Development Support Document
PRELIMINARY DRAFT, April 2009
DO NOT CITE OR QUOTE

Arsenic and Inorganic Arsenic Compounds

CAS Registry Numbers: 7440-38-2 (Arsenic)

Prepared by

Neeraja K. Erraguntla, Ph.D.
Toxicology Division

Chief Engineer's Office

TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Chapter 1 Summary Tables

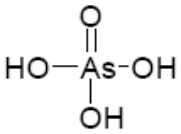
Table 1 provides a summary of health- and welfare-based values based on an acute and chronic evaluation of arsenic. Tables 2A and 2B provide physical/chemical data on arsenic and other inorganic arsenic compounds.

Table 1. Health- and Welfare-Based Values for Arsenic (As) - Particle size < 10 µm		
Short-Term Values	**Concentration**	**Notes**
^{acute}ESL [4 h] (HQ = 0.3)	0.33 µg/m^3 **Short-Term ESL for Air Permit Reviews**	**Critical Effects: Decrease in Fetal Weight in mice**
acute ReV [4 h] (HQ = 1.0)	1.1 µg/m^3 *	
^{acute}ESL$_{odor}$	N/A	There are no odors associated with arsenic
Long-Term Values	**Concentration**	**Notes**
^{chronic}ESL$_{nonlinear(nc)}$ (HQ = 0.3)	0.03 µg/m^3	**Critical Effects: Cardiovascular Effects in occupational workers**
chronic ReV (HQ = 1.0)	0.099 µg/m^3*	
^{chronic}ESL$_{linear(c)}$	Under development	Lung cancer in occupational workers
^{chronic}ESL$_{veg}$	N/A	No vegetation studies were identified for inorganic arsenic

* Screening value for air monitoring data.

Abbreviations used: **HQ**, hazard quotient; **µg/m^3**, micrograms per cubic meter; **h**, hour; **ESL**, Effects Screening Level; **ReV**, Reference Value; **^{acute}ESL**, acute health-based ESL; **^{acute}ESL$_{odor}$**, acute odor-based ESL; **^{acute}ESL$_{veg}$**, acute vegetation-based ESL; **^{chronic}ESL$_{linear(c)}$**, chronic health-based ESL for linear dose-response cancer effects; **^{chronic}ESL$_{nonlinear(nc)}$**, chronic health-based ESL for nonlinear dose-response noncancer effects; and **^{chronic}ESL$_{veg}$**, chronic vegetation-based ESL

Table 2A. Physical and Chemical Properties of Arsenic and Inorganic Arsenic Compounds

Name	Molecular Formula	Chemical Structure	Molecular Weight	Synonyms	Percent Arsenic by Weight	CAS Registry Number
Arsenic	As	As	74.92	Arsenic black, metallic arsenic	100%	7440-38-2
Arsenic acid	AsH_3O_4		141.94	Orthoarsenic acid	-	7778-39-4
Arsenic Trioxide	As_2O_3	$[As^{3+}]_2\,[O^{2-}]_3$	197.84	Arsenic (III) trioxide, arsenious acid, arsenious oxide, white arsenic	75.7%	1327-53-3
Arsenic Pentoxide	As_2O_5	$[As^{5+}]_2\,[O^{2-}]_5$	229.82	Arsenic(V) oxide, arsenic anhydride, arsenic acid, anhydride	65.2%	1303-28-2

Data in Table 2-A was obtained from Agency for Toxic Substances and Disease Registry (ATSDR 2007)

Table 2B. Physical and Chemical Properties of Arsenic and Inorganic Arsenic Compounds

Name	Physical State	Density	Boiling Point	Melting Point	Solubility	Vapor Pressure
Arsenic	Gray metal	5.778 g/cm^3 @ 25º C	603 (sublimation point)	817 (triple point at 3.7 Mpa)	Soluble in nitric acid, insoluble in water	7.5×10^{-3} mm Hg at 280ºC
Arsenic acid	Exists only in solution, white translucent crystals, very pale yellow syrupy liquid	2.2 g/cm^3	160º C	35.5º C	302 g/L at 12.5º C	No data
Arsenic Trioxide	White cubic crystals (arsenolite) white monoclinic crystals	3.86 g/cm^3	460º C	274º C	17 g/L at 16º C	2.47×10^{-4} mm Hg at 25ºC
Arsenic Pentoxide	White amorphous powder	4.32 g/cm^3	No data	315º C	2300 g/L at 20º C	No data

Data in Table 2-B was obtained from ATSDR (2007)

* Alberta Environment 2005

Chapter 2 Major Sources or Uses, Atmospheric Fate, Ambient Air Concentrations, and Routes of Exposure

2.1 Natural Sources

Arsenic is widely distributed in the earth's crust, which contains ~3.4 parts per million (ppm) arsenic (ATSDR 2007). In nature, a small proportion of arsenic exists in its elemental form. It is, however, present predominantly in minerals. Arsenic is released naturally into the environment during the weathering of rocks as wind blown dust, and during volcanic eruptions, forest fires, and during volatilization of methylarsines from the soil (ATSDR 2007).

2.2 Uses and Anthropogenic Sources

While natural sources contribute to a small extent, the majority of arsenic released into the environment is from anthropogenic sources. Arsenic found in mineral ores is released as a byproduct into the

environment during the mining and smelting of copper, lead, cobalt, and gold ores.

In addition to nonferrous metal mining and smelting operations, arsenic is also released into the environment during pesticide applications, coal combustion, wood combustion, and waste incineration processes. Arsenic in the form of gallium arsenide (GaAs) is a major component in semi-conductors for telecommunications, solar cells, and space research. Arsenic is an important alloying element in ammunition and as an anti-friction additive to metals used for bearings. It is also used to strengthen lead acid storage battery grids (ATSDR 2007). Further, arsenic trioxide and arsenic acid have long been used as decolorizers and are important components in the production and manufacture of glassware. Historically, various compounds of arsenic have been used in medicine to treat various disorders of the skin and respiratory system. Interestingly, arsenic trioxide has been re-introduced as a potential drug to treat acute promyelocytic leukemia (ATSDR 2007).

In the United States (US), the use of inorganic arsenicals has decreased to a large extent due to the ban on production. However, organic arsenicals are still present in the US as herbicides and as antimicrobial additives for animal and poultry feed (ATSDR 2007), and all of the arsenic used presently is imported from other countries. According to 2005 import/export data, the US was the world's largest consumer for arsenic in the form of copper chrominated arsenate, a wood preservative (ATSDR 2007).

2.3 Atmospheric Fate of Arsenic

As arsenic is an element, it cannot be destroyed in the environment. It can only change its form, or become attached or get separated from particles. In ambient air, arsenic exists predominantly in the particulate form, adsorbed onto the surface of fine particles that are in the respirable range (< 10 micrometer (μm)) in aerodynamic diameter. According to the USEPA (1983), the arsenic emitted from fugitive emissions produced by smelters and coal burning power plants is in the form of arsenic trioxide (As_2O_3). At the operating temperatures of these processes, the As_2O_3 in the inhalable particle size range can effectively enter and be retained in the respiratory tract. The anthropogenic arsenic in the atmosphere occurs as fine particles with a mass median diameter of about 1 μm and has a residence time of 7-9 days in the atmosphere (Coles et al. 1979, Pacyna et al. 1995). Various reports have indicated these particles can be transported by wind and air currents across distances greater than 1,000 kilometers (USEPA 1984a).

While the trivalent forms of arsenic (As_2O_3) are the primary forms released into the atmosphere, arsines are also present to a certain extent. In the atmosphere, the trivalent arsenics and methyl arsines undergo oxidation to the pentavalent state. Therefore, the arsenic in the atmosphere is a mixture of the both the trivalent and/or pentavalent forms (EPA 1984a, Robano et al. 1989). Also, arsenicals do not undergo photolysis and to a large extent remain unchanged in the atmosphere (EPA 984a).

2.4 Ambient Levels of Arsenic in Air and Routes of Exposure

The primary routes of arsenic entry into the human body are ingestion and inhalation (ATSDR 2007). In rural areas, atmospheric levels of arsenic range from 1 – 3 nanograms per cubic meter (ng/m^3), and in urban areas, the levels in the atmosphere range from 20 – 100 ng/m^3. The general population can potentially be exposed to both fine particles (≤ 2.5 μm) and coarse particles (2.5-10 μm). Coarse particles can be generated by many common mechanical processes such as grinding and spraying, and have the potential to penetrate and deposit throughout the respiratory tract (Polissar et al. 1990). According to Yager (1997), power plant workers were reported to be exposed to arsenic in coal fly ash, of which about

90% of the arsenic was in particles ≥ 3.5 µm. Arsenic naturally occurs in the earth's crust and is present in pesticides. Therefore, higher concentrations in both soil and water may occur in places where arsenic-rich minerals are present and from run off after pesticide applications. In general, ground-water concentrations are usually < 10 µg/L and soil arsenic levels can range from 1 to 40 mg/kg (ATSDR 2007). In the US, the estimated dietary intake of inorganic arsenic ranges from 4.8 – 12.7 µg/day, with 21 - 40% of the total dietary arsenic being the inorganic forms (Yost et al. 1989).

The organic forms of arsenic are generally considered to be non-toxic when compared to the inorganic forms of arsenic. The organic arsenicals such as the methyl and phenyl derivates of arsenic have wide-spread use as pesticides and have been reported to be toxic in chronic toxicity animal studies (Arnold 2006). Examples of methyl and phenyl derivatives include monomethylarsonic acid (MMA) and its salts (monosodium methane arsonate [MSMA] and disodium methane arsonate [DMSA], dimethylarsinic acid (DMA or cacodylic acid) and its sodium salt (sodium dimethyl arsinite, or sodium cacodylate), and roxarsone (3-nitro-4-hydroxyphenylarsonic acid). A few of the organic arsenicals such as arsenobetaine and arsenocholine have been found to accumulate in fish and shell fish and are commonly referred to as "fish arsenic." Estimates of the concentration of organic arsenicals indicate food to be the largest contributor to the background intakes of organic arsenicals. Although diet is the largest source of exposure to arsenic for most people (ATSDR 2007), this document addresses inhalation exposure to inorganic forms of arsenic.

Chapter 3 Acute Evaluation

3.1 Health-Based Acute ReV and ESL

3.1.1 Physical/Chemical Properties and Key Studies

3.1.1.1 Physical/Chemical Properties

The main physical and chemical characteristics of arsenic and select inorganic arsenic species are summarized in Tables 2A and 2B. Arsenic is in Group 15 of the periodic table and is classified as a metalloid, as it has both the properties of a metal and a non-metal. Arsenic is, however, frequently referred to as a metal (ATSDR 2007). Arsenic exists in various oxidation states. Elemental arsenic or metallic arsenic exists in the 0 oxidation state (As (0)) in two forms: the alpha- and beta-forms. The alpha-form is crystalline, brittle, and steel gray in color. The beta-form is amorphous and is dark grey in color. In addition, arsenic occurs in combination with other elements as inorganic and organic arsenic. In the inorganic form, arsenic occurs in combination with oxygen, chlorine, and sulfur. In the organic form, arsenic combines with carbon and hydrogen. Arsenic can exist in one of three oxidation states: -3, +3, and +5 (Carapella 1992).

