for the oral route, which assumes linearity, was derived:

Starting point for the assessment: $BMDL_{0.5}$ = 3 µg As/kg/day (0.5% excess risk of cancer)

Excess lifetime risk of lung tumours = 1.7 x 10^{-3} per µg As/kg bw/day

(as a systemic exposure)

Because there are inadequate data to support a threshold value for cancers associated with oral exposure, the dose response relationship can be regarded as linear and therefore, the oral exposure level associated with any chosen risk level can be calculated by simple arithmetic, as shown in the table below.

Table 22: Cancer risk estimates for the general population exposed to different oral daily doses of inorganic arsenic compounds, for an average follow-up period of 11.5 years

Constant average oral daily dose of As (µg/kg bw/day)	Excess lung cancer risk in the general population (x10^{-3})
10	17
5	8
2.5	4
1	1.7
0.5	0.8
0.25	0.4
0.1	0.17
0.01	0.017

References

Chen CL, Chiou HY, Hsu LI et al. (2010a). Arsenic in drinking water and risk of urinary tract cancer: a follow-up study from northeastern Taiwan. *Cancer Epidemiology, Biomarkers & Prevention* **19(1)**: 101–110.

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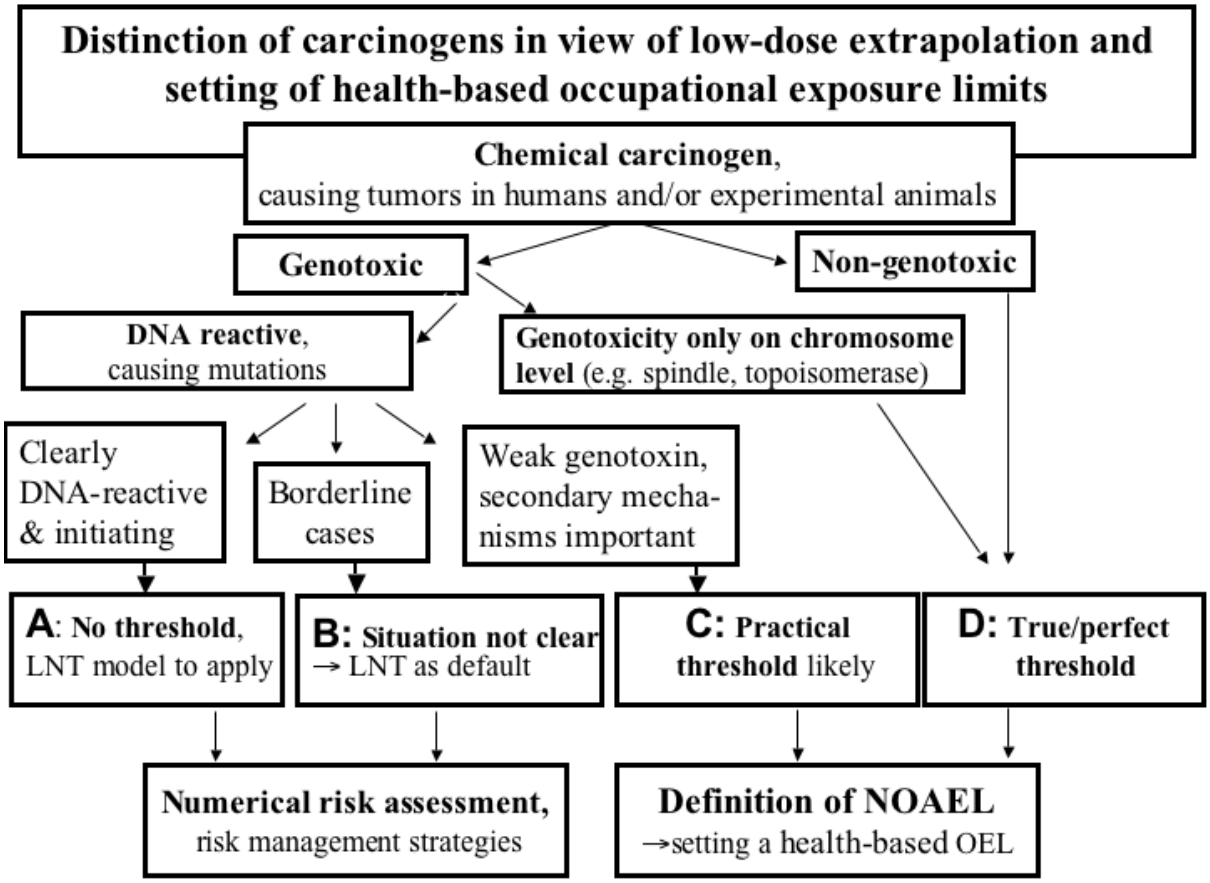
Lubin JH, Pottern LM, Stone BJ, Fraumeni JF, Jr (2000). Respiratory cancer in a cohort of copper smelter workers: results from more than 50 years of follow-up. *American Journal of Epidemiology* **151(6)**: 554-565.

