European Chemicals Agency (EChA), Helsinki

Services to support the assessment of remaining cancer risks related to the use of chromium- and arsenic-containing substances in Applications for Authorisation.

Service Request
under the Multiple Framework Contract with re-opening of competition
for scientific services for ECHA

REFERENCE: ECHA/2011/01 – SR-11

FINAL REPORT FOR

ARSENIC

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Consortium ETeSS
Expert Team providing scientific support for ECHA

CONTENTS

EXECUTIVE SUMMARY

A. Background

A review was performed of the carcinogenic dose responses of three inorganic arsenic compounds (diarsenic pentoxide, diarsenic trioxide and arsenic acid). 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 adrenals, bladder and liver have also been reported in some studies in animals.

The mode of carcinogenic action has not been defined but does not appear to involve mutagenicity. Inorganic arsenic compounds do not cause point mutations. Studies in experimental test systems show that inorganic arsenic is clastogenic, causing chromosome aberrations, sister chromatid exchanges and DNA damage. Increased frequencies of chromosome aberrations and sister chromatid exchanges associated with arsenic exposure have been reported in human populations. It is likely, but not proven, that the genotoxicity of arsenic is a threshold effect, however, the available data do not allow the identification of threshold exposure levels. Linear extrapolation is considered to be the most appropriate default position and has been used in determining the excess cancer risks from arsenic exposures.

B Bioavailability

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

Samples taken from the atmospheres associated with the epidemiology studies do not provide detailed information on the particle sizes of the atmospheres. With the systemic nature of arsenic associated lung carcinogenicity, it is unclear if particle size will be a critical element in inhalation risks as larger particles that do no reach the alveolae but are cleared by mucociliary clearance could be absorbed from the intestinal tract presenting a risk of lung cancer via systemic exposure.

Dermal absorption of inorganic arsenic compounds is reported to be low (<1% – 6%). Data specific to particular exposure scenarios would reduce the uncertainty in the dermal risk assessments. 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 scenarios 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.

C Carcinogenicity risk assessment

i Inhalation exposure

Based on human epidemiology data and linear extrapolation in line with the DECOS 2012 review (against a background lifetime lung cancer risk of 48 per 1000 for the EU population)

- Inhalable particles (CEN definition; D_{50} < 100µm)
  - Occupational

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

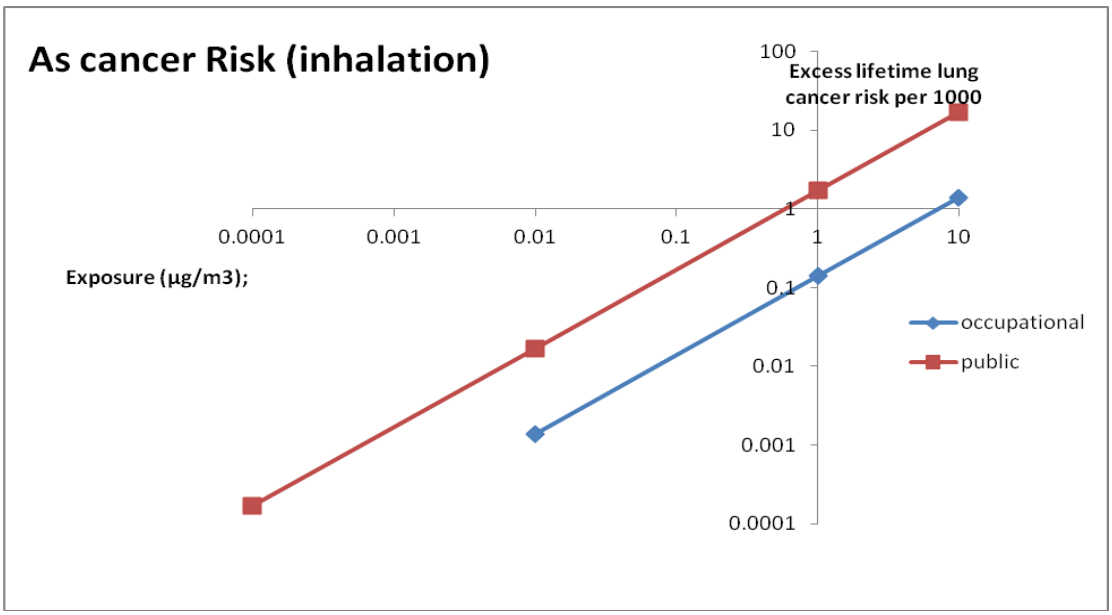
An excess lifetime lung cancer mortality risk = 1.4 x 10^{-4} per µgAs/m^3.

  - General public

Based on a 70 year exposure scenario (24h/day every day)

An excess lifetime lung cancer mortality risk = 1 x 10^{-3} per µg As/m^3.

On the available information it is not possible to differentiate between the risks from respirable and non-respirable particles.



ii Dermal exposure

There are no data specific for the cancer risk from dermal exposures to inorganic arsenic. Risk assessments should be performed using the oral exposure approach described below, with exposures corrected if appropriate data are made available for the level of dermal absorption and the impact of the first-pass liver metabolism.

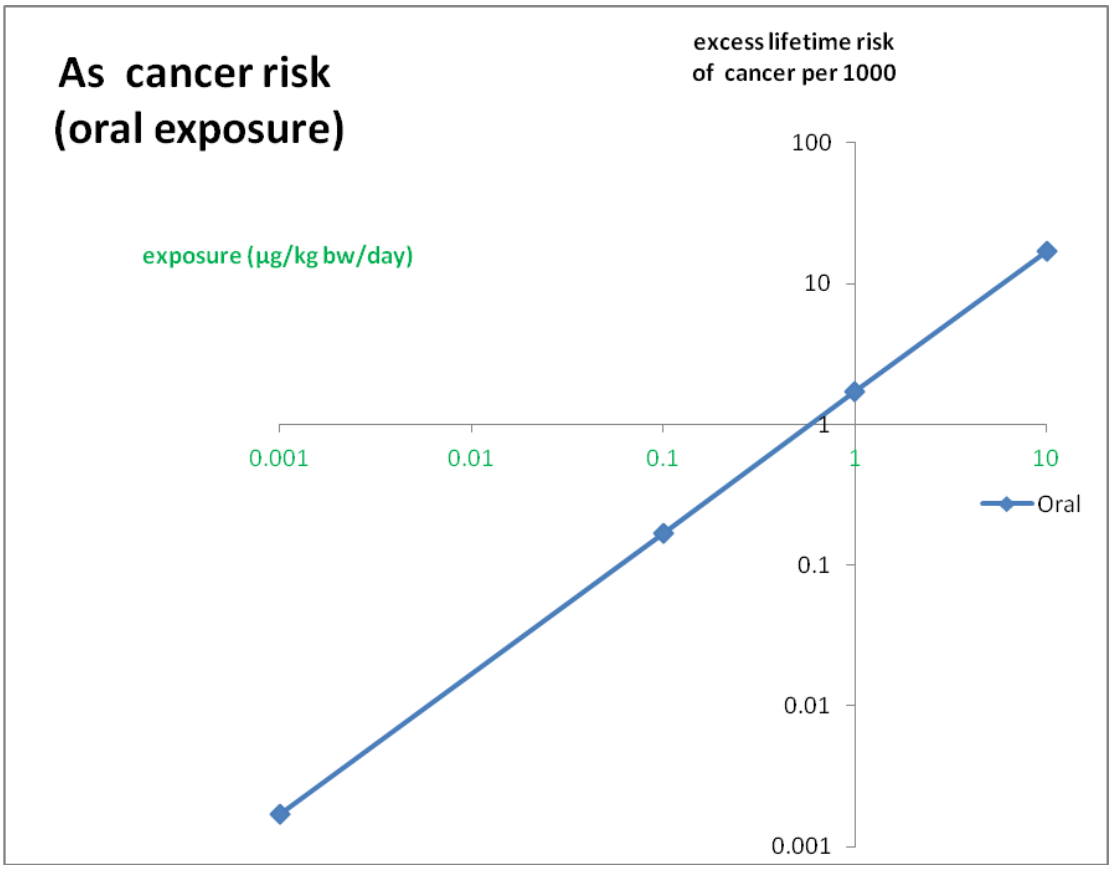
iii Oral exposure

- This estimate applies to both occupational and general public exposures.

Based on human epidemiology data, a lifetime exposure scenario and an 11.5 year follow-up period, based on the WHO/FAO (2011) review.

An excess lifetime cancer risk = 1.7 x 10^{-3} per µg As/ kg body weight/day.

There are inadequate data to support a threshold value for cancers associated with oral exposure to inorganic arsenic.



1 INTRODUCTION

The project specification requires a review of the relevant scientific literature related to the carcinogenicity of the inorganic arsenic compounds listed in Table 1 (WP1) and the establishment of relevant dose-response curves for each of these substances (WP 2) for the purpose of Authorisation under REACH.

Table 1 Arsenic compounds in the Authorisation list

No.	Name of substance	EC no.	CAS no.	Classification 1272/2008
1	Diarsenic pentoxide (also known as arsenic pentoxide)	215-116-9	1303-28-2	1a
2	Diarsenic trioxide (also known as arsenic trioxide)	214-481-4	1327-53-3	1a
3	Arsenic acid	231-901-9	7778-39-4	1a

We have identified and obtained a number of detailed, good-quality assessments of the carcinogenicity of arsenic and its inorganic compounds, published by a variety of national or international authorities, as presented in Table 2 below. The cancer hazard assessment (WP1) draws heavily on the first three reviews listed, which are comprehensive and up to date evaluations. The other assessments listed include cancer dose response assessments, which together with the DECOS review, are used as information sources for WP2. Literature searches have not identified any significant new publications of relevant cancer studies of relevance to this project that are not included in these cancer assessments.

As the focus of the project is cancer risk assessment of the three arsenic compounds attention has been given mainly to carcinogenicity data, which relate mainly to exposure to arsenic either in the air or via drinking water. In addition, toxicokinetic data and mode-of-action (MoA) information, including genotoxicity data have been considered, as this information is relevant to the characterisation of cancer risks.

Table 2 Outline of reviews used as the main basis for this report

Reference/year	Title	Organisation	Content/aim of publication
ATSDR (2007)	Toxicological profile for arsenic	Agency for Toxic Substances and Disease Registry (United States Department of Health and Human Services)	Hazard assessment of arsenic compounds, aimed a health care providers
IARC (2012)	A review of human carcinogens. Part C: Arsenic, metals, fibres, and dusts	International Agency for Research on Cancer	Cancer hazard assessment of arsenic compounds for categorisation purposes
DECOS (2012)	Arsenic and inorganic arsenic compounds. Health-based calculated occupational cancer risk values	Dutch Expert Committee on Occupational Safety, Health Council of the Netherlands	Hazard and risk assessment of arsenic compounds, to serve as a basis for setting occupational exposure limits in Netherlands
USAEPA (1984)	Toxicological review of inorganic arsenic	United States Environmental Protection Agency	Hazard and risk assessment of arsenic, to serve as a basis for regulatory decision making
USEPA IRIS (accessed 2013)	Arsenic, inorganic	United States Environmental Protection Agency, Integrated Risk information system	Summary of USEPA hazard and risk assessment conclusions
WHO (2000)	Environmental Health Criteria 224. Arsenic and arsenic compounds.	World Health Organization	Hazard assessment of arsenic compounds, aimed at assisting risk assessments by national and international authorities
EC (2000)	Ambient Air Pollution by As, Cd and Ni compounds (Position Paper-Final).	European Commission	Hazard and risk assessment of arsenic, proposes air quality limit values for general population
ACGIH (2004)	Arsenic	American Conference of Governmental Industrial Hygienists	Summary of hazard information. Recommends occupational exposure limits
UK EPAQS (2008)	Guidelines for metals and metalloids in ambient air for the protection of human health	Expert Panel on Air Quality Standards, UK Department for Environment, Food and Rural Affairs	Risk assessment of arsenic. Proposes air quality limit values for general population
EFSA (2009)	Scientific opinion on arsenic in food. EFSA Panel on Contaminants in the Food Chain	European Food Safety Authority	Hazard and risk assessment of arsenic. Proposes benchmark dose for dietary route. Aim is to inform regulatory decision making in EU
USEPA (2010)	Toxicological review of inorganic arsenic (draft document – permission to cite obtained from EPA)	United States Environmental Protection Agency	Hazard and risk assessment of arsenic. Proposes oral cancer potency factor
WHO (2011)	Arsenic in Drinking-water. Background document for development of WHO Guidelines for Drinking-water Quality	World Health Organization	Summary risk assessment of arsenic. Proposes drinking water guideline value
WHO/FAO (2011)	WHO food additives series 63, FAO JECFA monographs 8	World Health Organization/Food and Agriculture Organization of United Nations	Hazard and risk assessment of arsenic. Recommends benchmark dose in relation to exposure via dietary route
TCEQ (2012)	Proposed Development Support Document. Arsenic and Inorganic Arsenic Compounds	Texas Commission on Environmental Quality	Risk assessment of arsenic. Proposes inhalation cancer unit risk factor in relation to Texas ambient air monitoring

Arsenic and its inorganic compounds (a grouping that includes diarsenic pentoxide, diarsenic trioxide and arsenic acid) have been classified as *carcinogenic to humans* by the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) (IARC, 2012). This classification is based mainly on the results of epidemiological studies in workers exposed to arsenic principally via the inhalation route and in persons exposed to high concentrations of arsenic in drinking water. Under the CLP (classification, labelling and packaging) Regulations of the European Union diarsenic pentoxide, diarsenic trioxide and arsenic acid are classified as human carcinogens (Category 1A). Arsenic and its inorganic compounds have metabolic pathways that involve the formation of As^{III} and the production of common methylated metabolites that are believed to be its bioactivation products, therefore inorganic arsenic compounds are considered together in all of the published assessments listed above, and in this document.

2 PHYSICOCHEMICAL PROPERTIES

Arsenic exists in four common valence states, 0 (metalloid arsenic), +3 (e.g. the arsenites), +5 (e.g. the arsenates) and –3 (arsine gas). Diarsenic trioxide is a trivalent compound; diarsenic pentoxide and arsenic acid are pentavalent compounds. The trivalent arsenic compounds are considered generally to have greater toxicity than the pentavalent arsenic compounds (ATSDR 2007), possibly because of the greater reactivity of As^{III} and because As^{III} enters the cell more readily as compared to As^{V}.

The solubility of diarsenic trioxide and diarsenic pentoxide are 1.2-3.7 and 65.8 g/100 ml at 20^{o}C, respectively. Arsenic acid is highly soluble in water. Further detailed information on the uses and physical-chemical properties of the 3 inorganic arsenic compounds under consideration and information on is presented in **Annex I** to this document.

In many of the studies considered in this report the precise speciation of the arsenic compounds was not clearly defined.