3.1.1.2 Essential Data and Key Studies

This section is based on ATSDR's review on inorganic forms of arsenic (ATSDR 2007). In addition, the Toxicology Division (TD) also reviewed California EPA (Cal EPA)'s draft on the inorganic forms of arsenic. A review of the scientific literature since 2004 did not reveal any other acute studies that could be used other than those mentioned in the ATSDR review.

3.1.1.2.1 Rationale for the Evaluation of As_2O_3

The toxicological evaluation of arsenic is complicated due to the ability of arensic to exist in various oxidation states and as many inorganic and organic compounds. Evidence indicates that inorganic arsenicals as opposed to organic arsenicals are the principal forms associated with human toxicity. Among inorganic arsenicals, arsenic trioxide (As_2O_3) is most common in air, while inorganic arsenates (AsO_4^{-3}) or arsenites (AsO_2^{-}) occur mostly in water, soil, or food. According to ATSDR's toxicological profile on arsenic (ATSDR 2007), the trivalent arsenites tend to be relatively more toxic when compared to pentavalent arsenates. The TD concurs with ATSDR that the differences in the relative potency of inorganic arsenicals is reasonably small and within an order of magnitude. Therefore, the present Development Support Document (DSD) will focus mainly on As_2O_3, the most common form of inorganic arsenic in air and a soluble form, and for which toxicity information is present. The toxicological evaluation for other less common inorganic arsenicals and organic arsenicals will not be considered separately as they are expected to be of approximately equal or lesser toxicity than As_2O_3. One notable exception is arsine (AsH_3) and its methyl derivates, which are highly toxic and will be considered in a separate evaluation.

3.1.1.2.2 Human Studies

The majority of the available exposure data for arsenic toxicity via the inhalation pathway are from occupational exposure and epidemiology studies.

3.1.1.2.2.1 Respiratory and Gastrointestinal Effects

Short-term exposures to arsenic have been reported to result in severe irritation to both the upper and lower parts of the respiratory system, followed by symptoms of cough, dyspnea, and chest pain (Friberg et al. 1986). In addition, exposure to arsenic dust has been reported to cause laryngitis, bronchitis, and/or rhinitis (Dunlap, Pinto and McGill cited in ATSDR 2007). Further, exposure to arsenic via inhalation and/or ingestion can also cause gastrointestinal symptoms such as garlic-like breath, vomiting, and diarrhea (Pinto and McGill cited in ATSDR 2007). The TD did not use the above-mentioned reports of adverse health effects (i.e., respiratory and/or gastrointestinal effects) to develop short-term toxicity factors because the exposure concentrations and exposure durations were not adequately reported in these studies.

3.1.1.2.2.2 Developmental and Reproductive Studies

Airborne arsenic has been investigated as a developmental toxicant in a few epidemiology and case control studies. ATSDR (2007) reviewed the available developmental studies and indicated that the evidence for airborne arsenic as a developmental toxicant for humans to be inconclusive. The TD will provide a brief summary of the human developmental epidemiology studies conducted by Nordstrom et al. (1978, 1979) and the case control study conducted by Ihrig et al. (1998).

Nordstrom et al. (1978, 1979)

Occupational and environmental exposure to airborne arsenic has been investigated by Nordstorm and co-workers in a series of studies at the Ronnskar copper smelter in northern Sweden. On comparison to controls, female employees at the smelter had significantly increased incidence of spontaneous abortions and increased frequency of congenital malformations. In addition, the female employees at the smelter were reported to have significantly decreased average birth weights for their infants. Nordstrom et al. (1978, 1979) also investigated developmental effects in a population who lived in close proximity to the

smelter. Similar to the female employees at the smelter, pregnant women living in the vicinity of the smelter reported increased incidences of spontaneous abortions and decreased infant birth weights. While the evidence suggests arsenic's role as a developmental toxicant, the studies were limited as they did not include adequate information about potential confounders (e.g., smoking and other pollutants) and because they lacked data correlating the apparent effects with arsenic exposure. Therefore, the TD did not use the Nordstrom series (1978, 1979) as key studies.

Ihrig et al. (1998)

A case-control study by Ihrig et al. (1998) reported statistically significant increase in stillbirths in a group of people exposed to >100 ng As/m^3 (midpoint = 682 ng/m^3) in Texas. However, the authors concluded that the risk was limited to the Hispanic populations, who, in the opinion of the authors, have a genetic impairment in folate metabolism, an essential component to protect against arsenic toxicity. Also, the study was limited due to the small sample size and due to inadequate information on the smoking history and concurrent exposure of the study participants to other pollutants. Therefore, the Ihrig et al. study (1998) was not selected as a key study.

3.1.1.2.3 Animal Studies

3.1.1.2.3.1 Developmental and Reproductive Studies

The ability of arsenic to function as a developmental toxicant via the inhalation route has been examined in animal studies. The results from studies conducted in mice (Nagymajtenyi et al. 1985) and rats (Holson et al. 1999) indicate that mice are more sensitive than rats to developmental toxicity after arsenic exposure. The TD used a weight-of-evidence-approach in the evaluation of the available inhalation toxicity experiments. While, the Nagymajtenyi et al. (1985) study was limited in its exposure protocol (e.g., smaller sample size and few exposed groups) and reported fewer end points (e.g., dam weight) when compared to the Holson et al. (1999) study, the Nagymajtenyi et al. (1985) study exposure protocol (i.e, 4 hours (h)) met the criteria specified in the ESL Guidelines (TCEQ, 2006) unlike the Holson et al. (1999) study in which the exposure duration was for a longer duration (i.e., several weeks) The Nagymajtenyi et al. (1985) was therefore selected as the key study to determine the acute reference value (ReV) and short-term effects screening value (^{acute}ESL). Detailed descriptions of the animal studies are presented below.

The Nagymajtenyi et al. Study (Key Study)

Nagymajtenyi et al. (1985) conducted a study to investigate chromosomal damage and fetotoxicity in mice exposed to a range of concentrations of As_2O_3. Pregnant CFLP mice were exposed to different concentrations of As_2O_3 aerosols that were generated by spraying aqueous solution of As_2O_3 in the inhalation chamber. The authors reported that they measured the atmospheric concentrations in the chamber at least once daily during each exposure. However, no additional details were provided on how the aerosols were generated, characterized, and analyzed. Four groups (8 -11 per group) of pregnant mice were exposed to As_2O_3 for 4 h on the 9^{th}, 10^{th}, and 12^{th} days of gestation at the following concentrations: 0, 0.26 ± 0.01, 2.9 ± 0.04, and 28.5 ± 0.3 mg/m^3. The lowest concentration 0.26 mg/m^3 was close to the maximum allowable concentration (MAC) in Hungary where the experiments were conducted. In addition, the effects at 10- and a 100-fold higher than the MAC were also tested. The control mice were exposed only to distilled water.

The mice were sacrificed on the 18^{th} day of gestation and the fetuses were removed. The following fetal information was recorded for the 50 fetuses: average number of dead fetuses per dam, average fetal

weight, and skeletal malformations. Skeletal information on the fetuses was obtained from examination under a stereomicroscope. The reported abnormal skeletal malformations included: large fontanelles, wider cerebral sutures, flat and dumbbell-shaped ventral nuclei of vertebrae, missing ossification of nuclei in the sternum, metatarsals and phalanges. From each exposure group, livers of ten fetuses were selected to study chromosomal damage. Twenty mitoses in each fetus (200 in each group) were scored for chromosomal damage and 10% of these were karyotyped (Table A-2 of Appendix A). For fetal weight, the Dunnett's multiple comparison t-test was used to compare the treatment groups with the control. For the other end-points, the Fisher's exact probability test was used to discern statistical differences.

A statistically significant decrease in fetal weight was observed in all the three exposure groups with a 23%, 9.8%, and 3.5% reduction reported from the high-exposure to the low-exposure groups, respectively (Table 3). The Group 2 mice exposed to 0.26 mg/m^3 (260 µg/m^3) was the lowest exposure group in which the fetal weight was statistically different from controls (3.5%). Although statistically significant, the TD does not consider a <5% reduction in body weight in the fetus as being adverse (Kavlock et al. 1995; Allen et al. 1996). Therefore, the dose of 0.26 mg/m^3 (260 µg/m^3) from the key study is considered a no-observed-adverse-effect-level (NOAEL). ATSDR supports the position that a <10% reduction in body weight is not adverse (Personal Communications 2008). However, Cal EPA considers any statistically significant decrease in fetal weight as a cause of concern since it increases the probability of infant mortality (Public Draft 2007) and reported the 0.26 mg/m^3(260 µg/m^3) from the key study as a lowest-observed-adverse-effect-level (LOAEL). Further, the TD considers 2.9 mg/m^3 (2900 µg/m^3) as the LOAEL, although benchmark dose modeling for decreased fetal body weight was conducted to determine the appropriate point of departure (POD) for this endpoint (Refer to Section 3.1.4 *Points of Departure (PODs) for the Key Study and Critical Effect).*

Table 3. Effect of Exposure to Atmospheric Arsenic (4 h/day, on days 9, 10, & 12 of gestation) on Fetal Development In Mice

Groups	Concentration of As_2O_3 (mg/m^3)	Number of Litters	Average Number of Living Fetuses per Mother	Number of Examined Fetuses	Dead Fetuses (%)	Average Fetal Weight (g)	Number of Fetuses with Retarded Growth
1	0	8	12.5	100	8	1.272 ± 0.02	1
2	0.26 ± 0.01	8	12.5	100	12	1.225 ± 0.03*	2
3	2.9 ± 0.04	8	12.8	100	13	1.146 ± 0.03*	3
4	28.5 ± 0.3	11	9.6	100	29	0.981 ± 0.04*	51*

* Significantly different from control ($p < 0.05$)

In addition to reduction in fetal weights, the number of live fetuses decreased and the number of fetuses with retarded growth significantly increased in the highest exposure group of 28.5 mg/m^3 (Table 3). Also, the number of dead fetuses was reported to be 4% and 5% higher in groups 2 and 3, when compared to the control group. The frequency of skeletal malformations also increased significantly in the highest exposure group (28.5 mg/m^3). Of a total of 50 fetuses that were examined in the highest exposure group,

32 fetuses showed retarded ossification of the limbs (delayed bone maturation). The frequency of sternal, vertebral, and skull abnormalities also increased in the high exposure group. In the second highest exposure group of 2.9 mg/m^3, the frequency of skeletal malformations was not significantly different when compared to controls (Table A1, Appendix A).