WHO/FAO (2011) WHO food additives series 63, FAO JECFA monographs 8. Safety evaluation of certain contaminants in food / prepared by the Seventy-second meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Arsenic (addendum).

Appendix 2. SCOEL classification of carcinogens

Taken from current SCOEL 'Methodology for the Derivation of Occupational Exposure Limits' (SCOEL, 2013; version 7[23]),



Group A: Non-threshold genotoxic carcinogens; for risk low-dose assessment the linear non-threshold (LNT) model appears appropriate.

Group B: Genotoxic carcinogens, for which the existence of a threshold cannot be sufficiently supported at present. In these cases the LNT model may be used as a default assumption, based on the scientific uncertainty.

Group C: Genotoxic carcinogens for which a practical threshold is supported.

Group D: Non-genotoxic carcinogens and non-DNA reactive carcinogens; for these compounds a true ("perfect") threshold is associated with a clearly founded NOAEL.

[23] Available on Commission webpage on SCOEL [http://ec.europa.eu/social/main.jsp?catId=148&intPageId=684&langId=en]

Appendix 3. Arsenic compounds

Table 23: List (by counter ion) of common salts of arsenic acid (Restriction Annex XVII Entry 19, 2003).

Substance	EINECS	CAS	Comment
Arsenic acid	231-901-9	7778-39-4	
Triammonium arsenate	246-428-3	24719-13-9	
Diammonium hydrogenarsenate	232-067-9	7784-44-3	
Ammonium dihydrogenarsenate	236-667-1	13462-93-6	
Antimony arsenate	249-347-1	28980-47-4	
Antimony arsenic oxide	264-904-9	64475-90-7	
Tribarium diarsenate	236-762-8	13477-04-8	
Arsenic acid, calcium salt	233-287-8	10103-62-5	
Calcium arsenate	231-904-5	7778-44-1	
Tricobalt diarsenate	246-429-9	24719-19-5	
Arsenic acid, copper salt	233-286-2	10103-61-4	
Arsenic acid, copper(2+) salt	249-916-4	29871-13-4	
Ammonium copper arsenate	251-151-6	32680-29-8	
Iron arsenate	233-274-7	10102-49-5	
Iron bis(arsenate)	233-275-2	10102-50-8	
Trilead diarsenate	222-979-5	3687-31-8	
Lead hydrogen arsenate	232-064-2	7784-40-9	
Trilithium arsenate	236-773-8	13478-14-3	
Arsenic acid, magnesium salt	233-285-7	10103-50-1	
Arsenic acid (H3AsO4), magnesium salt, manganese-doped	310-019-9	102110-21-4	
Manganese hydrogenarsenate	232-063-7	7784-38-5	
Mercury hydrogenarsenate	232-062-1	7784-37-4	
Trinickel bis(arsenate)	236-771-7	13477-70-8	
Trisilver arsenate	236-841-7	13510-44-6	
Potassium dihydrogenarsenate	232-065-8	7784-41-0	
Arsenic acid, sodium salt		7631-89-2	
Trisodium arsenate	236-682-3	13464-38-5	
Disodium hydrogenarsenate	231-902-4	7778-43-0	
Sodium metaarsenate	239-171-3	15120-17-9	
Sodium arsenate dibasic heptahydrate	677-900-0	10048-95-0	
Sodium dioxoarsenate	232-070-5	7784-46-5	
Tristrontium diarsenate	236-684-4	13464-68-1	
Vanadium(4+) diarsenate (1:1)	308-917-0	99035-51-5	
Zinc arsenate	236-683-9	13464-44-3	

Substance	EINECS	CAS	Comment
Tris[(8α,9R)-6'-methoxycinchonan-9-ol] bis(arsenate)	208-971-4	549-59-7	Organic salt
Strychnine arsenate	233-970-0	10476-82-1	Organic salt