3 CANCER HAZARD ASSESSMENT (WP 1)

3.1 Toxicokinetics

The following summary of the toxicokinetics of arsenic and its compounds is adapted from ATSDR (2007), DECOS (2012) and IARC (2012)

3.1.1 Absorption

3.1.1.1 Inhalation route

As arsenic exists in air as particulate matter, absorption across the lung involves two processes, deposition of the particles onto the lung surface, and absorption of arsenic from the deposited material.

The absorption of arsenic via the inhalation route has been investigated in only a limited number of studies, In lung cancer patients exposed to arsenic in cigarette smoke, deposition was estimated to be about 40% and absorption was 75–85% on the deposited material (Holland et al 1959). Thus, overall absorption (expressed as a percentage of inhaled arsenic) was about 30–34%. In workers exposed to arsenic trioxide dusts in smelters, the amount of arsenic excreted in the urine (the main route of excretion) was about 40–60% of the estimated inhaled dose (Pinto et al. 1976; Vahter et al. 1986). Absorption of arsenic trioxide dusts and fumes (assessed by measurement of urinary metabolites) correlated with time weighted average arsenic air concentrations from personal breathing zone air samplers (Offergelt et al. 1992). Correlations were best immediately after a shift and just before the start of the next shift. Although the percent deposition was not measured in these cases, it seems likely that nearly all of the deposited arsenic was absorbed. This conclusion is supported by intratracheal

instillation studies in rats and hamsters, where clearance of oxy compounds of arsenic (sodium arsenite, sodium arsenate, arsenic trioxide) from the lung was rapid and nearly complete (60–90% within 1 day) (Marafante and Vahter 1987; Rhoads and Sanders 1985). In contrast, the less soluble arsenic sulphide and lead arsenate were cleared from the lung more slowly, indicating that the rate of absorption may be lower if the inhaled arsenic is in a highly insoluble form.

If a default inhalation deposition / absorption value for arsenic is needed in the risk assessment, a value of 100% of inhalable dose is recommended, based on a synthesis of the above data showing extensive absorption via this route of exposure. To move from this default position relevant data specific to the exposure scenario under consideration would be required.

3.1.1.2 Oral route

Several studies in humans indicate that low doses of arsenates and arsenites are well absorbed across the gastrointestinal tract. The most direct evidence is from a study that evaluated the 6-day elimination of arsenic in healthy humans who were given water from a high-arsenic sampling site (arsenic species not specified) and that reported approximately 95% absorption (Zheng et al 2002). A similar absorption efficiency can be estimated from measurements of faecal excretion in humans given oral doses of arsenite, where <5% was recovered in the faeces, indicating absorption of at least 95% (Bettley and O'Shea 1975). These results are supported by human volunteer studies in which urinary excretion was found to account for 55–87% of daily oral intakes of arsenate or arsenite (including diarsenic trioxide) (see ATSDR page 212 for study references). In contrast, ingestion of arsenic triselenide did not lead to a measurable increase in urinary excretion indicating that gastrointestinal absorption may be much lower if highly insoluble forms of arsenic are ingested.

These observations in humans are supported by a number of studies in animals (see ATSDR page 213 for study references). Faecal excretion of arsenates and arsenites ranged from 2 to 10% in monkeys and mice, with 70% or more appearing in urine. Oral absorption of [^{73}As] labelled sodium arsenate in mice was unaffected by dose (0.0005–5 mg/kg), with 82-89% being absorbed within 48 h at all doses. In contrast, the percentage of arsenate that was absorbed in rats decreased as the dose increased from 6 to 480 µg, suggesting saturable, zero-order absorption of arsenate in rats according to ATSDR (2007).

Studies of the bioavailability of arsenic suggest that absorption of arsenic in ingested dust or soil is likely to be considerably less than absorption of arsenic from ingested salts (see ATSDR page 213 for study references).

If a default oral absorption value for arsenic is needed in the risk assessment, a value of 100% of ingested dose is recommended, based on a synthesis of the above data showing extensive absorption via this route of exposure. To

move from this default position relevant data specific to the exposure scenario under consideration would be required.

3.1.1.3 Dermal route

Investigation of the extent of dermal absorption of arsenic compounds in humans is very limited. An i*n 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 [^{73}As] as arsenic acid passed through the skin, with 0.98% remaining in the skin after washing. Absorption was lower when [^{73}As] was mixed with soil.

Investigation of dermal absorption in animal models is also limited, though the available studies confirm that dermal absorption of arsenic compounds is likely to be relatively low. In Rhesus monkeys 6.4% a dose of [^{73}As] as arsenic acid was absorbed systemically at 24 h, as was 4.5% of [^{73}As] mixed with soil (Wester et al 1993). Similarly, in another study, 2.8% of a dose of soluble arsenic in water was detected in the urine 24 hours after exposure, but when mixed with soil only 0.12% was detected in the urine at 24 hours (Lowney et al 2005). Differences between the two studies in the uptake from soil may be due to the differences in forms of arsenic in the soil.

If a default dermal absorption value for arsenic is needed in the risk assessment, a value of 1% of dose is recommended, based on the *in vitro* data; the Rhesus monkey *in vivo* data are not considered to be key as this species is likely to over-predict human absorption due to the greater density of hair follicles. If specific dermal absorption data are available for the exposure scenario under consideration these should be used.

3.1.2 Distribution

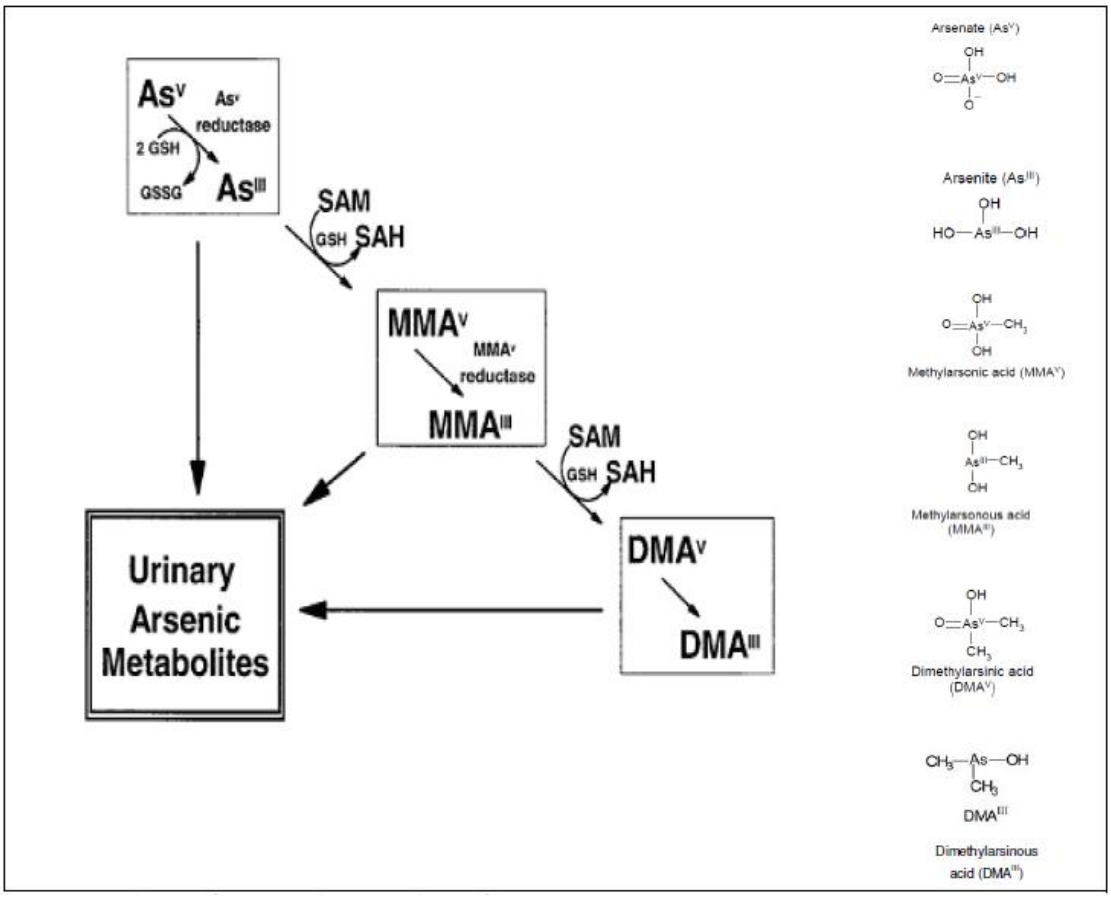
Data on distribution are limited, but it appears that absorbed arsenic is transported to nearly all tissues irrespective of the exposure route (see ATSDR page 216-218 for study references). Preferential distribution or accumulation in relation to internal organs or tissues has not been observed in humans at autopsy or in experiments with a number of animal species other than rat; in rats arsenic is known to concentrate in red blood cells. Because the liver is a major site for the methylation of inorganic arsenic, a first-pass effect after gastrointestinal absorption is possible; however this has not been investigated in animal models. Arsenic accumulates in keratin-rich tissues such as skin, hair and nails. Arsenic has been shown to readily pass though the placenta in humans and in experimental animals, and has been detected in human breast milk.

3.1.3 Metabolism

In the human body, inorganic arsenic compounds are converted to either As^{III} or As^{V} depending on their valency state. The metabolism of arsenic ions is characterised by two main types of reactions: (1) two-electron reduction reactions of As^{V} to As^{III} which can occur nonenzymatically via glutathione or

enzymatically, and (2) oxidative methylation reactions in which As^{III} is sequentially methylated to form mono-, di- and trimethylated products using S-adenosyl methionine as the methyl donor and glutathione as an essential co-factor. Methylation of inorganic arsenic facilitates the excretion of inorganic arsenic from the body. The main methylated metabolites that have been identified are monomethylarsonic acid (MMA^V), dimethylarsinic acid (DMA^V), monomethylarsonous acid (MMA^{III}) and dimethylarsinous acid (DMA^{III}). The trivalent metabolites MMA^{III} and DMA^{III} appear to be more reactive than the pentavalent metabolites. Figure 1 shows a simplified representation of the metabolic pathways for arsenic (taken from DECOS 2012)

Figure 1 Arsenic: metabolic pathways (from DECOS 2012)



SAM = S-adenosyl methionine SAH = S-adenosylhomocysteine GSH = glutathione reduced
GSSG = glutathione oxidised

There are major qualitative and quantitative interspecies differences in methylation, to the extent that some species exhibit minimal or no arsenic methylation (e.g. marmoset monkey, guinea-pig, chimpanzee). However, in humans and most common laboratory animals, inorganic arsenic is extensively methylated, with MMA^V and DMA^V predominating in humans. Factors such as dose, age, gender and smoking contribute only minimally to the large interindividual variation in arsenic methylation observed in humans. Studies in humans suggest the existence of a wide difference in the activity of methyltransferases, and the existence of polymorphism has been hypothesised. Animal and human studies suggest that arsenic methylation may be inhibited at high acute exposures. The metabolism of inorganic arsenic may be influenced by its valence state, particularly at high dose levels. Studies in laboratory animals indicate that administration of trivalent inorganic arsenic such as arsenic trioxide and arsenite initially results in higher levels in most tissues than does pentavalent arsenic. However, the trivalent form is more extensively methylated.

3.1.4 Excretion

In humans arsenic is largely excreted via the renal route as a mixture of As^V,

As^{III}, MMA^{V}, DMA^{V}, MMA^{III} and DMA^{III}. This excretion mechanism is not likely to be saturated within the dose range expected from human exposure, according to ATSDR (2007). The proportion of metabolites recovered in urine are roughly consistent in humans regardless of the exposure route. Smaller amounts are excreted in faeces. Some arsenic may remain bound to tissues (especially skin, hair, and nails), depending inversely on the rate and extent of methylation. Excretion via breast milk has also been demonstrated in humans.

3.1.5 Toxicokinetics conclusions

Inorganic arsenic compounds are likely to be extensively absorbed via the inhalation route, based on the observation that 40-60% of an inhaled dose of arsenic trioxide was absorbed in smelter workers. Oral absorption of inorganic arsenic compounds is rapid and extensive. Based on limited information, dermal absorption of inorganic arsenic compounds is low.

Absorbed inorganic arsenic undergoes widespread distribution, irrespective of the route of exposure.

The metabolism of inorganic arsenic involves the release of As^{III} or As^{V}, the reduction of As^{V} to As^{III} and the oxidative methylation of As^{III} to form mono-, di- and trimethylated products, predominately MMA^{V} and DMA^{V}.

Arsenic is largely excreted via the renal route as a mixture of As^{V}, As^{III} and the methylated metabolites, with MMA^{V} and DMA^{V} predominating in humans.

3.2 Genotoxicity

The following conclusions on the genotoxicity profile of arsenic are adapted from DECOS (2012).

3.2.1 Investigations in experimental test systems

The genotoxicity of arsenic and its compounds has been extensively investigated in experimental test systems.

Arsenic is not mutagenic, as no point mutations have been observed in bacterial or mammalian cell assays.

Arsenic is clastogenic. *In vitro*, significant increased numbers of micronuclei, chromosome aberrations and sister chromatid exchanges have been observed in Chinese hamster ovary cells after exposure to dimethylarsinous acid and monomethylarsonous acid. As^{III} and As^{V} induced chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells, but not micronuclei. Monomethylarsonous acid, dimethylarsinous acid and dimethylarsinic acid are capable of inducing DNA damage via formation of reactive oxygen species. *In vitro* studies in human lymphocytes and fibroblasts also showed genotoxic effects of arsenic, with the observation of

nicking (unwinding) of DNA, double-stranded DNA breaks, induction of alkaline labile sites, sister chromatid exchanges, oxidative damage and interference with the formation and repair of DNA adducts. Methylated trivalent arsenicals were found to be more potent DNA damaging compounds than the other arsenicals in some human lymphocyte studies.

In vivo, arsenite was positive in a number of chromosome aberration and micronuclei studies in mice or rats, using the oral or intraperitoneal routes. For example, sodium arsenite produced significantly high frequencies of chromosome aberrations in bone marrow cells in mice 24 h after a gavage dose of 2.5 mg/kg (one 10^{th} of the LD_{50}).

3.2.2 In vivo studies in humans exposed to arsenic

A number of studies conducted in people living in areas with relatively high arsenic concentrations in drinking water showed increased frequencies of chromosome aberrations and sister chromatid exchanges associated with arsenic exposure. Tissues investigated in these studies included peripheral blood lymphocytes, buccal and bladder cells and tumours from cancer patients. Higher frequencies of chromosomal aberrations in peripheral lymphocytes have also been seen in a cohort of copper smelter workers (in Rönnskär, Sweden). Although these studies must be interpreted with caution, as the numbers of subjects in each of these studies was small and other chemical exposures were possible, the overall weight of evidence indicates that arsenic can cause clastogenic damage in different cell types in humans exposed to arsenic.