The authors also investigated chromosomal aberrations on exposure to arsenic (i.e., chromosomal breaks and chromatid exchanges). While the frequency of chromosomal aberrations was increased significantly in the highest exposure group, the frequencies of the chromosomal aberrations were not statistically significant in the other two exposure groups (Table A2, Appendix A).

While the study described the number of malformations, it did not quantify malformations on a litter basis or discuss the severity of the malformations. In addition, the Nagymajtenyi et al. (1985) study did not document maternal effects (i.e, decrease in dam weights, and/or if the dams experienced respiratory distress) at any of the test concentrations. It is, therefore, difficult to discern if maternal effects occurred. Therefore, based on the above mentioned limitations, the TD's confidence in the Nagymajtenyi study is medium.

The Holson et al. Study (1999)

While the Holson et al. (1999) study had a relatively better exposure design when compared to the Nagymajtenyi et al. (1985) study, the Holson et al. (1999) study has limited use in determining the acute ReV or a ^{acute}ESL because the exposure scenario included multiple weeks of exposure that would not qualify the study as meeting the requirements for acute exposure as defined in the ESL Guidelines (TCEQ 2006). Therefore, the TD did not consider the Holson et al. (1999) study as a key study in the development of acute toxicity factors for arsenic.

Holson et al. (1999) evaluated arsenic trioxide (As_2O_3) as a developmental toxicant via the inhalation route in rats. The authors also conducted a preliminary exposure range–finding study and followed that with the actual study (i.e., definitive study). In both sets of experiments, female Crl:CD®(SD)BR female rats were exposed to As_2O_3 aerosol dust via whole body inhalation for 6 h beginning 14 days prior to mating with continued exposure through mating and gestation, until gestational day 19. Holson et al. (1999) reported the additional exposure period to be a deviation in the exposure protocols that is typically recommended by the Organization for Economic Cooperation and Development's Guideline for Testing of Chemicals: Teratogenicity (OECD, 1981) and the USEPA (1991). Controls for the range-finding study were kept in the non-exposure animal room and the controls for the definitive study were handled in the same manner as the exposed group except for being exposed to filtered air. Periodic chamber analysis was conducted to estimate the exposure concentrations.

In the preliminary study, maternal effects in the form of rales (i.e., labored respiration and gasping) were observed in the 10 and 25 mg/m^3 groups. Therefore, the highest As_2O_3 concentration in the definitive study was set at 10 mg/m^3 with the assumption that exposure to this concentration would cause acceptable levels of maternal distress (i.e., without excessive pulmonary congestion). In the definitive study, groups of 24 female rats were exposed to 0.3, 3, and 10 mg/m^3 As_2O_3. The aerosol sizes were reported as the median mass aerodynamic diameter (MMAD) and were: 2.1 ± 0.13, 1.9 ± 0.29 and 2.2 ± 0.13 (mean ± SD) µm respectively for the three exposure groups. The mean geometric standard deviations for the three exposure groups were: 1.74, 1.94, and 1.87 respectively.
Maternal effects: The authors reported no significant clinical signs for maternal effects for the control and

the two lower exposure levels. However, for the 10 mg/m^3 group, the female rats exhibited rales and dried red material around the nose. Also, statistical differences were reported in the food consumption and net body weight gain in the 10 mg/m^3 exposure group when compared to the control group. A NOAEL of 3 mg/m^3 and a LOAEL of 10 mg/m^3 was reported based on the maternal effects reported above.

Fetal effects*:* No exposure-related fetal effects (i.e., mean fetal body weight or the ratio of males/females in each litter) were reported from any of the exposure levels of the study. While three fetal malformations were observed, the authors reported them to be not statistically significant from the controls. Also, the authors did not observe any dose-related increase (even non-significant) in the incidence of individual and/or total malformations. As there was no evidence of developmental toxicity in pregnant rats exposed by inhalation of As_2O_3 up to 10 mg/m^3, the free-standing NOAEL is 10 mg/m^3 for developmental toxicity based on this study.

Table 4. provides summary information and compares the Holson et al. (1999) study with the Nagymajtenyi et al. (1985) study.

Table 4. Summary of Inhalation Reproductive/Developmental Animal Studies

Study	Species	Duration of Exposure	NOAEL (µg/m^3)	LOAEL (µg/m^3)	Critical Effect	Type of Arsenic
Nagymajtenyi et al. (1985) [1]	CFLP Pregnant mice	4 h/day on gestation days 9, 10, 12	260	2900	Decrease in fetal weight	As_2O_3 aerosol
Holson et al. (1999)	Female rats	6 h/day 14 days prior to mating through mating and until gestation day 19	3000	10,000	Maternal effects respiratory distress (rales)	As_2O_3 aerosol
			10,000	-	No fetal effects	

[1] Key study

3.1.2 Mode-of-Action (MOA) Analysis

ATSDR (2007) included several theories to explain the MOA for carcinogenic and/or noncarcinogenic effects after exposure to inorganic arsenic. The carcinogenic MOA is discussed in greater detail in latter sections, although the MOA for noncarcinogenic effects and carcinogenic effects share common elements. The noncarcinogenic MOA of arsenic is considered to be a threshold, non-linear MOA.

3.1.2.1 Toxicokinetic Summary

The database on the toxicokinetics of arsenic is extensive and is discussed in ATSDR (2007). Arsenic in air is present predominantly as inorganic arsenic and is in the particulate form. Short-term exposures to arsenic have been reported to result in point-of-entry (POE) effects and include severe irritation to both

the upper and lower parts of the respiratory system (Friberg et al. 1986). However, long-term arsenic exposure also causes systemic toxicity. For systemic toxicity to occur the particles have to undergo two processes: 1) the particles need to be deposited onto the lung surface and 2) the deposited particles need to be absorbed from the lung.

The rate of absorption of arsenic is dependent on whether the arsenic is present in soluble (i.e., arsenate and arsenite) *versus* insoluble form (i.e., arsenic sulfide, lead arsenate). The soluble forms of arsenic are better absorbed than the insoluble forms for both the inhalation and oral routes of exposure. Also, the toxicity of arsenic compounds is generally associated with soluble inorganic trivalent forms (AsIII). The pentavalent (AsV) inorganic compounds have to be first reduced in vivo to the trivalent forms prior to toxicity occurring (Harvey, 1970).

3.1.2.2 Interaction with Sulfhydryl-Containing Enzymes

At the cellular level, two mechanisms seem to exist by which inorganic arsenic can elicit toxicity. In the first mechanism, arsenic binds with sulfhydryl groups and disrupts sulfhydryl-containing enzymes. The disruption of these critical enzymes results in an inhibition of a suite of enzyme pathways that includes: the pyruvate and succinate oxidation pathways and the tricarboxylic acid cycle, impaired gluconeogenesis, and reduced oxidative phosphorylation. In the second mechanism, arsenic toxicity is thought to occur due to the ability of pentavalent arsenic to substitute for phosphorus in many biochemical reactions. The pentavalent arsenic anion is less stable when compared to the phosphorus anion in phosphate. This results in rapid hydrolysis of high-energy bonds in compounds such as adenosine triphosphate (ATP) and leads to loss of high-energy phosphate bonds and effectively "uncouples" oxidative phosphorylation (ATSDR 2007).

3.1.2.3 Metabolism

The toxicity and carcinogenicity of inorganic arsenic is reported to be associated with the metabolic process which is depicted in Figure 1. Arsenate or AsV that is absorbed gets reduced rapidly to AsIII or arsenite and the AsIII then gets distributed to tissues and is taken up by cells particularly hepatocytes. As the AsIII is more toxic than the AsV, the reduction of the AsV to the AsIII is considered a “bioactivation” step rather than a “detoxification” step. Glutathione appears to mediate the reduction of AsV to AsIII, and the reduction step is necessary before methylation can occur. S-adenosylmethionine is the methyl donor and the methylation of arsenic results in monomethylated arsenic (MMA) and dimethylated arsenic (DMA), which are often considered to be relatively less toxic forms of arsenic as they react to a lesser extent with tissue constituents when compared to the inorganic forms of arsenic and are also readily excreted in the urine. However, some of the intermediates of the methylation process include trivalent metabolites MMAIII and DMAIII. These trivalent metabolites are very reactive, and have been detected in the urine of humans chronically exposed to inorganic arsenic in drinking water. In addition, many in vitro studies have demonstrated both MMAIII and DMAIII have genotoxic and DNA-damaging properties (ATSDR 2007).

It is important to note that the availability of methyl donors (e.g., methionine, choline, cysteine) is different under normal conditions and under severe conditions such as dietary restrictions. While the availability of the methyl donors is not rate limiting under normal conditions, under severe diet restriction, the methylating capacity can become rate-limiting.

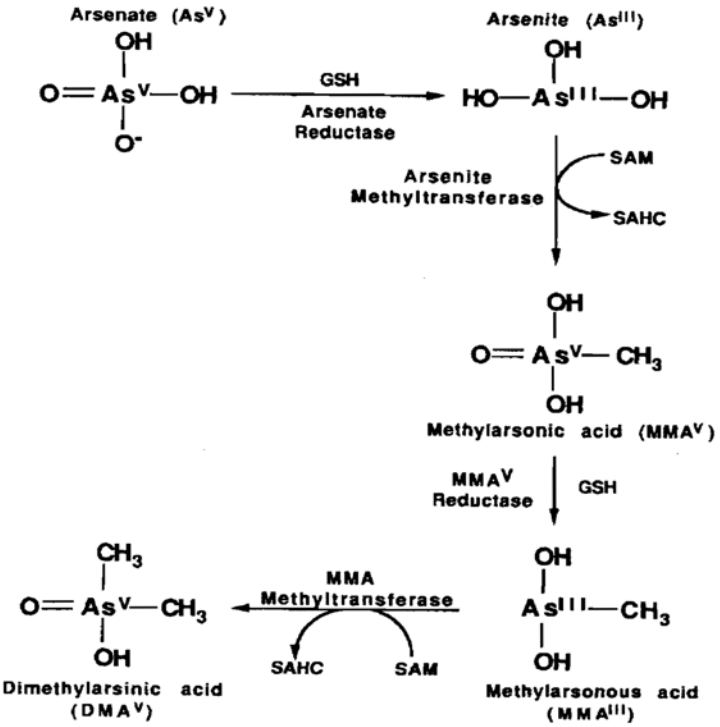


Figure 1: Inorganic arsenic biotransformation pathway. SAM, S-adenosylmethionine, SAHC, S-adenosylhomocysteine *Source: Aposhian et al. 2000 as cited in ATSDR (2007)

ATSDR (2007) also reviewed an alternate biotransformation pathway proposed by Hayakawa et al. (2005). The alternate pathway is based on the nonenzymatic formation of glutathione complexes with arsenite resulting in the formation of arsenic triglutathione. According to ATSDR (2007), in the first pathway, inorganic arsenic biotransformation pathway, MMA(V) is converted to the more toxic MMA(III). In contrast, in the alternative pathway, MMA(III) is converted to the less toxic MMA(V). ATSDR (2007) did not prefer or select one metabolic pathway over the other. Please refer to ATSDR (2007) for a more detailed description of arsenic metabolism.