Table 24: List of arsenic (V) compounds unrelated to arsenic acid and its salts (Restriction Annex XVII Entry 19, 2003)

Substance	EINECS	CAS	Comment
Diarsenic pentaoxide	215-116-9	1303-28-2, 12044-50-7	
Pentafluoroarsorane	232-061-6	7784-36-3	
Pentahydroxyarsorane AsH5O5	232-096-7	7786-36-9	

Table 25: List of metallurgical slimes, sludges and dross containing variable proportions of arsenic and in some cases arsenate salts (Restriction Annex XVII Entry 19, 2003).

Substance	EINECS	CAS	Comment
Slimes and Sludges, copper refining: A complex combination resulting from copper processing---other than electrolytic.	266-977-2	67712-00-9	
Lead alloy, base, dross: A scum formed on the surface of molten lead-base alloys. Includes those cases in which aluminum is used to remove **arsenic**, nickel and antimony.	273-700-9	69011-59-2	
Lead, antimonial, dross: A scum formed on the surface of antimonial lead. Consists primarily of **sodium arsenate** and **sodium antimonate** with some lead oxide and free caustic soda.	273-795-7	69029-51-2	
Slimes and Sludges, copper electrolytic refining, decopperized, **arsenic-rich**: Product obtained by centrifuging the slime discharged at the bases of cells for decopperization of electrolytic copper solutions. Composed primarily of a copper powder rich in arsenic.	309-772-6	100995-81-1	
Flue dust, arsenic-contg.: Formed when arsenic and metal oxide particles are driven off during the roasting and converting of copper concentrates and matte in the production of anode copper.	232-434-3	8028-73-7	

Flue dust, lead-refining: By-product of refining lead ores obtained from baghouse and electro-static precipitator and as slurry from scrubbers.	273-809-1	69029-67-0	

Table 26: As(III) inorganic salts, organic salts and organoarsenic compunds (sorted by counter ion), not fitting the descriptor arsenic acid and its salts (Restriction Annex XVII Entry 19, 2003)

Substance	EINECS	CAS	Comment
Diarsenic trioxide	215-481-4	1327-53-3, 7440-38-2	
Aluminium arsenide	245-255-0	22831-42-1	
Triantimony arsenide	235-505-7	12255-36-6	
Antimony oxide (Sb2O3), mixed with arsenic oxide (As2O3)	273-156-2	68951-38-2	
Arsenic bromide	265-296-8	64973-06-4	
Arsenic sulfide	215-117-4	1303-33-9	
Arsenic sulfide	235-720-6	12612-21-4	
Arsenic tribromide	232-057-4	7784-33-0	
Arsenic trichloride	232-059-5	7784-34-1	
Tribarium diarsenide	235-508-3	12255-50-4	
Tricalcium diarsenide	235-509-9	12255-53-7	
Tricalcium diarsenite	248-266-9	27152-57-4	
Tricopper arsenide	234-472-6	12005-75-3	
Cobalt arsenide	248-168-6	27016-73-5	
Cobalt arsenide	265-784-0	65453-05-6	
Copper diarsenite	240-574-1	16509-22-1	
Diarsenic triselenide	215-119-5	1303-36-2	
Diarsenic tritelluride	234-955-1	12044-54-1	
Dichromium arsenide	235-499-6	12254-85-2	
Digallium arsenide phosphide	234-948-3	12044-20-1	
Diiron arsenide	234-474-7	12005-88-8	
Disilver arsenide	274-573-2	70333-07-2	
Dysprosium arsenide	234-473-1	12005-81-1	
Erbium arsenide	235-501-5	12254-88-5	
Europium arsenide	251-206-4	32775-46-5	
Trifluoroarsine	232-060-0	7784-35-2	
Gadolinium arsenide	234-475-2	12005-89-9	
Gallium arsenide	215-114-8	1303-00-0	
Gallium zinc triarsenide	308-577-3	98106-56-0	
Germanium arsenide	235-547-6	12271-72-6	
Holmium arsenide	234-476-8	12005-92-4	