3.2.3 Consideration of the genotoxicity mode of action (MoA)

DECOS (2012) draws attention to evidence that arsenic compounds bind to thiol-groups in proteins which may lead to inhibition of for example DNA repair enzymes. There is also evidence that arsenic exposure can result in hypo- or hypermethylation of cellular DNA, changes which can be caused for example by an influence of arsenic on DNA methyltransferases. Furthermore, although arsenic does not generate reactive oxygen by itself, it can inhibit the scavenging systems of reactive oxygen species which indirectly leads to an increase of reactive oxygen species. There is also evidence that arsenic can cause gene amplification. All these processes can lead to altered gene expression. As these possible MoAs do not involve the direct action of arsenic on DNA, the genotoxic activity of arsenic is likely to have a threshold exposure level below which effects will not occur. However, the available data do not allow the identification of threshold exposure levels.

3.2.4 Genotoxicity conclusions

Inorganic arsenic compounds do not cause point mutations. Studies in experimental test systems show that inorganic arsenic is clastogenic, causing chromosome aberrations, sister chromatid exchanges and DNA damage. Increased frequencies of chromosome aberrations and sister chromatid exchanges associated with arsenic exposure have been reported in human

populations. It is likely that the genotoxicity of arsenic is a threshold effect, although the available data do not allow the identification of threshold exposure levels.

3.3 Carcinogenicity

3.3.1 Animal studies

The IARC Monograph (IARC 2012) provides details of a number of cancer studies conducted on arsenic compounds conducted in several laboratory animal species, published 1985-2007. These studies are summarised in Table 3. Ten studies were conducted by the oral route (either by incorporation in drinking water or food), three studies involved transplacental exposure, and two were by the inhalation route; several other studies were conducted by the intratracheal, intravenous or subcutaneous routes. Additionally, in twelve studies the ability of arsenic to enhance the carcinogenicity of other chemicals, under conditions in which arsenic alone is not carcinogenic, was investigated.

The IARC Monograph draws the following conclusions from these studies:-

- Oral administration of sodium arsenate and DMA^V induced lung tumours in mice.
- Calcium arsenate induced lung tumours in hamsters by oral and intratracheal administration.
- Pre- and postnatal exposure in mice to arsenic trioxide, through subcutaneous injections (maternal and postnatal), induced lung tumours in the offspring.
- Transplacental exposure via maternal oral exposure in mice to sodium arsenite during gestation induced lung, liver, ovary and adrenal tumours in the offspring in several studies, and the uterus in one study.
- Early life transplacental and perinatal exposure to sodium arsenite appears to be a time of particular sensitivity in terms of carcinogenesis.
- Oral exposure to DMA^V induced urinary bladder tumours in several studies in rats and among studies in mice only one showed negative results.
- Oral trimethylarsine induced liver tumours in rats.
- Chronic oral exposure to MMA^V did not produce tumours in rats and mice.
- Inhalation of gallium arsenide causes lung and adrenal tumours in female rats but not in male rats or mice.
- In a number of studies, initiating, promoting or co-carcinogenic activity of arsenicals or DMA^V compounds was demonstrated following drinking water or transplacental exposure in the urinary bladder, skin, female reproductive tract, kidney, lung, liver and thyroid.

The IARC Monograph notes that that earlier bioassays for arsenicals conducted in adult rodents using traditional methodology were frequently negative for carcinogenicity.

The contractor has considered whether a threshold exposure level for arsenic carcinogenicity can be reliably identified from the 10 modern animal studies involving long term repeated exposure to arsenic via the oral route. The lowest dose causing tumours was 0.04 mgAs/kg bw/day, reported in a mouse drinking water study with sodium arsenate in which lung tumours were induced (Cui et al. 2006); this was the lowest dose level tested in this particular study. From the other studies, the lowest study NOAELs identified for cancer were 0.34 mgAs/kg bw/day in a rat drinking water study with dimethylarsinic acid (Wei et al 1999, 2002), 1 mgAs/kg bw/day in a rat dietary study with dimethylarsinic acid (Arnold et al 2006), and 1.4 mgAs/kg bw/day in a rat drinking water study with sodium arsenite (Soffritti et al 2006), all based on the observation of kidney tumours at higher doses. Because these study NOAELs were higher than the lowest study LOAEL for cancer, it is concluded that a threshold dose for arsenic carcinogenicity for the oral route cannot be identified from these animal studies. It is noted that the lowest dose causing tumours of 0.04 mgAs/kg bw/day is only slightly higher than upper end of the 95^{th}-percentile range for total arsenic dietary exposures for humans in Europe of 0.0018-0.011 mgAs/kg/day (range from WHO/FOA 2011).

Table 3 Carcinogenicity studies in animals, published 1985-2007 (adapted from IARC, 2012)

Test substance/dosing regime	Species/strain/sex	Main carcinogenicity findings	Reference
Animals exposed to sodium arsenate (oral exposure)			
Sodium arsenate: 0, 1, 10, 100 ppm in drinking water, 18 mo Dose: 0, 0.04, 0.4, 4 mgAs/kg bw/day	Mouse, A/J (M). 30/group	Increased incidence of lung adenocarcinomas at 1, 10, 100 ppm Cancer LOAEL: 1 ppm (0.04 mgAs/kg bw/day)	Cui at al 2006
Animals exposed to dimethylarsenic acid (DMA^V) (oral exposure)			
Dimethylarsinic acid: 0, 50, 200, 400 ppm in drinking water, 50 wk Dose: 0, 2.4, 10, 20 mgAs/kg bw/day	Mouse, A/J, (M). 24/group	Increased incidence of lung adenomas or adenocarcinomas at 50, 200, 400 ppm Cancer LOAEL: 50 ppm (2.4 mgAs/kg bw/day)	Hayashi et al 1998
Dimethylarsinic acid: 0, 200 ppm in drinking water, 72 wk Dose: 0, 10 mgAs/kg bw/day	Mouse, *Ogg1-/-* and *Ogg1+/+* (M, F) 10-12/group	Increased incidence of lung adenomas or adenocarcinomas in *Ogg1-/-* Increased incidence of lung hyperplasias in *Ogg1+/* Cancer LOAEL: 200 ppm (10 mgAs/kg bw/day)	Kinoshita et al 2007
Dimethylarsinic acid: 0, 12.5, 50, 200 ppm in drinking water, 104 wk Dose: 0, 0.34, 1.4, 5 mgAs/kg bw/day	Rat, F344 (M) 26/group	Increased incidence of urinary bladder papillomas and carcinomas (combined) at 50 and 200 ppm Cancer NOAEL: 12.5 ppm (0.34 mgAs/kg bw/day)	Wei et al 1999, 2002
Dimethylarsinic acid: 0, 2, 10, 40, 100 ppm in diet, 104 wk Dose: 0, 0.06, 0.27, 1, 2.7 mgAs/kg bw/day	Rat, F344 (M, F) 60/group	Increased incidence of urinary bladder papillomas and carcinomas combined at 100 ppm in F Increased incidence of urothelial cell hyperplasia at 40 and 100 ppm in M, F Cancer NOAEL 40 ppm (1 mgAs/kg bw/day)	Arnold et al 2006
Dimethylarsinic acid: 0, 8, 40, 200, 500 ppm in diet, 104 wk Dose: 0, 0.7, 3, 16, 41 mgAs/kg bw/day	Mouse, B6C3F1 (M, F) 56/group	No treatment related tumours Cancer NOAEL: 500 ppm (41 mgAs/kg bw/day)	Arnold et al 2006
Animals exposed to trimethylarsine oxide (oral exposure)			
Trimethylarsine oxide: 0, 50, 200 ppm in	Rat, F344, (M) 42-45/group	Increased incidence of liver adenomas at 200 ppm	Shen et al 2003

Test substance/dosing regime	Species/strain/sex	Main carcinogenicity findings	Reference
drinking water, 2 yr Dose: 0, 1.4, 5.5 mgAs/kg bw/day		Cancer NOAEL: 50 ppm (1.4 mgAs/kg bw/day)	
Animals exposed to monomethylarsonic acid (MMA^V) (oral exposure)			
Monomethylarsonic acid (MMA^V): 0, 10, 50, 200, 400 ppm in diet, 104 wk Dose: 0, 0.8, 4, 16, 32 mgAs/kg bw/day	Mouse, B6C3F1 (M,F). 52/group/sex	No treatment related tumours Cancer NOAEL: 400 ppm (32 mgAs/kg bw/day)	Arnold et al 2003
Monomethylarsonic acid (MMA^V): 0, 10, 50, 400, 1300 ppm in diet, 104 wk Dose: 0, 0.3, 1.4, 10.7, 34.8 mgAs/kg bw/day	Rat, F344, (M,F). 60/group/sex	No treatment related tumours Cancer NOAEL: 1300 ppm (34.8 mgAs/kg bw/day)	Arnold et al 2003
Animals exposed to sodium arsenite (oral exposure)			
Sodium arsenite: 0, 50, 100, 200 mg/L in drinking water, 167 wk Dose: 0, 1.4, 2.9, 5.8 mgAs/kg bw/day	Rat, Sprague Dawley (M,F). 50/group/sex	Increase incidence of kidney tumours in females at 100 and 200 mg/L Cancer NOAEL: 50 ppm (1.4 mgAs/kg bw/day)	Soffritti et al 2006
Animals exposed to calcium arsenate (intratracheal instillation)			
Calcium arsenate: 0, ~3 mg As/kg bw in 0.15 ml saline, once a week for 15 wk, observed for 145 wk	Hamster, Syrian golden (M). 29-41/group	Increased incidence of lung adenomas	Pershagen & Bjorklund 1985
Calcium arsenate: 0, 0.25 mg As/kg bw in 0.1 ml saline, once a week for 15 wk, observed for up to 121 wk	Hamster, Syrian golden (M). 22-30/group	Increased incidence of lung adenomas	Yamamoto et al 1987
Animals exposed to arsenic trioxide (intratracheal instillation)			
Arsenic trioxide: 0, ~3 mg As/kg bw in 0.1 ml saline, once a week for 15 wk, observed for up to 140 wk	Hamster, Syrian golden (M). ~68/group	Increased incidence of larynx, trachea, bronchus, or lung carcinomas Increased incidence of larynx, trachea, bronchus, or lung adenomas, adenomatoid lesions, and papillomas combined	Pershagen et al 19845
Animals exposed to sodium arsenate (intravenous exposure)			
Sodium arsenite: 0, 0.5 mg As/kg bw in	Mouse, CR:NIH(S) (M, F).	Increased incidence of testicular interstitial	Waalkes et al 2000

Test substance/dosing regime	Species/strain/sex	Main carcinogenicity findings	Reference
10 ml/kg in saline once a week for 20 week, observed for 96 wk	25/group/sex	hyperplasia, skin hyperkeratosis (M), uterine cystic hyperplasias	
Animals exposed to arsenic trioxide (perinatal exposure)			
Arsenic trioxide: maternal single sc dose 1.2 mg/kg on gestation day 14, 15, 16 or 17; offspring sc dose 5 µg/animal postnatal day 1, 2 and 3, offspring observed for 1 yr	Mouse, CFLP(NR), group size not reported	Increased incidence of lung adenomas and adenocarcinomas in gestation day 15 group	Rudnai & Borzsanyi 1980, 1981
Animals exposed to sodium arsenite (transplacental exposure)			
Sodium arsenite: maternal exposure 0, 42.5, 85 ppm As in drinking water gestation days 8-18, offspring observed for up to 90 weeks of age	Mouse C3H/HeNCr (M, F), 25 offspring/group/sex	Increased incidence of ovary tumours, lung tumours (F), liver tumours (M), adrenal cortex tumours (M) at 42.5 & 85 ppm	Waalkes et al 2003
Sodium arsenite: maternal exposure 0, 42.5, 85 ppm As in drinking water gestation days 8-18, offspring topical exposure TPA 2 µg/animal twice a week 4-25 wk of age, offspring observed to 104 weeks of age	Mouse C3H/HeNCr (M, F), 25 offspring/group/sex	Increased incidence of liver tumours (F, with TPA), ovary tumours (with TPA), liver tumours (M, with or without TPA), adrenal cortex tumours (M, with or without TPA), lung tumours (M, with TPA) at 42.5 & 85 ppm	Waalkes et al 2003
Sodium arsenite: maternal exposure 0, 85 ppm As in drinking water gestation days 8-18, offspring sc on days 1, 2, 3, 4 & 5 postpartum DES 2 µg/animal or TAM 10 µg/animal, offspring observed to 90 weeks of age	Mouse C3H/HeNCr (M, F), 35 offspring/group/sex	Females: Increased incidence of ovary tumours (As, As + DES, As + TAM), uterus adenomas + carcinomas (As, As + DES), vagina (As + DES), adrenal cortex tumours (As, As + DES, As + TAM), urinary bladder proliferative lesions (As + DES, As + TAM), liver tumours (As + DES) Males: Increased incidence of liver tumours (As, As + DES, As + TAM), lung tumours (As), adrenal cortex tumours (As, As + DES, As + TAM), urinary bladder proliferative lesions (As + DES, As + TAM)	Waalkes et al 2006a,b
Arsenicals given to experimental animals after other agents enhance carcinogenesis, while arsenical has no effect alone			
Initiation 10 mg 4NQO/kg bw sc then 200	Mouse ddy (M), 9-15/group	Increased incidence of lung tumours at high dose	Yamanaka et al 1996

Test substance/dosing regime	Species/strain/sex	Main carcinogenicity findings	Reference
or 400 ppm DMA^V in drinking-water for 25 wk			Lung only examined
Single 50 µg dose of DMBA/mouse topical at week 1; then topical 3.6 mg DMA^V/mouse twice/wk, week 2–19	Mouse K6/ODC (M), 7-8/group	Increased incidence of skin tumours	Morikawa 2000 Skin only examined
Partial heptectomy, 18-24 h later DEN ip 30 mg/kg, 7 d later 160 ppm sodium arsenite in drinking water to 175 days	Rat, Wistar (M), group size not reported	Increased incidence of renal tumours	Shirachi et al 1983
Initial pretreatment with 5 known carcinogens (termed DMBDD) then 0, 50, 100, 200, 400 ppm DMA^V in the drinking-water during week 6–30	Rats, F344/DuCrj (M). 20/group	Increased incidence of urinary bladder papilloma + carcinomas or transitional cell carcinomas, kidney adenomas + adenocarcinomas, liver carcinomas, thyroid gland tumours, at 200 and/or 400 ppm	Yamamoto et al 1995
Pretreatment with BBN 0.05% in drinking-water for 4 wk then 0, 2, 10, 25, 50, or 100 ppm DMA^V in drinking-water for 32 wk	Rat, F344 (M). 20/group	Increased incidence of urinary bladder papillary/nodular hyperplasia, papillomas, carcinomas in As + TPA groups, at As at 25, 50, 100 ppm.	Wanibuchi et al 1996 Urinary bladder only examined
Arsenicals given to experimental animals concurrently with other agents enhance carcinogenesis, while arsenical has no effect alone			
0, 0.02% As in drinking water, throughout. 0, 2.5 µg TPA/mouse topical twice/wk, week 5 and 6	Mouse, Tg.AC homozygous (F). 20/group	Increased incidence of skin papillomas in As + TPA groups	Germolec et al 1997 Skin lesions only investigated
0 or 0.02% As in drinking water, throughout. 0, 1.25, 2.5 µg TPA/mouse topical twice/wk, Week 5 and 6	Mouse, Tg.AC homozygous (F). 20/group	Increased incidence of skin papillomas in As + TPA groups	Germolec et al 1998 Skin lesions only investigated
0, 10 mg/L sodium arsenite in drinking water throughout plus topical 1.7 kJ/m^2 solar irradiation (85% UVB, <1% UVC, 4% UVA,	Mouse, Crl:SKI-*hr*BR (hairless) (F). 5-15/group	Incidence of skin tumours greater in As + UVR than in UVR alone	Rossman et al 2001 Skin lesions only investigated