3.1.2.4 Oxidative Stress

Results of in vitro and in vivo studies in human and animals suggest generation of reactive oxygen species as necessary for increased lipid peroxidation, superoxide production, hydroxyl radical formation, and/or oxidant–induced DNA damage. Mechanistic studies exist that support the hypothesis of arsenic-induced oxidative stress and include findings that inhaled arsenic can predispose the lung to oxidative damage and that chronic low-dose arsenic can alter genes and proteins associated with oxidative stress and inflammation.

3.1.3 Dose Metric

In the key and the supporting studies, data on the exposure concentration of the parent chemical are available. Since data on other specific dose metrics (e.g., blood concentration of parent chemical, area under blood concentration curve of parent chemical, or putative metabolite concentrations in blood or

target tissues) are not available for these studies, exposure concentration of the parent chemical will be used as the default dose metric.

3.1.4 Points of Departure (PODs) for the Key Study and Critical Effect

The key study is the Nagymajtenyi et al. (1985) study and the critical effect is developmental toxicity as demonstrated by decreased fetal body weight. This effect is considered to be relevant to humans. Skeletal malformations were only observed at the highest concentration (Table 3 and Table A-1 of Appendix A) and will not be considered. The NOAEL for maternal toxicity in rats (10 mg/m^3) reported from the subchronic study conducted by Holson et al. (1999) was 12 times more than the NOAEL for developmental toxicity observed in mice (0.26 mg/ m^3) based on the Nagymajtenyi et al. (1985) study. The data from maternal toxicity in rats (Holson et al (1999) will not be considered because the exposure duration in the study did not meet TCEQ's criteria for short-term exposures and mice appear to be the most sensitive species. For the Nagymajtenyi et al. (1985) study, which has continuous data, TD performed benchmark concentration (BMC) modeling using the continuous models in USEPA's BMD software (version 2.0) to derive the study POD based on decrease in fetal weight.

3.1.4.1 Benchmark Response Level and Critical Effect Size(CES)

The BMC approach is increasingly being used as an advancement over the NOAEL approach for establishing the POD. According to Kavlock et al. (1995), fetal weight changes are often a very sensitive measure of effect in developmental toxicity studies, thus making it an important endpoint in the risk assessment process. Kavlock et al. (1995) and Allen et al. (1996) further emphasize the importance of defining what constitutes an affected litter or fetus in terms of a weight decrement and have reported a 5% decrease in mean litter weight relative to control mean litter weight as an adverse effect.

If there is an accepted level of change in an endpoint that is considered to be biologically adverse, then that amount of change is selected as the benchmark response (BMR) level for BMC modeling (USEPA 2000). For dichotomous data, this level is typically expressed as a certain increase in the incidence of adverse outcomes and is referred to as the benchmark response (BMR). In order to distinguish continuous data from dichotomous data, Dekkers et al. (2001) recommended the term "critical effect size" (CES) to be used for continuous data instead of BMR since the effect measured is expressed on a continuous scale. A CES defines the demarcation between non-adverse and adverse changes in a toxicological effect parameter for continuous data (Dekkers et al. 2001). For example, a CES of 10% or CES_{10} for continuous data (i.e., a 10% change in the mean of a treated group compared to the control mean) is not the same as a BMR of 10% or BMR_{10} (i.e., 10% of the total animals responding for dichotomous data).

Changes in fetal weight were analyzed using average fetal weight for each litter. For decrease in fetal body weight, a CES was defined in terms of a pre-specified level of response, corresponding to a 5% relative decrease in the mean when compared to controls (CES_{05}) (Kavlock et al. 1995, Allen et al. 1996). The BMC and BMCL results for one standard deviation (SD) (CES_{1SD}) were also calculated and are presented in Table 6 for comparison sake according to guidance in USEPA (2000).

3.1.4.2 Benchmark Concentration Modeling

While decreases in fetal weight were modeled using the continuous linear, polynomial, Hill, and power models using four doses, only the power model provided an adequate statistical fit to the data (goodness of fit p-value and scaled residual values did not imply rejection at the 5% significance level). The power

model was fit with unrestricted parameters, a homogenous variance, and is monotone. Appendix B provides the BMC modeling output file. Decreased fetal body weight had a BMC_{05} of 0.478 mg/m^3 and a $BMCL_{05}$ of 0.205 mg/m^3 and a BMC_{1SD} of 0.064 mg/m^3 and a $BMCL_{1SD}$ of 0.018 mg/m^3 (Table 5). The POD for decreased fetal body weight is the $BMCL_{05}$ of 0.205 mg/m^3 (205 µg/m^3).

Table 5. BMC Modeling Results for Fetal Body Weight

BMD Model	BMC_{05} (mg/m^3)	$BMCL_{05}$ (mg/m^3)	$BMC_{1\ SD}$ (mg/m^3)	$BMCL_{1\ SD}$ (mg/m^3)	p-value for fit	AIC	Scaled Residue
Power (Unrestricted)	0.478	0.205	0.064	0.018	0.289	-202.4	< | 2 |

3.1.5 Dosimetric Adjustments

3.1.5.1 Default Exposure Duration Adjustments

Reproductive/developmental studies are usually conducted by exposing animals to repeated doses over several days (e.g., 6 h per day for gestational day 6-15). The TD uses a single day of exposure from the experimental study as the exposure duration (TCEQ 2006). In doing so, the TD recognizes that the reproductive/developmental effects may have been caused by only a single day's exposure that occurred at a critical time during gestation. The averaging time for ESLs based on the reproductive/developmental effects is the number of hours of the single day of exposure, not a 1-h averaging time. As the key study was a developmental/reproductive study, the averaging time for the acute ESL was based on the number of hours of a single day of exposure (i.e., 4 h) and an exposure duration adjustment to 1-h was not conducted.

3.1.5.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

According to ATSDR (2007), the Mann model (Gentry et al. 2004, Mann et al. 1996a, 1996b) is a well-derived physiological based pharmacokinetic (PBPK) model consisting of multiple compartments and metabolic processes, and models four chemical forms of arsenic (two organic and inorganic). The Mann model simulates the absorption, distribution, metabolism, elimination, and excretion of As(III), As(V), MMA, and DMA after oral and inhalation exposures in mice, hamsters, rabbits, and humans. However, the Mann model was not used in the present DSD to perform animal-to-human dosimetric adjustments as it includes both the inhalation and ingestion pathways and does not provide the ability to separately study the inhalation pathway by itself. For a detailed description of PBPK models, please refer to ATSDR (2007).

Since arsenic in air in primarily in the particulate form (Table 2), and the key study was conducted in mice, the USEPA regional deposition dose ratio (RDDR) model (v) 2.3 was used to calculate the depositional fraction for inorganic arsenic in the target respiratory region (USEPA 1994).

As the mass median aerodynamic diameter (MMAD), geometric standard deviation (sigma g (σ_g)), and the body weight of the mice were not reported in the key study and are necessary parameters for calculating the RDDR, the TD obtained these values from ATSDR (2007), Holson et al. (1999), and the EPA's Reference Concentration (RfC) methodology document (EPA 1994), respectively. The TD used a MMAD of 1.0 µm and based it on ATSDR's (2007) review that most anthropogenic arsenic emitted to the atmosphere arises from high temperature processes (e.g., coal and oil combustion, smelting operations, and refuse incineration) and occurs as fine particles with a MMAD of about 1 µm (Coles et al.

1979, Pacyna 1987). The TD also used a σ_g of 1.74 from the Holson et al. (1999) paper. As the POD_{ADJ} was estimated to be 205 µg/m^3 from the BMC modeling, the TD used the σ_g from the 300 µg/m^3 exposure group of the Holson et al. (1999) study as 300 µg/m^3 was the closest exposure concentration to the POD_{ADJ} (205 µg/m^3).

For the body weight of the mice, the TD used a value of 22.5 grams, which is an average of the default body weight of female mice from the subchronic exposure category, and was obtained from Table 4-5 of the RfC methodology document (EPA 1994). As the particles inhaled in the key study were expected to be deposited throughout the respiratory tract (extrathoracic, tracheobronchial, pulmonary, and thoracic regions), the target region for arsenic was considered to be the entire respiratory tract. The RDDR program was executed with the above mentioned default parameters and the RDDR was calculated to be 2.067 or 2.07 (rounded to 2 significant figures). The RDDR output is presented in Appendix C. The animal-based POD_{ADJ} was then adjusted with the RDDR to calculate the human equivalent POD or the POD_{HEC} as follows:

The $POD_{HEC} = POD_{ADJ} \times RDDR = 205$ µg/m^3 x 2.07 = 424 µg/m^3

3.1.6 Adjustments of the POD_{HEC}

The MOA by which inorganic arsenic can produce toxicity is discussed in Section 3.1.2, and is considered to be a threshold, nonlinear MOA. Therefore, a POD was determined and appropriate UFs were applied to derive a ReV.

The following UFs were applied to the POD_{HEC} derived from the key study by Nagymajtenyi et al. (1985): 3 for interspecies extrapolation (UF_A), 10 for intraspecies variability (UF_H), and 10 for database uncertainty (UF_D). A UF_A of 3 was used for extrapolation from animals to humans because default dosimetric adjustments using the RDDR were conducted to account for toxicokinetic differences but not toxicodynamic differences. The TD conducted BMC modeling with a 5% reduction in fetal body weight when compared to controls as the CES so a LOAEL-to-NOAEL UF was not applicable (please see Section 3.1.4 *Points of Departure (PODs) for the Key Study and Critical Effect*). A UF_H of 10 was used to account for potential sensitive human subpopulations as genetic polymorphisms have been reported for arsenic metabolism. Also, a UF_D of 10 was used to account for the lack of acute human studies and the limited number of animal studies relevant to the short-term inhalation exposure scenarios. The total UFs applied to the POD_{HEC} were (3 x 10 x 10 = 300).