Indium arsenide	215-115-3	1303-11-3	
Indium arsenide	310-063-9	102110-62-3	
Iron arsenide	234-947-8	12044-16-5	
Iron diarsenide	234-485-7	12006-21-2	
Lanthanum arsenide	235-502-0	12255-04-8	
Lead arsenite	233-083-9	10031-13-7	
Trilithium arsenide	234-950-4	12044-22-3	
Lutetium arsenide	234-477-3	12005-94-6	
Manganese arsenide	234-478-9	12005-95-7	
Trimanganese arsenide	262-667-6	61219-26-9	
Trimagnesium diarsenide	234-954-6	12044-49-4	
Neodymium arsenide	235-504-1	12255-09-3	
Nickel arsenide	248-169-1	27016-75-7	
Nickel diarsenide	235-103-1	12068-61-0	
Niobium arsenide	235-503-6	12255-08-2	
Phenylarsine oxide	211-275-3	637-03-6	
Potassium arsenite	236-680-2	13464-35-2	
Tripotassium arsenide	234-949-9	12044-21-2	
Praseodymium arsenide	234-953-0	12044-28-9	
Samarium arsenide	235-506-2	12255-39-9	
Trisilver arsenide	235-652-7	12417-99-1	
Trisilver arsenite	232-048-5	2149310	
Trisodium arsenide	234-952-5	12044-25-6	
Trisodium arsenite	236-681-8	13464-37-4	
Tristrontium diarsenide	254-407-5	39297-24-0	
Terbium arsenide	234-479-4	12006-08-5	
Thallium arsenide	234-481-5	12006-09-6	
Thallium triarsenide	281-902-3	84057-85-2	
Thulium arsenide	234-482-0	12006-10-9	
Ytterbium arsenide	234-483-6	12006-12-1	
Yttrium arsenide	235-507-8	12255-48-0	
Zinc diarsenide	234-956-7	12044-55-2	
Trizinc diarsenide	234-486-2	12006-40-5	
Zirconium arsenide	262-524-8	60909-47-9	
Tris[(8α)-6'-methoxycinchonan-9(R)-ol] arsenite	303-002-2	94138-87-1	Org. salt
Strychnidin-10-one, arsenite (1:1)	309-388-9	100258-44-4	Org. salt
Diphenyldiarsenic acid	224-845-1	4519-32-8	Organoarsenic
N-(p-arsenosophenyl)-1,3,5-triazine-2,4,6-triamine, Melarsen oxide	244-612-8	21840-08-4	Organoarsenic

Table 27: Inorganic and organic hexafluoroarsenate salts not fitting the descriptor arsenic acid and its salts (Restriction Annex XVII Entry 19, 2003)

Substance	EINECS	CAS	Comment
Tritylium hexafluoroarsenate Triphenylmethyl hexafluoroarsenate	207-111-5	437-15-0	Inorg salt
Lithium hexafluoroarsenate	249-963-0	29935-35-1	Inorg salt
Sodium hexafluoroarsenate	624-772-9	12005-86-6	Inorg salt
Potassium hexafluoroarsenate	241-102-7	17029-22-0	Inorg salt
Hydrogen hexafluoroarsenate	241-128-9	17068-85-8	Inorg salt
3-methyl-4-(pyrrolidin-1-yl)benzenediazonium hexafluoroarsenate	248-532-4	27569-09-1	Org salt
Triphenylsulphonium hexafluoroarsenate(1-)	261-009-5	57900-42-2	Org salt
Diphenyliodonium hexafluoroarsenate	263-638-0	62613-15-4	Org salt
4-(ethylamino)-2-methylbenzenediazonium hexafluoroarsenate	264-026-6	63217-32-3	Org salt
4-(diethylamino)-2-ethoxybenzenediazonium hexafluoroarsenate	264-027-1	63217-33-4	Org salt
Tris(pentane-2,4-dionato-O,O')silicon hexafluoroarsenate, Tris(acetylacetonato)silicon(IV), hexafluoroarsenate	266-621-6	67251-38-1	Org salt
Bis(pentane-2,4-dionato-O,O')boron(1+) hexafluoroarsenate(1-)	272-591-5	68892-01-3	Org salt
2,6-dimethyl-4-(1-naphthyl)pyrylium hexafluoroarsenate	282-682-1	84282-36-0	Org salt
2,6-dimethyl-4-phenylpyrylium hexafluoroarsenate	282-700-8	84304-15-4	Org salt
4-cyclohexyl-2,6-dimethylpyrylium hexafluoroarsenate	282-701-3	84304-16-5	Org salt