Test substance/dosing regime	Species/strain/sex	Main carcinogenicity findings	Reference
remainder visible; termed UVR) 3x/wk starting 3 wk after As until termination at 29 wk			
Expt 1: 0, 1.25, 2.5, 5,10 mg/L sodium arsenite in drinking water from onset plus topical 0, 1.0 kJ/m^2 solar irradiation (UVR) 3x/wk, starting 3 wk after As to termination at wk 29	Mouse, SKI (hairless). Gender & group size not recorded	Incidence of skin tumours greater in all As + UVR groups than in UVR alone	Burns et al 2004 Skin lesions only investigated
Expt 2: 10 mg/L sodium arsenite in drinking water from onset plus topical 1.7 kJ/m^2 UVR 3x/wk starting 3 wk after As to termination at wk 29			
0, 5 mg/L sodium arsenite in drinking water from onset; diet unsupplemented or with added vitamin E (62.5 IU/ kg diet; basal 49.0 IU/kg) or *p*-XSC (10 mg/kg diet) from onset. Topical 1.0 kJ/m2 UVRc 3x/wk starting 3 wk after As to termination.	Mouse, Crl:SKI-*hr*BR (hairless) (F). 10-30/group	Incidence of skin tumours greater in As + UVR than in UVR alone. Dietary supplements appeared to protect against the carcinogenic influence of As	Uddin et al 2005 Skin lesions only investigated
Treatment with 2 mg BA/mL in 25 µL topical once/wk for 2 wk sodium arsenate 0 or 25 mg/L drinking water for 25 wk	Mouse, Swiss-bald hairless (M). 10/group	Increased incidence of skin tumours in As + BA group, compared with BA	Motiwale et al 2005 Skin lesions only investigated
Arsenic given to experimental animals before another other agent enhances carcinogenesis, while arsenic has no effect alone			
Sodium arsenite: maternal exposure 0, 42.5, 85 ppm As in drinking water gestation days 8-18; offspring topical exposure to TPA at 2 µg/animal twice a week 4-25 wk of age, then 0, 42.5, 85 ppm As in drinking water offspring to	Mouse, Tg.AC (M,F) 50/group	Increased incidence of skin tumours in As + TPA groups compared to TPA alone	Waalkes et al 2008 Skin lesions only investigated

Test substance/dosing regime	Species/strain/sex	Main carcinogenicity findings	Reference
termination at 40 weeks of age			
Animals exposed to gallium arsenide (inhalation exposure)			
Gallium arsenide: 0, 0.1, 0.5, 1.0 mg/m^3, 6 h/d, 5 d/w, 105 wk	Mouse, B6C3F$_1$ (M, F). 50/group/sex	Increased incidence of lung epithelial alveolar hyperplasias at 0.5 and 1 mg/m^3 in M, F. No increases in tumour incidence	NTP 2000
Gallium arsenide : 0, 0.01, 0.1, 1.0 mg/m^3, 6 h/d, 5 d/w, 105 wk	Rat, F344 (M, F) 50/group/sex	Increased incidence of lung adenomas in F at 0.1 and 1 mg/m^3, lung atypical hyperplasia in M at 0.1 and 1 mg/m^3, adrenal medulla tumours in F at 1 mg/m^3, mononuclear cell hyperplasia in F at 1 mg/m^3	NTP 2000

For the oral studies with chronic exposure the arsenic dose as mgAs/kg bw/day has been calculated using the EFSA (2012) default factors for converting substance concentration in feed or water to daily doses
M: Males; F: Females

3.3.2 Human data

The epidemiological evidence on arsenic and cancer risk comes from two distinct sets of population studies. One set addresses the cancer risk associated with the inhalation route, conducted mainly in persons exposed to air contaminated by arsenic and other agents at work and based on death certificate analyses. The second set of studies was carried out in locations where the general population ingested arsenic in drinking-water at relatively high concentrations over prolonged periods of time; based on cancer registry data or specific diagnoses .

There are no human cancer studies that measured arsenic exposure for the dermal route.

3.3.2.1 Inhalation studies

The IARC Monograph (IARC, 2012) provides summaries of 21 investigations: five case-control studies, ten cohort studies and six nested case control studies, all published between 1987 and 2007. Brief details of these studies are presented in Table 4. These studies incorporate diverse qualitative and quantitative indices of arsenic exposure that include measures of average airborne concentration of exposure, cumulative exposure across the work experience, and duration of exposure. These studies provide consistent evidence for a positive exposure-response relationship between the indicators of arsenic exposure and lung cancer risk. Typically, the cohort studies report elevated lung cancer risks of 2 to 3-fold in the arsenic exposed groups. All the groups studied will have been exposed to other chemicals in addition to arsenic compounds, but it is considered unlikely that there could be some other common factor that would account for excess lung cancer risk.

Table 4 Arsenic inhalation cancer epidemiology studies, 1987-2007, adapted from IARC Monograph tables 2.1, 2.2 and 2.3

a) Case control studies

Cases	Controls	Arsenic exposure assessment	Results	Reference
155 orchardists who died of respiratory cancer, Washington state, 1968-1980	155 orchardists not dying of respiratory cancer; also non-orchardist controls, Washington state	Standardised questionnaire, next of kin interview	Odds ratio not significantly increased for arsenic exposure	Wicklund et al. (1988)
264 non-melanoma skin cancer cases from hospital in Slovenia, 1996-1999	286 population controls matched to cases	Standardised questionnaire, considering occupational and dietary exposure to arsenic	Odds ratio significantly increased (~2-fold) for 'high' arsenic exposure	Pesch et al. (2002)
645 melanoma cases, Iowa, 1999-2000	732 cases colorectal cancer in Iowa	Measurement of toenail arsenic content	Odds ratio significantly increased (~2-fold) for toenail arsenic 0.04-0.083 and >0.084 µg/g	Beane Freeman et al. (2004)
161 squamous cell carcinoma cases, 302 nodal basal cell carcinoma, 152 superficial multifocal basal cell carcinoma, 12 with malignant melanoma, Leiden	386 controls (no further information)	Personal interview	Odds ratio significantly increased (7-fold) for arsenic exposure for malignant melanoma cases only	Kennedy et al.(2005)
3174 lung cancer death cases among uranium miners, East Germany, 1946-1990	4892 circulatory disease deaths among uranium miners, East Germany	Airborne measurements from company records and modelling	Odds ratio significantly increased (1.4 to 1.8-fold) for arsenic exposure	Taeger *et al.* (2008)

Table 4 Arsenic inhalation cancer epidemiology studies, 1987-2007, adapted from IARC Monograph tables 2.1, 2.2 and 2.3 (continued)

b) Cohort studies

Cohort	Arsenic exposure assessment	Results	Reference
6078 workers at 8 copper smelters, 1949-1980, USA	Method of assessment unclear	Dose response relationship for arsenic exposure and lung cancer at one plant	Enterline et al (1987a,b)
4393 workers at zinc-lead-cadmium smelter before 1970, London	Air measurements by company hygienists	Relative risk for lung cancer increased (2-fold) for high arsenic exposure	Ades and Kazantzis (1988)
611 arsenic exposed workers, 1919-1982, Michigan	Air measurements and job classification by company hygienists	SMR increased (2 to 3-fold) for respiratory cancer	Sobel et al. (1988)
3916 copper smelter workers, 1928-1967, Rönnskär, Sweden*	Air measurements by company hygienists	SMR significantly increased (~3 to 11 fold) for respiratory cancer deaths	Järup et al. (1989)
54128 miners, Ontario	Based on arsenic measurements for the ores at each mine	SMR increased (up to 5.7-fold) for respiratory cancer with increasing index of arsenic exposure	Kusiak et al. (1991)
2802 copper smelter workers, 1940-1964, Tacoma, Washington State*	Air measurements and urinary arsenic concentrations, by company hygienists	SMR significantly increased (~2 to 3-fold) for respiratory cancer deaths	Enterline et al. (1995)
2039 male & 2957 female fertilizer plant workers, 1963-1990, Moscow	Modelled estimates expressed as an index	Relative risk not significantly increased	Bulbulyan et al. (1996)
6000 tin miners, 1973-1993, Yunnan, China	Standardised questionnaire, index of arsenic exposure calculated	Relative risk significantly increased (~3 to 5-fold) for higher exposure groups	Qiao et al., (1997)
8014 copper smelter workers, 1938-1957, Anaconda, Montana*	Air measurements from company records	Relative risk increased (2 to 3-fold) with increasing cumulative exposure	Lubin et al. (2000)
Subcohorts of 710 and 383 lead smelter workers, 1958-1987, Sweden	Air measurements from company records	Findings not reported specifically for arsenic exposure, though all but one of 10 lung cancer cases has significant arsenic exposure	Englyst *et al*. (2001)

* see text for more detailed description of study

Table 4 Arsenic inhalation cancer epidemiology studies, 1987-2007, adapted from IARC Monograph tables 2.1, 2.2 and 2.3 (continued)

c) Nested case control studies

Cases	Controls	Arsenic exposure assessment	Results	Reference
302 copper smelter workers who died of respiratory cancer, 1925-1947, Anaconda, Montana*	6 controls for each case, selected from copper smelter cohort of 8045 workers	Air measurements from company records	Relative risk significantly increased (2.5 to 2.8-fold) for mid and high arsenic exposure	Lee-Feldstein (1989)
103 copper smelter workers who died of lung cancer, 1928-1981, Sweden	2 deceased control for each case, not dying from lung cancer, selected from copper smelter cohort or 2916 workers	Air measurements by company hygienists	Relative risk significantly increased (8.7-fold) for high arsenic exposure	Järup and Pershagen (1991)
319 miners with lung cancer, 1972-1989, China	1358 controls, selected from an original cohort of 68285 workers	Exposure matrix developed from work histories, historical hygiene records and special monitoring program	Relative risk increased for tin miners with high arsenic exposure	Mc Laughlin *et al.* (1992)
130 tin miners who died of lung cancer, 1994, southern China	627 controls selected from cohort of 7855 workers	From industrial hygiene records. Questionnaire administered to subjects & next of kin interview	Relative risk significantly increased (~2 to 3.5-fold) for all arsenic exposure bands	Chen & Chen (2002)
213 nickel refinery workers diagnosed with lung cancer, 1952-1995, Norway	525 controls, selected from cohort	Exposure matrix developed from available data	Relative risk slightly increased for all arsenic exposure bands	Grimsrud *et al.* (2005)
518 workers for mining and pottery industries who died of lung cancer, 1994, China	1884 controls, selected from cohort of 65285 workers	Exposure matrix developed from employment records	Relative risk significantly increased (1.9-fold) for arsenic exposure	Chen et al (2007)

* see text for more detailed description of study

All the published quantitative estimates of arsenic lung cancer risk for the inhalation route focus on three occupational cohorts, all copper smelter workers exposed to arsenic trioxide, in Tacoma (Washington State, USA), Anaconda (Montana, USA) and Rönnskär (Sweden). A more detailed account of these cancer mortality investigations follows, adapted from the DECOS (2012) appraisals and with reference to the original publications. These investigations contain the best information on ambient exposure levels.

Tacoma copper smelter

The results for the Tacoma cohort have been published in a series of reports, the most recent being Enterline et al (1987a) and Enterline et al (1995). In the 1995 update, 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 and the 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 known deaths, death certificates were obtained for 96.6%. SMRs were calculated by reference to death rates for cancers for white males in the state of Washington (all studied workers were males and nearly all were white). Similar results were seen if local, county death rates were used.

Exposure to arsenic was estimated from departmental measurements of arsenic in air from the annual company reports, available since 1938 (the factory began operation in 1913), and by conversion from measurements of urinary arsenic made since 1948. Before 1971, the airborne arsenic concentrations came from “spot” samples and “tape” samples (apparently 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 report did not include any information on the particle size distribution of the airborne arsenic, although it can be assumed that the cumulative exposure estimates relate to the inhalable dust fraction, as it is the usual practice of hygienists to determine this fraction unless otherwise stated. The analysis did not take account of smoking as a potential confounding factor.

The standard mortality ratio (SMR) for lung cancer was 188 in the group with less than 20 years exposure and 217 among those with more than 20 years exposure, indicating a rather short latency period. An increase in lung cancer risk related to cumulative arsenic exposure was evident, as shown in Table 5. Figure 2 presents a plot of the SMR against cumulative arsenic exposure on an arithmetic exposure scale, highlighting apparently relatively larger increments in respiratory cancer risk at the lower exposure levels.