3.1.7 Health-Based Acute ReV for As_2O_3

As discussed in the previous section, UFs were applied to the POD_{HEC} to derive the acute ReV. In the key study, the test chemical was As_2O_3:

acute ReV = $POD_{HEC} / (UF_A \times UF_H \times UF_D)$
= 423.735 µg/m^3/300
= 1.4125 µg/m^3 or 1.4 µg/m^3 (rounded to 2 significant figures)

3.1.8 Health-Based Acute ReV and ^{acute}ESL for Arsenic

In the key study, the test chemical was As_2O_3 and not arsenic. Therefore, the acute ReV was initially calculated for As_2O_3 and then adjusted for arsenic.

Acute ReV for As_2O_3 = 1.4 µg/m^3
As_2O_3 is 76% by weight of arsenic (ATSDR 2007).
Therefore acute ReV of arsenic = 76/100 x 1.4 µg/m^3
= 1.064 or 1.1 µg/m^3
^{acute}ESL = 0.3 x 1.1µg/m^3 = 0.33 µg/m^3 (rounded to 2 significant figures)

Table 6. Derivation of the Acute ReV and ^{acute}ESL for Arsenic Trioxide and Arsenic	
Study	Nagymajtenyi et al. (1985)
Study population	CFLP female pregnant mice
Study quality	Medium
Exposure Methods	Whole-body inhalation
LOAEL	2900 µg/m^3
NOAEL	260 µg/m^3
POD	205 µg/m^3 ($BMCL_{05}$)
Critical Effects	Decrease in fetal weight
POD	205 µg/m^3
Exposure Duration	4 h/day on the 9th, 10th, and 12th d of gestation
Extrapolation to 1 h	None
POD_{ADJ} [4 h]	205 µg/m^3
POD_{HEC}	423.735 µg/m^3 (RDDR = 2.067)
Total Uncertainty Factors (UFs)	300
Interspecies UF	*3*
Intraspecies UF	*10*
LOAEL UF	*1*
Incomplete Database UF	*10*
Database Quality	*Low*
acute ReV [4 h] (HQ = 1) Arsenic Trioxide	**1.4 µg/m^3**
acute ReV [4 h] (HQ = 1) Arsenic	**1.1 µg/m^3**
^{acute}ESL [4 h] (HQ = 0.3) Arsenic	**0.33 µg/m^3**

3.1.9 Comparison of Results

The database on the acute effects of arsenic via inhalation exposure is limited. The USEPA does not have a Reference Concentration (RfC) and ATSDR does not have a Minimal Risk Value (MRL) via inhalation exposure for inorganic arsenic. California EPA (Cal EPA) has an Acute Reference Exposure Level (REL) for inorganic arsenic of 0.2 µg/m^3 (Public Review Draft 2007) based on the same key study as the TD. While the TD conducted BMD modeling and calculated the deposition fraction of arsenic in the target region, Cal EPA followed the traditional NOAEL/LOAEL approach and did not conduct BMD modeling or calculate the deposition fraction of arsenic in the target respiratory region. However, the TD's ^{acute}ESL (0.33 µg/m^3) and Cal EPA's acute REL (0.2 µg/m^3) are comparable.

3.2. Welfare-Based ^{acute} ESLs

3.2.1 Odor Perception

Elemental arsenic is odorless (ATSDR 2007). No odor data were available for arsenic or inorganic arsenic compounds.

3.2.2 Vegetation Effects

No data on vegetative effects were found due to exposure to inorganic arsenic in the ambient air. While organic arsenicals have been used as pesticides on cotton plants, no data was available on the adverse vegetative effects from organic arsenic in ambient air. The TD will evaluate the vegetation effects on exposure to inorganic arsenic in ambient air as new studies and/or data becomes available.

3.3 Short-Term ESL and Values for Air Monitoring Evaluation

The acute evaluation resulted in the derivation of the following values for arsenic:

- acute ReV [4 h] = 1.1 µg/m^3
- ^{acute}ESL [4 h] = 0.33 µg/m^3

The acute ReV of 1.1 µg/m^3 will be used for the evaluation of air monitoring data. If measured 1-h ambient air monitoring data is less than or equal to the 4-h acute ReV, then no acute health effects would be expected. If the health-based 4-h acute ReV is exceeded, and it is possible to calculate a 4-h value (i.e., automatic gas chromatographic data), then a 4-h averaged value will be used to evaluate potential health effects. The health-based ^{acute}ESL is only for air permit reviews, and not for the evaluation of ambient air monitoring data.

3.4 Short-Term ESL for Air Permit Evaluation

The short-term ESL for air permit reviews is the health-based ^{acute}ESL of 0.33 µg/m^3 (Table 1). If the predicted 1-h maximum ground level concentration (GLC_{max}) is equal to or less than the health-based 4-h ^{acute}ESL, then no acute health effects would be expected. If the GLC_{max} exceeds the health-based 4-h ^{acute}ESL, then it will be necessary to model or estimate a 4-h GLC_{max} in order to evaluate potential health effects.

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

4.1.1 Physical/Chemical Properties and Key Studies

Physical/chemical properties of arsenic and inorganic arsenic compounds have been previously discussed in Chapter 3, Section 3.1.1.1. Only a few chronic animal inhalation studies exist. Many of the available animal studies are for the oral ingestion route and will not be discussed here. Refer to ATSDR (2007) for a discussion of animal studies. While chronic inhalation exposure to inorganic arsenicals has been reported to cause neurological effects in humans, no characteristic neurological symptoms were reported in monkeys, dogs, or rats that were chronically exposed to inorganic arsenicals at doses of 0.7 – 2.8 mg

As/kg/day (EPA 1980 as cited in ATSDR 2007). ATSDR (2007) attributes the lack of chronic response in these animal studies to insufficient exposure duration and/or due to smaller sample sizes.
The TD will use human data to derive chronic toxicity factors and will mainly use the ATSDR (2007) review of arsenic to discuss and determine the chronic ReV and ESL for inorganic arsenic.

4.1.1.1 Key Human Studies - Vascular and Cardiovascular Effects

Long-term exposure to arsenic in drinking water has been reported to cause vascular (i.e., gangrene or black foot disease) (Lagerkvist et al. 1986). Evidence from epidemiological studies indicates cardiovascular effects may also occur after long-term exposure to inhaled arsenic. Blom et al. (1985) and Lagerkvist et al. (1986, 1988) conducted cross-sectional studies of workers exposed to As_2O_3 dust in the Ronnskar smelter in northern Sweden to discern changes in peripheral circulation via sensitive physiological methods.

Urinary arsenic metabolite measurements have been routinely used in occupational exposure studies as a means to monitor exposure to arsenic (Vahter 1986). However, Pinto et al. (1976) and others have reported a weak correlation between airborne arsenic and the total concentration of arsenic in urine. One of the explanations for this lack of correlation is that urinary arsenic is greatly influenced by the amount of seafood consumed by the arsenic workers, because fish and certain crustaceans contain high concentrations of organic arsenic (e.g., arsenobetaine).

The TD will primarily use exposure concentrations of arsenic in the air and/or ATSDR's estimated exposure concentrations for determining the applicable chronic toxicity values for the non-carcinogenic evaluation. The urinary arsenic metabolite concentrations, if provided in the study, will be used as supporting/supplemental evidence. The terms "referent" and "control" will be used intermittently throughout the DSD and will refer to unexposed workers.

The TD selected the Lagerkvist and Zetturland (1994) and the Lagerkvist et al. (1986) study as key studies to determine the chronic ReV and the chronic ESL for non-carcinogenic effects ($^{chronic}ESL_{nonlinear(nc)}$). It is to be noted that both key studies were follow-up studies of the Blom et al. (1985) study. Therefore, the TD will first discuss the Blom et al. (1985) study and the two key studies will be reviewed in later sections.

4.1.1.1.1 Blom et al. (1985)

Blom et al. (1985) examined peripheral nervous function in copper and lead smelter workers chronically exposed to airborne arsenic for 8 – 40 years (mean 23 years). A total of 47 workers from the Ronnskar copper smelter were selected as the arsenic-exposed group. While an additional 15 workers were employed in the smelter, they were not included in the study because they were diagnosed as having chronic illness unrelated to arsenic exposure and/or because they declined to participate in the study. In addition to arsenic exposure, the workers at the smelter were exposed to sulfur dioxide and heavy metals such as gold, silver, copper, and lead.

The control group included 50 workers from a mechanical industrial enterprise located in the same county as the arsenic workers, and were matched to the arsenic workers by age, use of tobacco, and use of vibrating tools. Vibrating tools have been considered as a risk factor for developing neurological symptoms. Both the exposed group and the control group were screened for pre-existing medical conditions such as diabetes and peripheral vascular disease.

Blom et al. (1985) estimated the arsenic concentration in the air at the smelter to be below 500 µg/m^3 before 1975 and about 50 µg/m^3 after 1975. The workers underwent a thorough clinical and physical examination. Toe and finger plethysmography (a test used to measure changes in blood flow or air volume in different parts of the body, to check for blood clots in the arms and legs, or to measure how much air you can hold in your lungs) was performed with a mercury strain gauge in a warm room at a skin temperature of about 30º C. Systolic blood pressure (BP) in the fingers after cooling was measured according to Nielsen et al. (1980). In addition, the BP in the arm was measured with the cuff method and a BP difference of 40 mm between arm and digit was taken as a sign of arterial obstruction.

Finger systolic pressure (FSP) was measured simultaneously in two fingers of the same hand according to Nielsen (1980) and expressed as a percentage. While a decrease in BP occurs after cooling in normal subjects, the decrease becomes more pronounced in subjects with peripheral damage as observed in subjects with Raynaud's phenomenon, a peripheral vascular disease characterized by spasm of digital arteries and numbness of the fingers.

The mean urinary arsenic levels in the exposed group were reported to be 71 µg/L (1 µmol/L). According to Blom et al. (1985) urinary arsenic levels greater than 71 µg/L were generally associated with clinical neuropathy in previous studies. In the present study, minor neurological and electromyographic abnormalities were reported among the arsenic workers with mean urinary arsenic concentrations of 71 µg/L. A slightly reduced nerve conduction velocity (NCV) in two or more peripheral nerves was reported among the exposed group of arsenic workers when compared to the referent population (control group). In regards to chronic arsenic exposure, a statistically significant correlation was reported for cumulative arsenic exposure and reduced NCV in five peripheral motor nerves. Blom et al. (1985) hypothesized the reduction in the NCV was a sign of subclinical neuropathy and indicated that detection of these subclinical changes could help prevent the onset of other adverse health effects due to chronic arsenic exposure. The Blom et al. (1985) study was not chosen as a key study due to the availability of more recent smelter data .which are discussed in the following sections (Lagerkvist et al. 1986; Lagerkvist and Zetturland 1994).