Table 5 Tacoma cohort: observed and expected deaths and SMRs for respiratory cancer by cumulative arsenic exposure

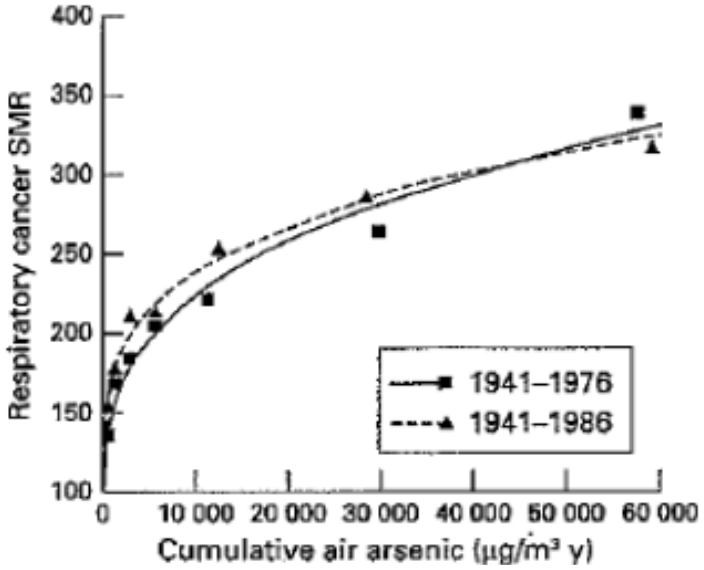
Cumulative exposure band ($mgAs/m^3.y$)	Mean exposure ($mg/m^3.y$)	Person years	Observed no. of respiratory cancer deaths	Expected no. of respiratory cancer deaths	SMR
<0.75	0.45	20445	22	14.29	154
0.75 –2	1.305	19111	30	17.10	175**

2- 4	2.925	15804	36	17.17	210**
4 - 8	5.708	13747	36	17.00	212**
8 - 20	12.334	10934	39	15.48	252**
20 - 45	28.336	4114	20	7.04	284**
>45	58.957	761	5	1.58	316*

The 1995 publication reports that there was a linear correlation between log dose and SMR for the entire cohort. The following regression equation was derived:

$$SMR = 100 + 10.5 \times (\text{cumulative exposure})^{0.279}$$

Figure 2 Tacoma copper smelters: SMRs for cancer risk vs. cumulative Airborne arsenic exposure for the years 1941 to 1976 and 1941 to 1986



Anaconda copper smelter

An elevated risk of lung cancer in the Anaconda cohort was originally reported in 1969. Updates and further cohort and nested case-referent analyses were subsequently published. The study population of the latest cohort update consisted of 8,014 white males, who were employed for more than 12 months from 1938 to 1957 (Lubin et al 2000). Their vital status was followed from January 1938 to December 1987. Causes of death were obtained from death certificates. At the end of the follow-up period a total of 4,930 (63%) were deceased, including 446 from respiratory cancer. The vital status was not determined for 1175 workers.

Some 700 airborne exposure measurements, collected between 1943 and 1958, were used to assign each work area to an exposure category on a scale 1-10, and work areas were then grouped as representing light, medium or heavy exposure. Time-weighted average (TWA) exposures for the three

exposure groups were estimated to be 0.29, 0.58 and 11.3 mgAs/m^3, respectively. It can assumed that these exposure estimates relate to the inhalable dust fraction, as it is the usual practice of hygienists to determine this fraction unless otherwise stated. It is noted that the representativeness of the exposure measurements is questionable, as data were available for less than half of the 29 working areas, measurements were often made after an exposure control measure was instituted or a process change occurred and most often in areas where arsenic was thought to be a hazard.

Altogether 446 deaths from respiratory cancer (SMR 155, 95% CI 141-170, with reference to US mortality rates for white males) were observed. A trend of increasing risk with increasing cumulative exposure was seen; the risk increased linearly with time of employment in each exposure category, as shown in Table 6. Also, the data show that relative risk has a relationship with increasing mean airborne concentration of arsenic independent of duration of exposure. In addition, it was found that relative risk for respiratory cancer declined with calendar year of follow-up. Measurements of arsenic in air were available only for the years 1943-1958, and the exposure assessment implicitly assumed that arsenic levels were constant over time. Available monitoring data and anecdotal information indicated that airborne arsenic levels declined over time in work areas with heavy and medium exposures with lesser reductions of airborne arsenic in work areas with light exposure. These variations in exposure probably accounted at least partly for the observed significant downward trend in the relative risk for respiratory cancer by year of follow-up. In support of this, it was found that the trend in the relative risks with duration of exposure declined with follow-up for medium and heavy, but not for light, arsenic exposures.

Table 6 Anaconda cohort: relative risks for respiratory cancer by years of employment in heavy, medium or light arsenic-exposed work areas

Years exposed	No. cases	Person years	Relative risk	95% CI
Light and unknown airborne arsenic work areas: estimated 0.29 mgAs/m^3 TWA				
1 - 4	63	39689	1.00	
5 - 14	49	34197	0.95	0.6 - 1.4
15 - 24	39	22040	1.22	0.8 – 1.9
25 - 34	51	15558	1.89	1.2 – 2.9
≥35	50	9436	1.98*	1.3 – 3.1
Medium airborne arsenic work areas: estimated 0.58 mgAs/m^3 TWA				
0	117	67914	1.00	
1 - 4	79	37232	1.39	1.0 – 1.9
5 - 9	12	5896	1.30	0.7 – 2.4
≥10	44	9585	3.01*	2.0 – 4.6
Heavy airborne arsenic work areas: estimated 11.3 mgAs/m^3 TWA				
0	201	103805	1.00	
1 - 4	30	13211	1.11	0.8 – 1.6
5 - 9	4	1590	1.4	0.5 – 3.8
≥10	15	2294	3.68*	2.1 – 6.4

* test for trend, significant $p<0.005$

Although information on smoking was not available, according to the authors it is noteworthy that mortality from smoking-related illness, except for chronic obstructive pulmonary disease, was not excessive. In a sample of 1469 workers from the original cohort, there was a higher proportion of smokers compared with US white males. However, the proportion of cigarette smokers did not vary significantly by extent of exposure to airborne arsenic, indicating that it was unlikely that smoking confounded the assessment of lung cancer risk with arsenic exposure according to the authors. The DECOS (2012) analysis of this study concluded that the following linear model can be applied to this dataset:

RR = 1 + 0.19 x cumulative exposure

A later analysis of data from same Anaconda cohort used an exposure reduction factor (nominal value of 0.1) in the higher exposure categories to account for the use of personal protection equipment (Lubin et al, 2008). Calculations of time related exposures as mg As/m^3 . yr were performed, which is consistent with the Tacoma and Ronnskar data. SMRs were calculated using data for US white males both uncorrected and with a correction for calendar year and country of birth (Table 7). Additional analyses confirmed that exposures to Arsenic concentrations above 0.29ug/m^3 presented a greater risk in terms of cumulative exposure (mg/m^3.yr).

Table 7 Anaconda cohort: observed respiratory cancer deaths and SMRs (crude and corrected) by cumulative arsenic exposure

Cumulative exposure band (mgAs/m^3.y)	Mean exposure (mg/m^3.y)	Person years	Observed no. of respiratory cancer deaths	SMR crude	SMR corrected (95% CI)
<0.75	0.47	71424	62	97	84 (60 – 110)
0.75 –2	1.24	66757	96	150	128 (100 – 160)
2- 5	3.43	55332	74	135	108 (90 – 140)
5 - 10	7.27	39257	83	149	111 (90 – 140)
10 - 14	11.9	16804	84	240	168 (140 – 210)
>15	21.9	7275	47	362	235 (180- 310)

The Lubin et al (2000 and 2008) reports did not include any information on the particle size distribution of the airborne arsenic. However, some information on particle size for the Anaconda site is available from a published report of an investigation of arsenic exposure and excretion (Smith et al 1977). For a 'low' exposure group (mean airborne concentration 8.3 µgAs/m^3) exposure 67.7% of the particles were deemed to be 'irrespirable' (defined by the authors as particles with >5 µm diameter) and the remainder were 'respirable' (<5 µm diameter). A similar proportion of particles were 'irrespirable' for a 'high exposure group (concentration 52.1µgAs/m^3). For a medium exposure group (concentration 46.1 µgAs/m^3) 19.3% of particles were 'irrespirable'. Urinary

arsenic excretion was found to be correlated to both 'respirable' and 'irrespirable' arsenic, although the correlation was stronger with 'irrespirable' arsenic, indicating that non-respirable particles are effectively captured by the respiratory system and transported to the gastrointestinal system for absorption.

Rönnskär copper smelter

The elevated lung cancer incidence among workers of the Rönnskär smelter was originally reported in a population-based case-referent study in 1978. Since then, studies using both cohort and case-referent approaches have been published. The following summary describes the cohort study of Järup et al (1989). The cohort of smelter workers consisted of 3916 males 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 ascertained. Mortality of different causes, taken from death certificates, was compared to rates of the general Swedish male population.

Air concentrations of arsenic were estimated by company occupational hygienists. The first measurements were carried out in 1945, and from 1951 exposure data were more generally available; production figures were used to extrapolate exposures before 1951. Each work site was characterised by an exposure level during three consecutive time periods, and the workers' cumulative exposure was assessed on the basis of their working history in these different work sites. The report did not include any information on the particle size distribution of the airborne arsenic, although it can be assumed that the cumulative exposure estimates relate to the inhalable dust fraction, as it is the usual practice of hygienists to determine this fraction unless otherwise stated.

The SMRs for respiratory cancer were very similar whether calculated with no latency, 10 years minimum latency (i.e. excluding cancer cases appearing within 10 years of start of employment) or 10 years minimum latency with exposure lagged 5 years, as shown in Table 8. 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). A statistically significantly increased risk was observed even in the lowest exposure category of <0.25 mgAs/m^3.years.

Table 8 Rönnskär cohort: relative risks for respiratory cancer by cumulative exposure

Cumulative exposure (mgAs/m^3.years)	No. of cases of lung cancer	SMR (95% CI) no latency	SMR 10 years latency	SMR 10 years latency and 5 years exposure lag
<0.25	14	271 (148 - 454)	272	269
0.25 - 1	13	360 (192 - 615)	384	366
1 - 5	17	238 (139 - 382)	230	249
5 - 15	15	338 (189 - 558)	350	352
15 - 50	29	461 (309 - 662)	468	456
50 - 100	6	728 (267 - 1585)	742	750
100+	12	1137 (588 - 1986)	1152	1164

Total	106	372 (304 - 450)	379	379

Little difference was observed in the SMRs for workers hired before 1940, in 1940-1949, or after 1949, when the estimated level of exposure was similar, meaning that a longer follow-up did not increase the apparent risk. In most subcohorts, and in the total cohort, the mortality increased with increasing average intensity of exposure, but no clear-cut trend was observed for the duration of exposure. Exposure to sulphur dioxide was also assessed. The lung cancer risk was elevated in all groups exposed to sulphur dioxide, but there was no exposure-response with cumulative sulphur dioxide exposure levels.

In a nested case-referent study on the interaction between smoking and arsenic exposure as lung cancer-causing agent in the cohort as described above (Järup and Pershagen, 1991) lung cancer risks were positively related to cumulative arsenic exposure with relative risks, standardised for smoking, ranging from 0.7 to 8.7 in different exposure groups. A negative confounding by smoking was suggested in the highest exposure category. The interaction between arsenic and smoking for the risk of developing lung cancer appeared less pronounced among heavy smokers.

In a cancer incidence study (Sandström et al., 1989), partly overlapping with the above described study, the cancer risk of the Rönnskär smelter workers over a moving 5-year period was found to decrease steadily from 1976-1979 to 1980-1984, showing that the later the date of first employment the lower the incidence of cancer, especially for lung cancer. This trend may be explained by decreasing exposure levels to arsenic. Further follow-up of an expanded Rönnskär cohort (n = 6,334) by Sandström and Wall (1992) showed also a decreasing trend in lung cancer incidence and mortality, but there was still an elevated lung cancer incidence among the workers when compared with the Swedish rates.

3.3.2.1 Oral (drinking water) studies

The IARC Monograph highlights a number of ecological, case-control or cohort studies, published between 1985 and 2007, conducted in areas of Taiwan, Chile, Argentina and Bangladesh with relatively high levels of arsenic in the drinking water, which consistently report elevated risks of lung cancer associated with increasing levels of arsenic exposure. In two of these studies the increased risk appeared to be greater in smokers. The drinking water studies conduced in Taiwan, Chile and Argentina also found increased risks of urinary bladder and those conducted in Taiwan and Chile found increased risks of skin cancer. Summaries of these studies are included in IARC Monograph Tables 2.6, 2.7 and 2.8. IARC also draw attention to evidence of an association between arsenic exposure and cancer of the kidney, liver and prostate provided by the drinking water studies, but for these cancers the possibility that the reported associations are due to chance or bias cannot be ruled out.

The published quantitative estimates of arsenic cancer risk for the oral route utilise mainly data from the dinking water studies conducted in Taiwan. The most recent of these studies, which focus on urinary tract and lung cancer, are briefly summarised below (Chen 2010a and 2010b).

The risks of urinary tract cancer (Chen 2010a) and lung cancer (Chen 2010b) were studied in a cohort of 6888 subjects, aged 40 or over, living in an area of north-eastern Taiwan. Information on demographics, smoking and alcohol consumption were obtained by trained interviewers using a standardised questionnaire. Incident urinary tract and lung cancers were ascertained from the national cancer registry. The follow-up time was 12 years for urinary tract cancer and 11 years for lung cancer. Arsenic concentration in drinking water was measured in 3901 samples taken from 4584 households at the time of the interview.

The results are summarised in Table 9. For urinary tract cancers the relative risks, adjusted for gender, age and smoking, showed a significant trend associated with increasing arsenic concentration in the drinking water. At arsenic concentrations greater than 100 µgAs/L the relative risks for urinary cancer were statistically significantly increased. For lung cancer risk there was also a significant trend associated with increasing arsenic concentration. However, statistically significant relative risks for lung cancer were seen only in the group with highest arsenic exposures, of ≥300 µgAs/L.

Table 9 Taiwan drinking water studies: relative risks of urinary tract and lung cancer by arsenic concentration in water, average follow up time 11.5 years

Arsenic conc. in drinking water (µg/L)	Arsenic total dietary exposure (µg/kg/day)[1]	No. of subjects	Urinary cancer		Lung cancer	
			No. of cases	Relative risk[2] (95% CI)	No. of cases	Relative risk[2] (95% CI)
<10	1.6	2288	5	1.00	48	1.00
10 - 49.9	3.0	2093	8	1.70 (0.56-5.19)	51	1.10 (0.74-1.63)
50 - 99.9	5.5	907	5	2.49 (0.72-8.59)	20	0.99 (0.59-1.68)
100 – 299.9	12.3	909	8	4.18 (1.37-12.8)	28	1.54 (0.97-2.46
≥300	25.9	691	11	7.73 (2.69-22.3)	31	2.25 (1.43-3.55)

[1]total dietary exposure to arsenic was estimated by WHO/FAO (2011), taking account additional arsenic intake from food estimated to be 75 µg/person, and assuming bodyweight of 55 kg.
[2]relative risks adjusted for gender, age and smoking

3.3.3 Toxicity and cancer mode of action (MoA)

This MoA summary is adapted from DECOS (2012)

Trivalent inorganic arsenicals readily react with sulfhydryl groups in proteins and inactivate many enzymes, thereby inhibiting critical functions such as gluconeogenesis and DNA repair. The pentavalent inorganic arsenic compounds require activation via reduction to a trivalent form, which occurs rapidly. In addition, as a phosphate analogue, pentavalent arsenic could potentially affect a number of biological processes, for example oxidative phosphorylation could be uncoupled. The metabolic products of inorganic arsenic compounds, the organic monomethylarsonous acid and

dimethylarsinous acid, have greater potency than the inorganic compounds in relation to cytotoxicity, enzyme inhibition and genotoxicity.

The cancer MoA of arsenic has not been established. There is experimental evidence providing some support for four possible MoAs: clastogenic damage, oxidative stress, inhibition of DNA repair, and a continuum involving altered growth factors leading to cell proliferation and the promotion of carcinogenesis. Because arsenic has not been shown to be a direct genotoxicant it is likely that arsenic carcinogenicity is a threshold effect. However, the available data do not allow the identification of threshold exposure levels with respect to the hypothesised cancer MoAs.