4.1.1.1.2 Lagerkvist and Zetturland (1994) (Key Study)

A total of 43 male workers and 46 referents previously examined by Blom et al. (1985) were re-examined by Lagerkvist and Zetturland (1994). In the study, the arsenic-exposed workers from the Blom et al. (1985) study were exposed to arsenic dust from the smelter for an additional five years. Therefore, the duration of arsenic exposure as arsenic trioxide in the follow-up study ranged from 13 – 45 years with mean exposure duration of 28 years. While one of the arsenic workers and two of the referents died of heart infarction, another referent died of liver cancer. A few of the arsenic workers retired or did not want to participate in the study. One of the arsenic workers was excluded from the study as he was diagnosed with hereditary polyneuropathy (i.e., reduced NCV's).

As the Lagerkvist and Zetturland (1994) study is a follow-up to the Blom et al. (1985) study, the estimated arsenic levels in the air were adjusted for an additional five years of exposure. The arsenic levels at the smelter were reported to be 500 µg/m^3 from 1950's to 1975 (mean of 16 years), 50 µg/m^3 from 1975 to 1987 (mean of 11 years), and 30 µg/m^3 from 1987 (one year).

Previous studies had identified the average particle size of the airborne dust at the smelter to be about 5µm (Leffler et al. 1984 as cited in the Lagerkvist and Zetturland 1994 study). Seventy-five percent of the

inhaled arsenic as As_2O_3 is reported to be absorbed in the lungs. In the study, the mean total estimated absorption of arsenic for the arsenic workers was reported to be 25 mg per year. The exposed and control groups were compared for differences using two-tailed Student's test, chi-square test or the Fisher's exact probability test. In addition, the correlation coefficients were calculated with Spearman's rank correlation and regression equations between variables with the method of least squares (Colton 1974, Siegel 1956).

While the arsenic-exposed workers were examined for a period of five years from 1982 - 1987, the results were extrapolated to long-term exposure with a mean duration of 28 years as the arsenic workers and referents were re-examined from the Blom et al. (1985) study. The general health of the arsenic-exposed workers was poor and they reported a larger number of symptoms than the referents. The authors attributed the poor health of the arsenic workers to exposure to inorganic arsenic. In addition, four of the arsenic workers were reported to be diagnosed as having diabetes during the follow-up period while none of the referents were diagnosed as having diabetes. There is increasing evidence that inorganic arsenic can adversely affect glucose metabolism in humans via oral ingestion. However, there is only limited evidence in regards to inhalation exposure to inorganic arsenic and diabetes in humans.

Similar to the Blom et al. (1985) study, reduction in the NCV was studied to determine peripheral nerve function both in the arsenic workers (exposed) and control groups. The differences in the NCV between the arsenic workers and controls was increased in all the examined nerves, with the greatest difference in the tibial and the sural nerves when examined from 1982-1987. However, the nerves in the arm seemed to be less affected. Further, in both the Blom et al. (1985) and the Lagerkvist and Zetturland (1994) studies, there was a significant negative correlation between the estimated total arsenic absorption and NCV's in the peripheral nerves. According to ATSDR (2007), the time-weighted average (TWA) exposure for arsenic (as As_2O_3) based on the Lagerkvist and Zetturland (1994) study was calculated as follows:

$$\frac{(500\mu g/m^3 x\ 16 years) + (50\mu g/m^3 x\ 11 years) + (30\mu g/m^3)}{28 years}$$

$$= \frac{8580\mu g/m^3}{28 years} = 306.43\ \mu g/m^3\ (0.306\ mg/m^3)$$

The prevalence of abnormally low NCV remained significantly increased in the exposed workers in the follow-up study, and the decrease in mean NCV was also statistically significant in the tibial (motor) and sural (sensory) nerves. Based on the Lagerkvist and Zetturland (1994) study, ATSDR (2007) estimated a LOAEL of 306.43 $\mu g/m^3$ (0.306 mg/m^3) for decreased NCV.

In addition to peripheral neuropathy, the arsenic-exposed workers were reported to have clinical manifestations of neuropathy (i.e., numbness, parasthesia, or muscle pain) that were significantly different from the referents. Similar results were reported by Oh (1991), who reported marked decrease in sensory nerve conduction both in the acute and in the moderate stage of recovery from neuropathy even after nine years after exposure to inorganic arsenic.

4.1.1.1.3 Lagerkvist et al. 1986 (Key Study)

As already mentioned, the Lagerkvist et al. (1986) study appears to be very similar to the Blom et al. (1985) study in many aspects such as the location (i.e, Ronnskar smelter in Sweden), the exposure duration, and the number of exposed workers. Only the number of control workers in the Blom et al.

(1985) study and the Lagerkvist et al. (1986) are different. As a detailed discussion was already provided in the Blom et al. (1985) study, only the aspects that are different will be explained in this section. Lagerkvist et al. (1986) reported the mean exposure duration for arsenic workers to be 23 years, of which they estimated that for 16 years the exposure was at 500 µg As/m^3 and for seven years the exposure was at 50 µg As/m^3. ATSDR (2007) estimated a time-weighted average (TWA) for inorganic arsenic exposure as follows:

$$\frac{(500\mu g/m^3 x\ 16 years) + (50\mu g/m^3 x\ 7 years)}{23 years} = \frac{8350\mu g/m^3}{23 years}$$

= 363 µg As/m^3 (0.363 mg As/m^3)

ATSDR (2007) reported that "a cross-sectional study of workers exposed to an estimated TWA of 0.36 mg As/m^3 at the Ronnskar copper smelter in Sweden for an average of 23 years showed that the smelter workers had significantly increased incidences of Raynaud's phenomenon and showed increased vasospasticity (constriction of blood vessels) in response to cold when tested in the fingers (Lagerkvist et al.1986). A follow-up study by Lagerkvist et al. (1988) indicated vasospasticity measurements to improve when exposure to arsenic was reduced. However, the symptoms of peripheral vascular effects (cold hands or feet, white fingers, numbness in fingers or feet) still persisted even after reduction in exposure.

The LOAEL for Raynaud's phenomenon and vasospasticity was estimated by ATSDR (2007) from the Lagerkvist et al. (1986) study to be 0.36 mg As/m^3. The Raynaud's phenomenon and increased vasospaticity are considered cardiovascular effects (ATSDR 2007).

4.1.1.1.4 Other Studies

4.1.1.1.4.1 Respiratory, Ocular, Dermal, and Gastrointestinal Effects

Although it has been established that inorganic arsenic dust is an irritant, relatively few systemic studies have been conducted. Respiratory, ocular, and gastrointestinal effects have been reported due to inhalation exposure. However, the available studies are limited due to small sample sizes, inadequate exposure concentrations, and the inability to relate exposure concentrations to specific health effects. This is especially true for ocular and gastrointestinal effects. For that reason, only a brief discussion of ocular and gastrointestinal effects as reviewed in ATSDR (2007) will be included in this DSD and a more detailed discussion of the respiratory and dermal effects will be included. Respiratory effects can also occur due to short-term exposure to arsenic as discussed previously in Section 3.1.1.2.2.1.

Human Studies

Workers exposed to arsenic dust in air have been reported to have experienced laryngitis, bronchitis, rhinitis (Dunlap 1921, Pinto and McGill, 1953, and Sandstorm et al. 1989 as cited in ATSDR 2007), and chemical conjunctivitis (i.e., redness, swelling and pain in the eyes (Dunlap 1921 as cited in ATSDR 2007).

While gastrointestinal effects are normally associated with arsenic exposure via oral ingestion (Pinto and McGill as cited in ATSDR 2007), case reports from workers occupationally exposed to arsenic dust reported nausea, vomiting, and diarrhea. According to ATSDR (2007), it is possible that mucociliary

transport of arsenic dust from the lungs to the gut could be responsible for the effects.

Perry et al. (1948)

Perry et al. (1948) conducted a cross-sectional study to investigate a factory where workers were exposed to arsenic dust during preparation and packing of sodium arsenite powder. All the workers underwent a thorough clinical examination. The duration of exposure for most workers ranged from 0.5 – 50 years. The workers in the high exposure group were reported to be exposed to arsenic dust in the range of 0.384 – 1.034 mg As/m^3 with an estimated average exposure of 0.613 mg As/m^3. Workers in the lower exposure group were estimated to be exposed to an average of 0.078 mg As/m^3.

Dermal Effects

The workers in the high exposure group were reported to be grossly pigmented with hyperkeratinization of the exposed skin and multiple warts. Workers in the lower exposure group were also reported to have a higher incidence of pigmentation keratosis when compared to the control group. Therefore, the LOAEL from this study for dermal effects is 0.078 mg As/m^3. No NOAELs was reported for dermal effects.

Respiratory Effects

In addition to dermal effects, Perry et al. (1948) compared differences in chest x-rays and/or respiratory performance (i.e., vital capacity and exercise-tolerance tests) amongst control and exposed worker groups and reported no differences. Based on the results of this study, ATSDR (2007) has estimated a NOAEL of 0.613 mg As/m^3 for respiratory effects.

Although it provided estimated exposure doses, the Perry et al. (1948) study did not include adequate quantitative dose-response information. Therefore, the TD did not consider it as a key study.

Lubin et al. (2000)

Respiratory Effects

Lubin et al. (2000), Lee-Feldstein (1983), and others have investigated the relative risks of non-cancer outcomes due to exposure to air-borne arsenic in cohort studies. Lubin et al. (2000) analyzed the increased risk of mortality due to respiratory disease (e.g., emphysema) for arsenic- exposed workers by duration of employment with varying arsenic exposure (i.e, light, medium, and heavy). There were elevated Standard Mortality Ratios (SMR) among workers and former workers last exposed at age 50 years and over for non-malignant respiratory diseases.

While an increased risk was observed with increase in the duration of employment, the gradients of risk was reported to be similar for all the work areas (i.e., light, medium, and heavy). Lubin et al. (2000) attributed the increasing relative risk of death due to non-malignant respiratory diseases to factors other than arsenic exposure (e.g., smoking). Similar conclusions were reported by Lee-Feldstein (1983 as cited in ATSDR 2007). The Lubin et al. (2000) and the Lee-Feldstein (1983) study were not selected as a key study.

4.1.1.1.4.2 Other Studies Reporting Neurological, Vascular, and Cardiovascular Effects

Neurological Effects

Several epidemiology studies indicate that inorganic arsenic is potentially neurotoxic. Long-term exposure to inorganic arsenic has been reported to adversely affect the peripheral nervous system (WHO

1981, Feldman 1979, Pershagen and Vahter 1979). A few key neurological studies will be discussed in more detail.

Feldman et al. (1979)

Peripheral neuropathy has been reported in copper smelter workers at the ASARCO smelter in Tacoma, Washington (Feldman et al. 1979). A high prevalence of clinical and subclinical neuropathy in smelter workers was found to be associated with high urinary arsenic levels (250 µg/l). While the clinically diagnosed peripheral neuropathy was higher in the arsenic-exposed workers than in the unexposed workers at the ASARCO plant, the differences were not statistically significant (Feldman et al. 1979).

Specifically, Feldman et al. (1979) reported intracellular damage to peripheral neurons resulting in distal axonopathy as a primary effect on long-term exposure to inorganic arsenic with segmental demyeliniation reported as a secondary effect. In general, damage to the sensory nerves was reported prior to any damage to the motor nerves, damage was reported in the distal parts of the extremities, and recovery following cessation of arsenic exposure was very slow. However, the studies were limited as an adequate dose-response relationship was not reported. Also, due to the availability of more recent smelter data discussed in 4.1.1.1, the Feldman (1979) study was not chosen as a key study.

Buchancova et al. (1998)

Buchancova et al. (1998) reported peripheral neurological effects due to arsenic trioxide exposure in power plant workers in Slovakia. The average length of exposure of the power plant workers was 22.3 years and the average concentration of arsenic in the air ranged from 4.6 – 142.7 µg/m^3. This study was not chosen as a key study.

4.1.2 MOA Analysis

The MOA by which arsenic may produce toxicity is discussed in Section 3.1.2.

4.1.3 Dose Metric

For the key studies, data on exposure concentration of the parent chemical for occupationally exposed workers are available, whereas data on more specific dose metrics such as metabolites in blood or target tissue are not available. Therefore, exposure concentration of the parent chemical will be used as the default dose metric.

4.1.4 PODs for Key Studies

Lagerkvist and Zetturland (1994)

The TD considered an ATSDR-estimated LOAEL of 0.306 mg As/m^3 (306 µg/m^3) for decreased NCV from the Lagerkvist and Zetturland (1994) study as the occupational POD (POD_{OC}).

Lagerkvist et al. (1986)

The TD considered an ATSDR-estimated LOAEL of 0.363 mg As/m^3 (363 µg/m^3) for increased incidence of vasospaticity and clinical Raynaud's phenomenon from the Lagerkvist et al. (1986) study as the occupational POD (POD_{OC}).

4.1.5 Dosimetric Adjustment

Using the LOAELs from the key studies, the occupational PODs (POD_{oc}) were adjusted to PODs applicable to the general population (POD_{HEC}) using the following dosimetric adjustments:

$POD_{HEC} = POD_{oc}$ x (VE_{ho} / VE_h) x (days per $week_{oc}$ / days per week $_{res}$)

Where: VE_{ho} = occupational ventilation rate for a 24-h day (20 m^3/day)
VE_h = occupational ventilation rate for an 8-h day (10 m^3/day)
days per $week_{oc}$ = occupational weekly exposure frequency (5 days per week)
days per week $_{res}$ = residential weekly exposure frequency (7 days per week)

Lagerkvist and Zetturland (1994)

POD_{HEC} = 306 µg/m^3 x (10/20) x (5/7) = 109.286 µg/m^3

Lagerkvist et al. (1986) study

POD_{HEC} = 363 µg/m^3 x (10/20) x (5/7) = 129.643 µg/m^3

4.1.6 Critical Effect and Adjustments of the POD_{HEC}

4.1.6.1 Critical Effect

Human occupational and epidemiology studies indicate chronic exposure of smelter workers to arsenic results in significantly decreased NCV (Lagerkvist and Zetturland 1994). In addition, chronic exposure to inorganic arsenic is associated with increased incidences of Raynaud's phenomenon and increased vasospasticity in response to cold when tested in the fingers (Lagerkvist et al. 1986).

4.1.6.2 Uncertainty Factors (UFs)

Section 3.12 discusses the MOA by which arsenic may produce toxicity, although the specific MOA for producing decreased NCV, increased incidences of Raynaud's phenomenon, and increased vasospasticity in response to cold when tested in the fingers is unknown. Since the MOA by which arsenic produces toxicity is not understood, the default for noncarcinogenic effects is to determine a POD and apply UFs (i.e., assume a threshold/non-linear MOA). Therefore, UFs were applied to the key and supporting studies POD_{HEC} to derive the chronic ReV. The following UFs were used to calculate the chronic ReV for the key and supporting studies.

Lagerkvist and Zetturland (1994)

A UF of 3 for extrapolation from a LOAEL to a NOAEL (UF_L), a UF of 10 for intraspecies variability (UF_H), and a UF of 10 for database uncertainty (UF_D) were applied. A total UF of 300 (UF_L x UF_H x UF_D) was used to calculate the chronic ReV .

Lagerkvist et al. (1986)

A UF of 10 for extrapolation from a LOAEL to a NOAEL (UF_L), a UF of 10 for intraspecies variability (UF_H), and a UF of 10 for database uncertainty (UF_D) were applied. A total UF of 1000 (UF_L x UF_H x UF_D) was used to calculate the chronic ReV.

The choices of UFs for both studies are further discussed:

- For both the Lagerkvist and Zetturland (1994) study and the Lagerkvist et al. (1986) study, a NOAEL was not reported. Therefore a UF_L was applied to the POD_{HEC}. For the Lagerkvist and Zetturland (1994) study, a UF_L of 3 was used because the effect was determined to be less serious (ATSDR 2007). However, in the Lagerkvist et al. (1986) study, a UF_L of 10 was used as the effect was considered serious as determined by ATSDR (2007).
- In both key studies, a UF_H of 10 was justified because of reports of genetic polymorphism for arsenic metabolism. In addition, Hispanic populations deficient in folate are more sensitive.
- While several epidemiology and/or occupational studies for arsenic workers exist, none of the studies had documentation on the actual exposure concentrations. The TD used estimated average exposure concentration as reported in ATSDR (2007). In addition, co-exposure to other pollutants and smoking were not adequately documented in the studies. A two-generation reproductive study is not available for arsenic. The TD's confidence in the database is medium and, therefore, the TD is of the opinion that a full UF_D of 10 is justified.

4.1.7 Health-Based Chronic ReV for As_2O_3

As discussed in the previous section, UFs are applied to the Lagerkvist and Zetturland (1994) study and the Lagerkvist et al. (1986) study POD_{HECs} to derive the chronic ReV. The test chemical in both studies was As_2O_3. Therefore, the TD initially calculated the chronic ReV for As_2O_3 for both studies using the following equation:

$$\text{chronic ReV} = \frac{POD_{HEC}}{(UF_L \times UF_H \times UF_D)}$$

Lagerkvist and Zetturland (1994)

$$\text{chronic ReV} = \frac{109.286\ \mu g/m^3}{(3 \times 10 \times 10)}$$
$$= 0.3643\ \mu g/m^3$$

Lagerkvist et al. (1986)

$$\text{chronic ReV} = \frac{129.643\ \mu g/m^3}{(10 \times 10 \times 10)}$$
$$= 0.1296\ \mu g/m^3$$

The chronic ReV of 0.1296 $\mu g/m^3$ for As_2O_3 determined from the Lagerkvist et al. (1986) study is lower than the chronic ReV of 0.3643 $\mu g/m^3$ for As_2O_3 determined from the Lagerkvist and Zetturland (1994) study. Therefore, the TD will use the chronic ReV of 0.1296 $\mu g/m^3$ for As_2O_3 from the Lagerkvist et al. (1986) study. The chronic ReV of 0.1296 $\mu g/m^3$ was rounded to two significant figures at the end of all calculations, which produced an As_2O_3 chronic ReV of 0.1296 $\mu g/m^3$. The chronic ReV was rounded to 2 significant figures and is 0.13 $\mu g/m^3$.

4.1.8 Health-Based Chronic ReV and ^{chronic}ESL $_{nonlinear(nc)}$ for Arsenic

In the key study, the test chemical was As_2O_3 and not arsenic. Therefore, the chronic ReV was initially calculated for As_2O_3 and then adjusted for arsenic based on the fact that As_2O_3 is 76% by weight of arsenic (ATSDR 2007):

The chronic ReV for As_2O_3 = 0.13 µg/m^3
Chronic ReV for arsenic = 76% of chronic ReV for As_2O_3
= 76/100 x 0.13 µg/m^3
= 0.09880 µg/m^3

The chronic ReV of 0.09880 µg/m^3 was rounded to two significant figures at the end of all calculations. The resulting chronic ReV for arsenic is 0.099 µg/m^3. At a target hazard quotient of 0.3, the ^{chronic}ESL $_{nonlinear(nc)}$ is 0.0297 µg/m^3. The ^{chronic}ESL $_{nonlinear(nc)}$ was rounded to two significant figures and is 0.03 µg/m^3 (Table 7).

Table 7. Derivation of the Chronic ReV and ^{Chronic}ESL $_{nonlinear(nc)}$ for Arsenic Trioxide and Arsenic

Study	Lagerkvist et al. (1986)
Study population	Ronnskar Smelter workers in Sweden
Study quality	Medium
Exposure Methods	Inhalation
Estimated LOAEL	363 µg/m^3
NOAEL	-
Critical Effects	Cardiovascular effects (increased incidences of Raynaud's phenomenon and increased vasospasticity in response to cold when tested in the fingers)
POD_{OC}	363 µg/m^3
Exposure Duration	23 years
POD_{HEC}	129.643 µg/m^3
Total Uncertainty Factors (UFs)	1000
Interspecies UF	*1*
Intraspecies UF	*10*
LOAEL UF	*10*
Incomplete Database UF	*10*
Database Quality	*Medium*
chronic ReV (HQ = 1) Arsenic trioxide	**0.13 µg/m^3 Arsenic**
chronic ReV (HQ = 1) Arsenic	**0.099 µg/m^3 Arsenic**
^{chronic}ESL $_{nonlinear(nc)}$ (HQ = 0.3) Arsenic	**0.03 µg/m^3 Arsenic**

4.1.9 Comparison Results

ATSDR does not have a chronic MRL for inhalation exposure to inorganic arsenic. There is also no

chronic Reference concentration factor (RfC) for exposure via inhalation to inorganic arsenic from the USEPA. Cal EPA has proposed an inorganic arsenic 8-h Reference Level (REL) and an inorganic arsenic chronic REL of 0.015 µg As/m^3 from the Wasserman et al. (2004) study on water arsenic exposure and children's intellectual function. Although Cal EPA has proposed an inhalation assessment using an oral study, route-to–route extrapolation is typically not recommended for metals, especially if inhalation studies are available, as explained in the USEPA's RfC document (EPA 1994). The TD determined the chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$ of 0.099 µg/m^3 and 0.03µg/m^3 respectively for cardiovascular effects from the Lagerkvist et al. (1986) study.

4.2. Welfare-Based Chronic ESLs

4.2.1 Vegetation Effects

While organic arsenicals have been used as pesticides on cotton plants, no data was available on the adverse vegetative effects from long-term exposure to arsenic in air.