3.3.4 Carcinogenicity hazard conclusion

Arsenic and its inorganic compounds are proven carcinogens in humans, based on epidemiological evidence. Studies of men exposed at work via the inhalation have demonstrated a causal association between arsenic trioxide and lung cancer. Studies in populations exposed to relatively high levels of arsenic in drinking water provide evidence of a causal association between oral arsenic exposure and cancer of the lung, urinary tract and skin, and possibly with cancers of kidney, liver and prostate.

Arsenic and its inorganic compounds have metabolic pathways that involve the formation of As^{III} and the production of common methylated metabolites that are believed to be its bioactivation products, so epidemiological evidence of a causal association between cancer and arsenic is considered to be applicable to all forms of inorganic arsenic, including diarsenic pentoxide, diarsenic trioxide and arsenic acid. There is little information on the relative carcinogenic potencies of As^{III} and As^{V}, but given the common metabolic pathways the two forms of arsenic can be considered to be of similar potency.

The cancer MoA of arsenic and is inorganic compounds has not been established, but it appears not to be related to direct DNA reactive genotoxicity and therefore it is possible the arsenic carcinogenicity has a threshold exposure level. However, the available data to not allow the identification of threshold exposure levels for key events in the hypothesized MoAs. Therefore, given the uncertainties regarding the cancer MoA and lack information on MoA thresholds the cancer dose response assessment and quantitative estimates of risk (see WP2) must be conducted with the assumption that the carcinogenicity of arsenic is a non-threshold effect.

4 DOSE RESPONSE ASSESSMENT AND QUANTITATIVE ESTIMATES OF CANCER RISK (WP 2)

Methodologies for cancer risk estimation based upon epidemiological data differ from those based on animal data.

4.1 Published dose-response assessment and quantitative estimates of cancer risk

In recent years, a number of expert groups have provided quantitative estimates of cancer risk related to arsenic exposures, or used other approaches to derive exposure reference values, for both the inhalation and oral routes. A comparison of the main conclusions of these cancer assessments for arsenic and its inorganic compounds is shown in Table 10.

4.1.1 *Inhalation route*

Quantitative cancer risk estimates for arsenic for the inhalation route have recently been published by USEPA (1984), WHO (2000) and TCEQ (2012) in relation to environmental exposure of the general population (i.e. continuous exposure for a lifetime) and by DECOS (2012) for occupational exposure (i.e. exposure for 8 hours/day, 5 days/week for 40 years). These estimates were made using approaches that assume there is no threshold exposure level for arsenic carcinogenicity. Additionally, EC (2000), UK EPAQS (2008) and ACGIH (2004) have produced recommended guidance values for environmental exposure (EC, UK EPAQS) or occupational exposure limits (ACGIH) based on the application of uncertainty factors to a LOAEC for lung cancer identified from epidemiology studies; using this approach implies it is assumed that arsenic carcinogenicity has a threshold exposure level.

4.1.1.1 USEPA (1984) and USEPA IRIS

Data for the Anaconda and Tacoma copper smelter cohorts, published in 1982 and 1983, were used to quantity lung cancer risk for environmental exposure. Cancer unit risks (which is the upper bound excess cancer risk associated with a lifetime exposure to 1 µg/m^3 in air, which assumes a linear dose response relationship at low doses) for lung cancer of 2.56 x 10^{-3} and 7.19 x 10^{-3} per µg/m^3 were determined from the Anaconda and Tacoma cohorts, respectively. A linear absolute risk model was found to have a satisfactory fit to the data. Adjustments were made to extrapolate the risks identified for an occupational cohort exposed for about 8 hours/day for a working life to the general population experiencing continuous environmental exposure for a lifetime. It was assumed that the increase in age-specific mortality rate of lung cancer was a function only of cumulative exposures. Taking a weighted geometric mean of these results, a final unit risk of 4.3 x 10^{-3} per µg/m^3 was estimated. From this unit risk value the concentration of arsenic in air associated with a 10^{-6} (i.e. 1 in a million) excess lifetime risk of cancer can be estimated as 0.23 ng/m^3 for the general population.

The EPA report notes that the two study cohorts were large, exposure assessments included air measurements for the Anaconda smelter and both air measurements and urinary arsenic for the Tacoma smelter, observed lung cancer incidence was significantly increased over expected values, and the range of the cancer estimates derived from data from two different exposure areas were within a factor of 6. These observations suggest that a high level of confidence can be accorded to the estimated cancer unit risk.

4.1.1.2 *WHO (2000)*

The WHO expert group estimated lung cancer risk for environmental exposure using a similar unit risk approach as EPA (1984), also assuming a linear relationship between the cumulative arsenic dose and the relative risk of developing lung cancer, based on data from the Anaconda, Tacoma and Rönnskär copper smelter cohorts, adjusting for continuous lifetime exposure. The WHO unit risk was calculated by pooling the EPA 1984 unit risk for the Anaconda plant of 2.56×10^{-3}, a unit risk of 1.28×10^{-3} for the Tacoma cohort calculated from updated 1987 data and a unit risk of 0.89×10^{-3} for the Rönnskär using data published in 1989. A lower unit risk, in comparison with the EPA estimates, was calculated for the Tacoma cohort because earlier analyses may have underestimated inhalation exposure, which was estimated from urinary arsenic measurements. The final WHO unit risk was 1.5×10^{-3} per $\mu g/m^3$, a risk estimate about 3-fold lower than the EPA 1984 estimate. From this unit risk value the concentration of arsenic in air associated with a 10^{-6} excess lifetime risk of cancer for the general population can be estimated as 0.66 ng/m^3.

4.1.1.3 *TCEQ (2012) and Erraguntla et al (2012)*

This expert group estimated lung cancer risk for environmental exposure by applying the unit risk approach to the cancer mortality data from the Anaconda (Lubin et al. 2000, Lubin et al. 2008), Tacoma (Enterline et al. 1995) and Rönnskär (Järup et al 1989) copper smelter cohorts, making appropriate adjustments for continuous lifetime exposure. Using Poisson regression and maximum likelihood estimation, with lifetable calculations, an LED_{10} (the lowest effective dose corresponding to a 10% additional lifetime cancer risk), relevant to the Texas population, was determined for each study. The LED_{10} values were then used to calculate cancer unit risk values, which involved linear extrapolation from the LED_{10} to zero dose and risk. Combining the unit risk values for the three studies, a final inhalation unit risk for arsenic of 1.5×10^{-4} per $\mu g/m^3$ was determined. To compare with the WHO (2000) unit risk value, this is a factor of 10 lower. From the TCEQ unit risk value, the concentration of arsenic in air associated with a 10^{-6} excess lifetime risk of cancer can be estimated as 6.6 ng/m^3.

4.1.1.4 *DECOS (2012)*

DECOS (a Committee of the Health Council of the Netherlands) considers lung cancer to be the lead (most sensitive) adverse health effect for arsenic in relation to inhalation exposure.

DECOS assessed the most recent studies of lung cancer in the three copper smelter cohorts for suitability for risk modelling, specifically the publications of Lubin et al. (2000) and Lubin et al. (2008) for the Anaconda cohort, Enterline et al (1995) for the Tacoma cohort and Järup et al. (1989) for the Rönnskär cohort. DECOS concluded that all these studies had shortcomings, with Lubin et al (2000) being the strongest study with the fewest limitations.

The main weaknesses identified in the Lubin et al. (2000) study were, firstly, that respiratory cancer mortality was determined rather than lung cancer mortality, but this is thought to result in a mortality rate difference of about 4% which would have a negligible influence on the risk ratios. Secondly, the proportion of subjects lost to follow up was higher than for the Tacoma and Rönnskär cohorts, but the DECOS experts thought it reasonable to assume that the follow up losses were similar across all the exposure categories. However, the exposure assessments for the Anaconda cohort were superior to those for the other two cohorts. Also, the Anaconda studies used an internal exposure-response analysis in which a relative risk (RR) can be calculated, whereas the other studies compared exposure-related mortality with mortality in the general population and the calculation of an SMR; this comparison with the general population can cause problems because there is the potential for systematic differences in mortality between the general population and the exposed workers. Regarding the Lubin et al 2008 updated analysis, the same cohort was used but an exposure reduction factor was used for the higher exposure groups to account for the use of personal protective equipment. According to DECOS, this is not common practice when conducting in occupational quantitative risk calculations, so the Lubin et al 2008 report was not considered further.

Significant limitations were identified in the study of the Tacoma cohort (Enterline et al 1995). The description of the exposure assessment component was limited and basic descriptive information was lacking. Information about exposure for the early part of the study period, before 1938, was absent. Furthermore, it was not clear how exposure was assigned to certain job titles. Strengths of the study included low loss-to-follow-up, the quantitative characterisation of a dose response relationship by the authors and the use of mortality data relating to lung cancer rather than respiratory tract cancer. The study of the Rönnskär cohort by Järup et al (1989) also had significant limitations in the exposure assessment, such that it is difficult to characterise the dose-response relationship. A strength of this study was that loss-to-follow-up was low and the study considered lung cancer mortality.

DECOS noted that the Lubin et al. (2000) data had a good fit to a linear excess risk model within each exposure area, and the fit did not improve significantly when applying a power model. For this reason DECOS applied a linear model to determine a lifelong additional risk of lung cancer death using lifetable calculations based on mortality data for the Netherlands. DECOS state that the SMR data for the Tacoma and Rönnskär cohorts had good fits with power models, but draw attention to the possibility that the strong fit of these models is caused by the fact that there is a clear difference in risk

between the exposed population and the comparison group while there is a very weak association within the groups of exposed study subjects. When an attempt was undertaken to model the exposure response curve in the low exposure range (steep part of the curve) for these two cohorts the fit of linear models was very poor indicating that there was no clear exposure response curve discernible in this range. According to DECOS this provides an additional demonstration that the comparison with the general population may be problematic.

For the Anaconda copper smelter cohort and using the exposure assessment of Lubin et al. (2000), DECOS calculate an excess lung cancer mortality risks for arsenic of:

4 per 1,000 (or 4 x 10^{-3}) for 40 year occupational exposure to 28 µg/m^3
4 per 100,000 (or 4 x 10^{-5}) for 40 year occupational exposure to 0.28 µg/m^3

Thus, the occupational arsenic exposure associated with a 10^{-6} lung cancer risk is 0.007 µg/m^3. For comparison with the WHO (2000) and USEPA (1984) assessments outlined above, this cancer risk estimate can be extrapolated to continuous lifetime exposure scenario, assuming occupational exposure of 8 h/d, 5 d/w and a lifetime exposure of 70 y. From this extrapolation, the concentration of arsenic in air associated with a 10^{-6} excess lifetime risk of cancer can be estimated as 0.9 ng/m^3, which is similar to the WHO (2000) cancer risk estimate.

4.1.1.5 *EC (2000) and UK EPAQS (2008)*

The EC expert group also based their assessment on the data for the Anaconda, Tacoma and Rönnskär copper smelter cohorts. A lung cancer LOAEC of 125 - 415 µgAs/m^3 x years was identified from the Rönnskär and Anaconda cohorts. To this LOAEC, an uncertainty factor 10 was applied, to obtain a level at which one would expect that increased risks would be difficult to detect in a reasonably sized epidemiological study. The resulting concentration was then converted to a continuous lifetime exposure level which was expressed as a yearly exposure level and, finally, another uncertainty factor of 10 was applied to account for sensitive subgroups in the general population. This resulted in an air quality limit value of 4-13 ngAs/m^3, for use in environmental risk assessments.

EPAQS (2008) adopted a similar approach, taking the occupational lung cancer LOAEC of 125 µgAs/m^3 x years from Rönnskär copper smelter cohort, extrapolating to continuous environmental exposure and applying uncertainty factors of 10 x 10 to derive a guideline value of arsenic in ambient air of 3 ng/m^3 in PM_{10} size range.

The EPAQS recommendation and the lower end of the limit value range recommended by EC (2008) are about 5-fold higher than the concentration of arsenic in air predicted to cause a 10^{-6} excess lifetime risk of cancer according to the unit risk value derived by WHO (2000).

4.1.1.6 *ACGIH (2004)*

The ACGIH occupational exposure limit of 0.01 mgAs/m^3 (TLV-TWA) for arsenic and its organic compounds was based on the identification of 0.2 mg/m^3 as the lowest concentration of arsenic in air at which a risk of lung cancer exists in humans, from an evaluation of data for the Anaconda and Tacoma copper smelter workers. At 0.2 mg/m^3 a SMR of 213 for lung cancer mortality was calculated for the Tacoma cohort (Enterline et al 1987, see table 3 of this publication). The precise reasoning for selecting a limit of 0.01 mgAs/m^3 from the 0.2 mg/m^3 point of departure is not reported in the published ACGIH support document. According to the DECOS (2012) cancer risk assessment, a 40 year occupational exposure to arsenic at 0.01 mg/m^3 would result in an excess lung cancer risk of 1.4 x 10^{-4} (or 1.4 in 10000).

4.1.2 *Oral route*

Quantitative cancer risk estimates for arsenic for the oral route have recently been published by USEPA IRIS (assessment dated 1995), EFSA (2009), USEPA (2010, draft assessment for which permission to cite has been given) and WHO/FAO (2011). Additionally, WHO (2008 & 2011) has proposed a pragmatic guideline value for arsenic in drinking water.

4.1.2.1 USEPA IRIS (assessment dated 1995)

This cancer assessment was based on prevalence rates of skin cancer in a Taiwanese population exposed to high levels of arsenic in drinking water, using early studies (Tseng et al 1968, Tseng, 1977). A multistage model with time was used to predict dose-specific and age-specific skin cancer prevalence rates. Arsenic intakes for the study population were estimated from the measured concentration of arsenic in the drinking water with the assumption that drinking water consumption was 3.5 L/day for males and 2.0 L/day for females. An oral cancer slope factor (upper bound excess cancer risk associated with a lifetime exposure to 1 mg/kg/day) of 1.5 per mg/kg bw/day was determined. A drinking water unit risk (excess cancer risk associated with a lifetime exposure to 1 µg/L in water) of 5 x 10^{-5} per µg/L was calculated. From the oral cancer slope factor value, the oral intake of arsenic associated with a 10^{-6} excess lifetime risk of cancer can be estimated as 0.67 ng/kg bw/day.

4.1.2.2 EFSA (2009)

The EFSA assessment focused on arsenic intake via food. The expert group noted that more information is needed on the speciation of arsenic present in food as inorganic forms of arsenic are the most toxic, but the data on arsenic levels in food usually relates to total arsenic. [The contractor has noted that in most of the studies considered in this review speciation was not reported]. Cancer dose response data from drinking water studies selected as being key were modelled for skin lesions such as hyperpigmentation and palmoplantar hyperkeratosis (Ahsan et al. 2006, study conducted in Bangladesh; Xia et al. 2009, in Inner Mongolia), lung cancer (Ferreccio et al. 2000, in Chile) and

bladder cancer (Chiou et al. 2000, in Taiwan). Skin lesions were regarded as a sensitive marker for arsenic toxicity. A benchmark dose lower confidence limit value for a 1% excess cancer risk ($BMDL_{01}$) of between 0.3 and 8 µgAs/kg bw/day for cancer was proposed. The lowest $BMDL_{01}$ values (0.3 – 0.7 µg/kg bw/day) were for lung cancer, calculated using a linear model. Highest $BMDL_{01}$ values (3 – 8 µg/kg bw/day) were for bladder cancer, calculated using a non-linear model. For skin lesions, the best fits were obtained using a log-logistic or a log-probit model. This expert group chose to calculate the doses associated with a 1% excess risk as these doses are likely to be within the range of exposures experienced by average and high level consumers in Europe.

If it is assumed that there is a linear dose response relationship, the oral intake of arsenic associated with a 10^{-6} excess lifetime risk of cancer can be estimated as 0.03 – 0.8 ng/kg bw/day based on the $BMDL_{01}$ range of 0.3 and 8 µgAs/kg/day.

4.1.2.3 USEPA (2010, draft assessment)

Lung and bladder cancer prevalence data from the Taiwanese drinking water study, taken from an analysis by Morales et al (2000), were fitted to a Poisson model using maximum likelihood methods and cancer risk estimates (LED_{01}, the lowest effective dose corresponding to a 1% additional lifetime cancer risk) relevant to the US population were calculated using a life-table method. The LED_{01} values were used to calculate a cancer slope factor and unit risk, which involved linear extrapolation from the LED_{01} to zero dose and risk. Linear low dose extrapolation was considered appropriate because insufficient mode of action data were available to justify the use of non-linear low-dose models. The data for the Taiwanese cohort were considered to be of superior quality to those generated in the drinking water studies in other populations. The highest cancer potency factor was 25.7 per mg/kg/day, for combined lung and bladder cancer in women, which translates to a cancer unit risk of 7.3×10^{-4} per µg/L drinking water. From this oral cancer slope factor value, the oral intake of arsenic associated with a 10^{-6} excess lifetime risk of cancer can be estimated as 0.039 ng/kg bw/day (assuming a bodyweight of 70 kg and water consumption of 2 L/day).

4.1.2.4 WHO/FAO (2011)

In common with the EFSA (2009) assessment, WHO/FAO focus on arsenic intake via food and concerns about the lack of information on the occurrence and bioavailability of difference species of arsenic are raised.

Lung and bladder cancer prevalence data from the Taiwanese drinking water cohorts, using data from the most recent publications of Chen et al (2010a, 2010b), were modeled using a number of dichotomous models. These studies were selected as they provided the greatest strength of evidence for a causal association. The Ferreccio et al. (2000) case-control study of lung cancer in Chile, used by EFSA (2009) was not used because of a potential bias in the selection of the unexposed cases. The WHO/FAO expert group considered

using drinking water studies reporting arsenic-associated skin lesions, but these studies were rejected because of issues relating to case definition, exposure assessment and adjustments for confounders such as smoking and sun exposure. $BMDL_{0.5}$ (i.e. the dose associated with a 0.5% excess lung cancer risk) values were calculated, which ranged from 3.0 -10.8 µg/kg/day for lung cancer and 5.2 - 13.7 µg/kg/day for urinary cancer depending on the model used. An overall cancer $BMDL_{0.5}$ of 3.0 µgAs/kg/day was selected as the lowest value from models with a good fit to the data. The four models with a good fit that resulted in this $BMDL_{0.5}$ were gamma, log-logistic, multistage and quantal linear. For comparison with the EFSA (2009) cancer risk estimate, the $BMDL_{0.5}$ of 3.0 µg/kg/day can be extrapolated to a $BMDL_{01}$ of 6.0 µg/kg/day, which is about 10-20 fold higher that the EFSA risk estimate.

Assuming a linear dose response relationship, which is reasonable as the data had a good fit to a linear model, the oral intake of arsenic associated with a 10^{-6} excess lifetime risk of cancer can be estimated as 0.6 ng/kg bw/day based on the $BMDL_{0.5}$ of 3.0 µg/kg/day. The intake of 0.6 ng/kg/day is some 20-fold greater than the lowest end of the intake range for a 10^{-6} excess risk based on the EFSA (2009) assessment and about 15-fold greater than intake for a 10^{-6} excess risk based on the USEPA assessment. It should be noted that the intake of 0.6 ng/kg/day is below the arsenic intake range investigated in the Chen et al (2010a, 2010b) studies.

4.1.2.5 WHO (2011)

Taking account of the WHO/FAO (2011) assessment outlined above, the retention of a guidance value of 10 µg/L for arsenic in drinking water was recommended as a pragmatic approach. The guidance value is regarded as provisional because a NOAEL for arsenic has not been established and because the control of arsenic in drinking water to below 10 µg/L is difficult in many locations; furthermore, the practical analytical quantification limit is in the range 1-10 µg/L.

Table 10 Comparison of arsenic cancer dose response assessments by various expert groups

Reference	Risk assessment target population	Cancer dose response conclusion	Arsenic lifetime concentration/dose associated with a 10^{-6} excess risk of cancer, assuming a linear dose response relationship
Inhalation route			
USEPA (1984) & USEPA IRIS	General population exposed via ambient air for lifetime	Inhalation cancer unit risk = 4.3×10^{-3} per $\mu g/m^3$	0.23 ng/m^3
WHO (2000)	General population exposed via ambient air for lifetime	Inhalation cancer unit risk = 1.5×10^{-3} per $\mu g/m^3$	0.66 ng/m^3
DECOS (2012)	Occupational, inhalation, 8 h/d for 40 y	Concentration associated with 4×10^{-5} risk = 0.28 $\mu g/m^3$	0.9 ng/m^3 (this value has been adjusted for continuous lifetime environmental exposure to allow a convenient comparison with other the other assessments)
TCEQ (2012)	General population exposed via ambient air for lifetime	Inhalation cancer unit risk = 1.5×10^{-4} per $\mu g/m^3$	6.6 ng/m^3
EC (2000)	General population exposed via ambient air	Limit value = 4-13 ng/m^3, derived by applying UF of 100 to LOAEC for cancer	-
UK EPAQS (2008)	General population exposed via ambient air	Limit value = 3 ng/m^3, derived by applying UF of 100 to LOAEC for cancer	-
ACGIH (2004)	Occupational, inhalation, 8 h/d, 40 y	TLV = 0.01 mg/m^3, 20-fold lower than LOAEC for cancer	-
Oral route			
USEPA IRIS (1995)	General population exposed via drinking water for lifetime	Oral exposure cancer slope factor = 1.5 per mg/kg/day	0.67 ng/kg/day
EFSA (2009)	General population exposed via drinking water/food for lifetime	$BMDL_1$ = 0.3 – 8 µg/kg/day	0.03 – 0.8 ng/kg/day
USEPA (2010) (draft document)	General population exposed via drinking water for lifetime	Oral exposure cancer potency factor = 25.7 per mg/kg/day	0.039 ng/kg/day
WHO/FAO (2011)	General population exposed via drinking water/food for lifetime	$BMDL_{0.5}$ = 3 µg/kg/day	0.6 ng/kg/day
WHO (2011)	General population exposed via drinking water for lifetime	Guideline value = 10 µg/L, a pragmatic limit for drinking water as a NOAEL cannot be identified	-

4.2 Contractor's proposed options and recommendations

4.2.1 *Inhalation, workers*

The contractor recommends using the cancer risk estimates published by DECOS (2012) as the most reliable for workers exposed by the inhalation route (8h/day, 5d/week, for 40 years), which is as follows:

Excess lifetime risk of lung tumours = 1.4 x 10^{-4} per µg As/m^3

The DECOS cancer risk estimates were derived from an epidemiology study in US (Anaconda) copper smelter workers by Lubin et al. 2000). A lifelong additional risk of lung cancer death was determined using lifetable calculations and by the application of a linear excess risk model. The cancer data had a good fit to a linear model, and the fit did not improve significantly when applying a power model.

The DECOS cancer risk estimates make the assumption that cancer dose response relationship is non-threshold, which is appropriate in the opinion of the contractor. Consideration of the carcinogenicity MoA indicates that this does not involve direct genotoxic activity and therefore it is possible that arsenic carcinogenicity has a threshold exposure level. However, there are uncertainties regarding the cancer MoA and, furthermore, there is no information the thresholds exposure levels in relation to the hypothesised MoAs. Consequently, there is insufficient information to permit the reliable application of a threshold approach to estimating cancer risk and therefore a non-threshold approach is appropriate.

The DECOS risk estimates for the inhalation route are recommended over the other published cancer risk estimates for several reasons. The DECOS assessment considered the most up to date publications of the epidemiology studies in the copper smelter occupational cohorts. Sound reasons, based on a well described critical comparison of available epidemiology studies, were given for using only the Anaconda cohort and data in the Lubin et al. (2000) publication to calculate cancer risks. The DECOS assessment used standard modelling techniques, involving lifetable calculations. Finally, the DECOS risk estimates were roughly similar to the quantitative estimates of other groups (USEPA1984, WHO 2000, TCEQ 2012), when adjusted for continuous lifetime environmental exposure.

Because of the apparently linear dose response relationship, the risk level associated with any chosen occupational arsenic exposure level can be calculated arithmetically, as shown in Table 11:

Table 11 Proposed lifetime lung cancer risk estimates for workers exposed to different 8h-TWA concentrations of arsenic for 40 years

Arsenic exposure concentration (µgAs/m^3)	Excess lung cancer risk (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

These cancer risk estimates are considered to apply equally to arsenic intake from diarsenic trioxide, diarsenic pentoxide and arsenic acid exposure. The risk estimates are based on copper smelter workers exposed to diarsenic trioxide. As the extent of systemic absorption of arsenic trioxide on smelter workers is very high, at 40-60% (see Toxicokinetics section) of inhaled dose, it is unlikely that absorption of diarsenic pentoxide and arsenic acid will be significantly higher, suggesting that the lung cancer risk estimates are likely to be worst case in relation to diarsenic pentoxide and arsenic acid.

Data on the particle size of the pure arsenic compounds are limited. For diarsenic trioxide the data on the pure chemical indicate approximately 10% of particles are below 2µm in diameter and would be readily absorbed by the inhalatory route. In addition as arsenic is a systemic lung carcinogen, any larger particles that are cleared from the respiratory tract into the stomach would also be systemically available and possibly contribute to the lung cancer risk. On the limited data available it is proposed to assume that as the arsenic trioxide form is well absorbed the cancer risk predictions based on the arsenic trioxide exposed smelter workers will provide a realistic worst case that can be applied equally to inhalation exposures of all forms of the three arsenic compounds.

The available data on particle size distributions are inadequate to permit any differentiation with any confidence between the risk of exposures to respirable and non-respirable atmospheres.

4.2.2 Inhalation, general population

Because the DECOS occupational cancer risk estimates assume linearity, these estimates can be extrapolated to continuous lifetime arsenic exposure (24h/day, 7d/week, 70 year lifetime) for the general population (assuming that the occupational risk estimates apply to a daily 8 h arsenic exposure for 5 d/w for 40 years) by simple arithmetic as shown below:

Excess lifetime risk of lung tumours = 1.0×10^{-3} per µg As/m^3

Because of the apparently linear dose response relationship, the risk level associated with any chosen lifetime continuous arsenic exposure level can be calculated arithmetically, as shown in Table 12:

Table 12 Proposed lifetime lung cancer risk estimates for the general population exposed to different continuous concentrations of arsenic for 70 years

Arsenic exposure concentration (µgAs/m^3)	Excess lung cancer risk (x10^{-3})
10	10.5
5	5.2
2.5	2.6
1	1.0
0.5	0.52
0.25	0.26
0.1	0.10
0.01	0.01

4.2.3 Dermal, workers

As there are no data for the dermal route, recommend extrapolation is from the oral route.

There may be a first pass metabolism effect that might result in risks extrapolated from the oral route underestimating those for the dermal route. However, this is countered by the fact that dermal absorption (*ca* 1%) will be considerably less than for the oral route (*ca* 100%).

Specific data on dermal absorption and the impact of the first-pass effect should be provided in order to reduce the uncertainties in the dermal exposure assessment.

Thus, extrapolating assessment for the oral route, we recommend using the following relationship for the dermal route, which assumes linearity:

$BMDL_{0.5}$ = 3 µgAs/kg bw/day

Excess lifetime risk of lung tumours = 1.7 x 10^{-3} per µg As/kg bw /day (*as a systemic exposure*)

Table 13 Proposed lung cancer risk estimates for persons with dermal exposure of arsenic, for an average follow-up period of 11.5 years

Arsenic total exposure (µg/kg/day)	Excess lung cancer risk (x10^{-3}) (assuming 1% dermal absorption)
10	0.17
5	0.08
2.5	0.04
1	0.017
0.5	0.008
0.25	0.004
0.1	0.0017
0.01	0.00017

4.2.4 Oral, general population

The contractor recommends using the cancer risk estimate published by WHO/FOA (2011), which is

$BMDL_{0.5}$ = 3 µgAs/kg bw/day

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

The $BMLD_{0.5}$ was derived 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. As is the case with the DECOS (2012) cancer risk assessment above, the WHO/FOA cancer assessment assumes that the dose response relationship is non-threshold which, for the reasons given above, the contractor is in agreement with.

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/FOA 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 to find the most conservative cancer risk estimates. This assessment used the most up to date data from the Taiwanese drinking water cohort. Nevertheless this estimate is not the most conservative.

Because dose response relationship can be regarded as linear, the oral exposure level associated with any chosen risk level can be calculated by simple arithmetic, as shown in Table 14.

Table 14 Proposed cancer risk estimates for persons with oral intake of arsenic, for an average follow-up period of 11.5 years

Arsenic total intake (µg/kg/day)	Excess lung cancer risk (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

Though linearity can be assumed, it is probable not wise to conduct linear extrapolations beyond the range of exposures experienced by the Taiwanese drinking water cohort, which ranged from about 2 to 25 µgAs/kg/day as the shape of the response curve is uncertain. Although there is evidence to

indicate a threshold approach could be valid, there is insufficient evidence to show where the threshold lies. The use of a linear extrapolation is considered the most appropriate default position.

5 OVERALL CONCLUSIONS

The project specification required a review of the relevant scientific literature related to the carcinogenicity of the three arsenic containing compounds listed in table 15 (Work Package [WP] 1) and the establishment of relevant carcinogenicity dose-response curves for each of these substances (WP 2) for the purpose of Authorisation under REACH.

Table 15: Arsenic compounds considered in this project (with their chemical identifiers and carcinogenicity classification in Annex VI of CLP Regulation)

No.	Name of substance	EC no.	CAS no.	Classification 1272/2008
1	Diarsenic pentoxide (also known as arsenic pentoxide)	215-116-9	1303-28-2	1a
2	Diarsenic trioxide (also known as arsenic trioxide)	214-481-4	1327-53-3	1a
3	Arsenic acid	231-901-9	7778-39-4	1a

The contractor identified and obtained existing detailed, good-quality reviews of the carcinogenicity of arsenic and its inorganic compounds, including quantitative risk assessments, published in the scientific literature or by particular authorities around the world since the year 2000. In addition, the contractor identified and obtained the individual studies cited in these reviews that have been crucial to the overall position developed by each review. A literature search has not identified any significant new publications of cancer studies of relevance to this project that are not included in these cancer assessments.

Arsenic exists in four common valence states, 0 (metalloid arsenic), +3 (e.g. the arsenites), +5 (e.g. the arsenates) and –3 (arsine gas). Diarsenic trioxide is a trivalent compound; diarsenic pentoxide and arsenic acid are pentavalent compounds. The trivalent arsenic compounds are considered generally to have greater toxicity than the pentavalent arsenic compounds (ATSDR 2007), possibly because of the greater reactivity of As^{III} and because As^{III} enters the cell more readily as compared to As^{V}. Arsenic and its inorganic compounds have metabolic pathways that involve the formation of As^{III} and the production of common methylated metabolites that are believed to be bioactivation products. Because of the related metabolism and general absence of information on the valence (speciation) of arsenic to which people were exposed inorganic arsenic compounds are considered together in all of the published assessments listed above, and in this document. Absorbed inorganic arsenic undergoes widespread distribution, irrespective of the route of exposure.

Particle size data are available only for diarsenic trioxide, as marketed. All three compounds have water solubilities of >10 g/L and are considered very water soluble based on IUCLID 5 criteria (Details are in Annex 1).

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 adrenals, bladder and liver have also been reported in some studies in animals. The mode of carcinogenic action has not been defined but does not appear to involve mutagenicity. Inorganic arsenic compounds do not cause point mutations. Studies in experimental test systems show that inorganic arsenic is clastogenic, causing chromosome aberrations, sister chromatid exchanges and DNA damage. Increased frequencies of chromosome aberrations and sister chromatid exchanges associated with arsenic exposure have been reported in human populations. It is likely that the genotoxicity of arsenic is a threshold effect, although the available data do not allow the identification of threshold exposure levels.

Lung carcinogenic potency of the three arsenic compounds following oral exposures to their solid form is expected to be similar as solubility will not be a limiting factor. With the systemic nature of the lung carcinogenicity, it is unclear if particle size will be a critical element in inhalation risks as larger particles that do no reach the alveolae but are cleared by mucociliary clearance could be absorbed from the intestinal tract, presenting a risk of lung cancer from systemic exposure.

5.1 Inhalation, workers

A summary of the quantitative cancer risk assessments of arsenic for the inhalation route, published by several authorities around the world and in the scientific literature in recent years, is given in Table 16 below. The assessments can be divided into two groups, those that used a linear extrapolation approach (USEPA, WHO, DECOS and TCEQ) and those following a threshold approach of applying a safety factor to a derived cancer LOAEC (EC, UKEPAQS, ACGIH).

All of the assessments used the same data sets based on death certificates of exposed workers from the Tacoma (USA), Anaconda (USA) and Ronnskar (Sweden) smelting plants. There are a number of uncertainties in these studies in terms of actual exposure parameters and corrections for confounding factors such as smoking. Analyses were based on cumulative exposures to arsenic ($mg/m^3.yr$) The USEPA, WHO and DECOS values are all very similar (Table 16). The TCEQ value is significantly different, described as possibly due to the use of revised exposure data from the Anaconda plant (Lubin et al, 2008), with an unsupported correction for the use respiratory protective equipment .

The threshold based analyses are consistently less conservative than the linear extrapolation values. Notably, the ACGIH limit value for workers is several orders of magnitude higher than the EC and UK values for the general population. However, the basis for the ACGIH point of departure is not described or justified and the contractor considers it to be unreliable.

No details are available of the particle sizes in the atmosphere in the three smelting plants. Analyses by Lubin et al indicate that risks are greater for a given cumulative exposure when this is associated with higher ambient concentrations rather than longer duration exposure.

Table 16: Comparison of arsenic cancer dose response assessments by various expert groups

Reference	Risk assessment target population	Cancer dose response conclusion (Smelter plant data)	Arsenic lifetime concentration/dose associated with a 10^{-6} excess risk of cancer, assuming a linear dose response relationship
Inhalation route			
USEPA (1984) & USEPA IRIS	General population exposed via ambient air for lifetime	Inhalation cancer unit risk = 4.3×10^{-3} per $\mu g/m^3$	0.23 ng/m^3
WHO (2000)	General population exposed via ambient air for lifetime	Inhalation cancer unit risk = 1.5×10^{-3} per $\mu g/m^3$	0.66 ng/m^3
DECOS (2012)	Occupational, inhalation, 8 h/d for 40 y	Concentration associated with 4 $x10^{-5}$ risk = 0.28 $\mu g/m^3$	0.9 ng/m^3 (this value has been adjusted for continuous lifetime environmental exposure to allow a convenient comparison with other the other assessments)
TCEQ (2012)	General population exposed via ambient air for lifetime	Inhalation cancer unit risk = 1.5×10^{-4} per $\mu g/m^3$	6.6 ng/m^3
EC (2000)	General population exposed via ambient air	Limit value = 4-13 ng/m^3, derived by applying UF of 100 to LOAEC for cancer	-
UK EPAQS (2008)	General population exposed via ambient air	Limit value = 3 ng/m^3, (PM_{10} range) derived by applying UF of 100 to LOAEC for cancer	-
ACGIH (2004)	Occupational, inhalation, 8 h/d, 40 y	TLV = 0.01 mg/m^3, 20-fold lower than LOAEC for cancer	-

The datasets used for risk estimation showed excess cancer risks over a range of different exposure levels and durations and fitted linear dose-

response models at least as well as other mathematical relationship. There are some limitations in the exposure characterisation and measurements conducted in the studies selected, deficiencies in the assessment of possible co-exposures to other lung carcinogens, incomplete assessment of confounding factors, especially smoking.

It is the contractor's view that the three smelting plant datasets represent the best available studies of the dose-response relationship between arsenic and lung cancer in terms of methodological quality, accounting for confounding by smoking and quantitative exposure-response information. No new epidemiological study on occupational arsenic exposure and lung cancer meeting these criteria has been published in recent years or since these assessments were completed. The data do not permit the reliable derivation of a threshold for lung tumours from arsenic inhalation and it is considered that a linear extrapolation approach is valid down to 3 ug/m^3 levels as increased risks were detected following 25 or more years exposure at 290 ug/m^3. The most reliable of the analyses is considered to be DECOS (2012)

The contractor recommends using the cancer risk estimates published by DECOS (2012) for workers exposed by the inhalation route, which are as follows:

Excess lifetime risk of lung tumours = 1.4 x 10^{-4} per µg As/m^3

The DECOS cancer risk estimates were derived from an epidemiology study in US (Anaconda) copper smelter workers by Lubin et al. (2000). A lifelong additional risk of lung cancer death was determined using lifetable calculations and by the application of a linear excess risk model. The cancer data had a good fit to a linear model, and the fit did not improve significantly when applying a power model.

Overall, therefore, for occupational inhalation exposure to all inorganic arsenic compounds independent of particle size, an excess lung cancer risk of 1.4 x 10^{-4} per µg As/m^3 is used. Given the indications of a threshold mode of action it is likely that this will overestimate the risk at low exposure levels.

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

Arsenic exposure concentration (µgAs/m^3)	Excess lung cancer risk (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

The limited evidence available shows that the proposed risk estimates are applicable to exposures to aerosols of all the inorganic arsenic compounds.

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, it seems reasonable to associate the above risk estimates with material in air of "total inhalable" particle size. The epidemiology studies contain insufficient information to discriminate particle sizes and likely deposition in the respiratory tract. Therefore, whether or not to reduce the risk estimates for particles that are non-respirable but still within the inhalable range needs further consideration and as a default, no correction should be made. *Note: particle size information should be an integral part of any Authorisation application.*

5.2 Inhalation, general population

Correcting the DECOS assessment from occupational exposure to lifetime environmental exposures gives an Excess lifetime risk of lung tumours = 1.0 x 10^{-3} per µg As/m^3

The cancer risk estimates for different levels of environmental exposure derived linearly from the proposed unit risk are shown in Table 18 below. However, 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.

Table 18: Proposed excess lifetime lung cancer risk estimates for the general population exposed at different ambient concentrations of As for 70 years

Ambient As exposure concentration (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

5.3 Dermal, workers

There is no evidence that dermal exposure to As 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 As compounds in experimental animals exposed via the dermal route are available.

If a dermal assessment of systemic cancer risk is required, the contractor recommends extrapolation from the oral route (described below).

There may be a first pass metabolism effect that might result in risks extrapolated from the oral route underestimating those for the dermal route. However, this is countered by the fact that dermal absorption (*ca* 1%) will be considerably less than for the oral route (*ca* 100%).

Thus, extrapolating the assessment for the oral route, we recommend using the following relationship for the dermal route, which assumes linearity:

$BMDL_{0.5}$ = 3 µgAs/kg/day

> Excess lifetime risk of lung tumours = 1.7×10^{-3} per µg As/kg bw /day (*as a systemic exposure*)

Table 19 Proposed cancer risk estimates for persons with dermal exposure of arsenic, for an average follow-up period of 11.5 years

Arsenic total inhalation exposure (µg/kg/day)	Excess lung cancer risk ($x10^{-5}$) (assuming 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

5.4 Oral, general population

Quantitative cancer risk estimates for arsenic for the oral route have recently been published by USEPA IRIS (assessment dated 1995), EFSA (2009), USEPA (2010, draft assessment) and WHO/FAO (2011). Additionally, WHO (2008 & 2011) has proposed a pragmatic guideline value for arsenic in drinking water. These are summarised in Table 20. The analyses are based on epidemiology studies on populations exposed to high levels of As in drinking water.

Table 20 Comparison of oral arsenic exposure cancer dose response assessments by various expert groups

Reference	Risk assessment target population	Cancer dose response conclusion	Arsenic lifetime concentration/dose associated with a 10^{-6} excess risk of cancer, assuming a linear dose response relationship
Oral route			
USEPA IRIS (1995)	General population exposed via drinking water for lifetime	Oral exposure cancer slope factor = 1.5 per mg/kg/day	0.67 ng/kg/day
EFSA (2009)	General population exposed via drinking water/food for lifetime	$BMDL_1$ = 0.3 – 8 µg/kg/day	0.03 – 0.8 ng/kg/day
USEPA (2010) (draft document)	General population exposed via drinking water for lifetime	Oral exposure cancer potency factor = 25.7 per mg/kg/day	0.039 ng/kg/day
WHO/FAO (2011)	General population exposed via drinking water/food for lifetime	$BMDL_{0.5}$ = 3 µg/kg/day	0.6 ng/kg/day
WHO (2008) & (2011)	General population exposed via drinking water for lifetime	Guideline value = 10 µg/L, a pragmatic limit for drinking water as a NOAEL cannot be identified	-

The derived values vary by over an order of magnitude. This can be explained by a number of factors:

- The USEPA (1995) is based on skin cancer prevalence data from Taiwan; using a multistage model;
- USEPA (2010) is based on lung and bladder cancer data from Taiwan; using a maximum likelihood method.
- EFSA (2009) evaluated a wide range of data focusing on arsenic in food and tumours at a number of sites. The most sensitive results were for lung cancer ($BMDL_1$ = 0.3 – 0.7ug/kg bw/d) and the least sensitive for bladder cancer ($BMDL_1$ = 3 – 8 ug/kg bw/d).
- WHO/FAO (2011) was based on lung and bladder cancer data from Taiwan; using various models to derive a $BMDL_{0.5}$. The value of 3ug/kg bw/day is based on lung tumours using the lowest model with a good fit.

The WHO (2008; 2011) guideline value is a pragmatic value based on a number of considerations including natural background levels and analytical capabilities as well as cancer risks.

The contractor recommends using the cancer risk estimate published by WHO/FOA (2011), which is

- $BMDL_{0.5}$ = 3 µgAs/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

The $BMLD_{0.5}$ was derived 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/FOA 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 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.

Because dose response relationship can be regarded as linear, the oral exposure level associated with any chosen risk level can be calculated by simple arithmetic, as shown in Table 21

Table 21 Proposed cancer risk estimates for persons with oral intake of arsenic, for an average follow-up period of 11.5 years

Arsenic total oral intake (µg/kg/day)	Excess lung cancer risk ($x10^{-3}$)
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

Though linearity can be assumed, it is probable not wise to conduct linear extrapolations beyond the range of exposures experienced by the Taiwanese drinking water cohort, which ranged from about 2 to 25 µgAs/kg/day as the shape of the response curve is uncertain. Although there is evidence to indicate a threshold approach could be valid, there is insufficient evidence to show where the threshold lies. The use of a linear extrapolation is considered the most appropriate default position.

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7 GLOSSARY

ELR (Excess Lifetime Risk) is the risk attributable to the exposure of interest (i.e. risk in the exposed group minus risk in the unexposed group). It is also defined as the additional or extra risk of developing the disease due to exposure to a toxic substance incurred over the lifetime of an individual.

JEM (Job-Exposure Matrix) comprises a list of levels of exposure to an agent for selected occupational titles.

Rate is the frequency of occurrence of disease in a population. It can be directly observed by the number of subjects developing disease divided by the total time experienced for the subjects followed. This parameter is applicable to incidence (number of new cases of the disease detected) or mortality (number of cases died as a result of the disease).

RR (Relative Risk) is the ratio of two rates (e.g., rate among exposed group divided by rate among unexposed group). The standardized ratio, such as standardized mortality ratio (SMR) or standardized incidence ratio (SIR), which are used in cohort studies if the unexposed reference group is the general population, is also a measure of relative risk as is the *odds ratio* (OR), which is derived from case-control studies.

Risk is measured as the number of subjects developing disease during a time period divided by the number of subjects followed for the time period and represents the average risk of disease in the population. It is a proportion.

SMR (Standardized Mortality Ratio) is a quantity, expressed as either a ratio or percentage quantifying the increase or decrease in mortality of a study cohort with respect to the general population.

Unit risk is an excess lifetime risk per unit of exposure.

8 LITERATURE SEARCH STRATEGY

Reviews were identified by google search using the following key terms: “arsenic”, “risk assessment”, “review”, “evaluation”.

New publications not included in the reviews were identified by searching PubMed for the period 2012 – present (24 May 2013) using the following key terms: “arsenic”, “carcinogenicity”, “risk assessment”, “genotoxicity”, “mutagenicity”, “mode of action”, “mechanism”.