4.3 Long-Term ESL and Values for Air Monitoring Evaluation

The chronic evaluation resulted in the derivation of the following values for arsenic:

- chronic ReV = 0.099 µg/m^3
- $^{chronic}ESL_{nonlinear(nc)}$ = 0.03 µg/m^3

The long-term ESL for air permit reviews is the health-based $^{chronic}ESL_{nonlinear(nc)}$ of 0.03 µg/m^3 (Table 1). The chronic ReV of 0.099 µg/m^3 will be used for the evaluation of air monitoring data.

Chapter 5 References

5.1 References Cited in the Development Support Document

Agency for Toxic Substances and Disease Registry (ATSDR). 2007. Toxicological profile for arsenic.

Alberta Environment. 2005. Assessment report on arsenic for developing ambient air quality objectives.

Allen, BC, PL Strong, CJ Price, et al. 1996. Benchmark dose analysis of developmental toxicity in rats exposed to boric acid. *Fund Applied Tox* 32: 194-204.

Aposhian, HV, B Zheng, MM Aposhian, et al. 2000. DMPS-arsenic challenge test. 11. Modulation of arsenic species, including monomethylarsonous acid (MMA) (111), excreted in human urine. *Toxicol Appl Pharmacol* 165: 74-83.

Arnold, LL, M Eldan, A Nyska, et al. 2006. Dimethylarsinic acid: Results of chronic toxicity/oncogenicity studies in F344 rats and B6C3F1 mice. *Toxicology* 223(1-2):82-100.

Blom, S, B Lagerkvist, H Linderholm. 1985. Arsenic exposure to smelter workers: Clinical and neurophysiological studies. *Scand J Work Environ Health* 11:265-269.

Buchancová, J, G Klimentova, M Knizkova, et al. 1998. Health status of workers of a thermal power

station exposed for prolonged periods to arsenic and other elements from fuel. *Cent Eur J Public Health* 6(1):29-36.

Carapella, SC. 1992. Arsenic and arsenic alloys. In: Kroschwitz JI, Howe-Grant M, eds. Kirk-Othmer encyclopedia of chemical technology. Vol. 3. New York, NY: John Wiley and Sons, 624-633.

Coles, DG, RC Ragaini, JM Ondov, et al. 1979. Chemical studies of stack fly ash from a coal-fired power plant. *Environ Sci Tech* 13(4):455-459.

Colton, T. 1974. "Statistics in Medicine". Little, Brown. Boston.

Dekkers, S, C de Heer, and MAJ Rennen. 2001. Critical effect sizes in toxicological risk assessment: A comprehensive and critical evaluation. *Env Tox Pharm* 10: 33-52

Dunlap, LG. 1921. Perforations of the nasal septum due to inhalation of arsenous oxide. *JAMA* 76(9):568-569.

Feldman, RG, CA Niles, M Kelly-Hayes, et al. 1979. Peripheral neuropathy in arsenic smelter workers. *Neurology* 29:939-944.

Friberg, L, G Nordberg G, V Vouk (eds). 1986. Handbook on the Toxicology of Metals. Elsevier Amsterdam p59.

Gentry, PR, TR Covington, S Mann, et al. 2004. Physiologically based pharmacokinetic modeling of arsenic in the mouse. *J Toxicol Environ Health* A 67(1):43-71.

Harvey, SC. 1970 Heavy metals In Goodman LS, Gilman A (Editors) The pharmacological basis of therapeutics. Collier - Macmillan,Toronto, pp. 958-965.

Hayakawa, T, Y Kobayashi, X Cui, et al. 2005. A new metabolic pathway of arsenite: Arsenite-glutathione complexes are substrates for human arsenic methyltransferase Cyt19. *Arch Toxicol* 79:183-191.

Holson, JF, DG Stump, CE Ulrich, et al. 1999. Absence of prenatal developmental toxicity from inhaled arsenic trioxide in rats. *Toxicol Sci* 51:87-97.

Ihrig, MM, SL Shalat, C Baynes. 1998. A hospital-based case-control study of stillbirths and environmental exposure to arsenic using and atmospheric dispersion model linked to a geographical information system. *Epidemiology* 9(3):290-294.

Kavlock, RJ, BC Allen, EM Faustman, et al. 1995. Dose-response assessments for developmental toxicity IV. Benchmark doses for fetal weight changes. *Fund App Tox* 26:211-22.

Lagerkvist, BJ, B Zetterlund. 1994. Assessment of exposure to arsenic among smelter workers: A five-year follow-up. *Am J Ind Med* 25(4):477-488.

Lagerkvist, B, H Linderholm, GF Nordberg 1986. Vasospastic tendency and Raynaud's phenomenon in smelter workers exposed to arsenic. *Environ Res* 39:465-474.

Lagerkvist, BEA, H Linderholm, GF Nordberg. 1988. Arsenic and Raynaud's phenomenon: Vasospastic

tendency and excretion of arsenic in smelter workers before and after the summer vacation. Int *Arch Occup Environ Health* 60:361-364.

Lee-Feldstein, A. 1983. Arsenic and respiratory cancer in man: Follow-up of an occupational study. In: Lederer W, Fensterheim R, eds. Arsenic: Industrial, biomedical and environmental perspectives. New York, NY: Van Nostrand Reinhold, 245-265.

Lubin, JH, LM Pottern, BJ Stone, et al. 2000. Respiratory cancer in a cohort of copper smelter workers: Results from more than 50 years of follow-up. *Am J Epidemiol* 151(6):554-565.

Mann, S, PO Droz, M Vahter. 1996a. A physiologically based pharmacokinetic model for arsenic exposure. I. Development in hamsters and rabbits. Toxicol Appl Pharmacol 137(1):8-22.

Mann, S, Droz PO, Vahter M. 1996b. A physiologically based pharmacokinetic model for arsenic exposure. II. Validation and application in humans. *Toxicol Appl Pharmacol* 140(2):471-486.

Nagymajtényi, L, A Selypes, G Berencsi. 1985. Chromosomal aberrations and fetotoxic effects of atmospheric arsenic exposure in mice. *J Appl Toxicol* 5(2):61-63.

Nielsen, S, CJ Sorensen, N Olsen. 1980. Thermostatted measurement of systolic blood pressure on cooled fingers. *Scan J Clin Invest* 40:683-687.

Nordström, S, L Beckman, I Nordenson. 1978a. Occupational and environmental risks in and around a smelter in northern Sweden. I. Variations in birthweight. *Hereditas* 88:43-46.

Nordström, S, L Beckman, I Nordenson. 1978b. Occupational and environmental risks in and around a smelter in northern Sweden. III. Frequencies of spontaneous abortion. *Hereditas* 88:51-54.

Nordström, S, L Beckman, I Nordenson. 1979a. Occupational and environmental risks in and around a smelter in northern Sweden. V. Spontaneous abortion among female employees and decreased birth weight in their offspring. *Hereditas* 90:291-296.

Nordström, S, L Beckman, I Nordenson. 1979b. Occupational and environmental risks in and around a smelter in northern Sweden. VI. Congenital malformations. *Hereditas* 90:297-302.

Organization for Economic Cooperation and Development. 1981. Guideline for Testing Chemicals. Teratogenicity. OCED, Paris.

Pacyna, JM, MT Scholtz, Y Li. 1995. Global budget of trace metal sources. *Environ. Rev* 3(2):145-159.

Perry, K, RG Bowler, HM Buckell, et al. 1948. Studies in the incidence of cancer in a factory handling inorganic compounds of arsenic--II: Clinical and environmental investigations. *Br J Ind Med* 5:6-15.

Pershagen, G, Vahter M. 1979. "Arsenic: A Toxicological and Epidemiological Appraisal." The National (Swedish) Environmental Protection Board PM 1128.

Personal Communication (2008) Selene Chou.

Pinto, SS, CM McGill. 1953. Arsenic trioxide exposure in industry. *Ind Med Surg* 22(7):281-287.

Pinto, SS, MO Varner, KW Nelson, et al. 1976. Arsenic trioxide absorption and excretion in industry. *J Occup Med* 18(10):677-680.

Sandstrom, AIM, SGI Wall, A Taube. 1989. Cancer incidence and mortality among Swedish smelter workers. *Br J Ind Med* 46:82-89.

Siegel, S. 1956. "Nonparametric Statistics". McGraw-Hill, New York.

Texas Commission on Environmental Quality (TCEQ). 2006. Guidelines to develop effects screening levels, reference values, and unit risk factors. Chief Engineer's Office. RG-442.

United States Environmental Protection Agency (USEPA). 1983. Effluent guidelines and standards. Electrical and electronic components point source category. Washington, D.C. Code of Federal Regulations. 40 CFR 469.

United States Environmental Protection Agency (USEPA). 1984. Health Assessment Document for Arsenic. Research Triangle Park, NC: U.S. Environmental Protection Agency. EPA600823021F

United States Environmental Protection Agency (USEPA). 1989. Interim methods for development of inhalation reference doses. Washington, D.C. Office of Health and Environmental Assessment. EPA600888066F. PB90145723.

United States Environmental Protection Agency (USEPA). 1991. Guidelines for developmental toxicity risk assessment. Federal Register 56: 63798-63826.

United States Environmental Protection Agency (USEPA). 1994. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Office of Research and Development. Washington, D.C. EPA/600/8-90/066F.

United States Environmental Protection Agency. (USEPA 2000). Benchmark Dose Technical Guidance Document. EPA/630/R-00/001. Risk Assessment Forum. Washington, D.C.

Vahter, M. 1986. Environmental and occupational exposure to inorganic arsenic. *Acta Pharmacol Toxicol* 59:31-34.

Wasserman GA, X Liu, F Parvez, et al. 2004. Water arsenic exposure and children's intellectual function in Araihazar, Bangladesh. *Environ Health Perspect* 112(13):1329-1333.

WHO. 1981. Environmental health criteria 18: Arsenic. IPCS International Programme on Chemical Safety. Geneva, Switzerland: World Health Organization.

Yager J, B Hicks, E Fabianova. 1997. Airborne arsenic and urinary excretion of arsenic metabolites during boiler cleaning operations in a Slovak coal-fired power plant. *Environmental Health Perspectives* 105:836-842.

Yost LJ, RA Schoof, R Aucoin. 1998. Intake of inorganic arsenic in the North American diet. *Human Ecol Risk Assess* 4(1):137-152.

Appendix A

Table A1: Summary of Skeletal Malformations in Mice Exposed to Arsenic							
Group	**As_2O_3 (mg/m^3)**	**Number of Fetuses Observed**	**Number of Fetuses with Skeletal Malformations**	**Ossification Defects**			
				Sternum	**Vertebrae**	**Skull**	**Limbs**
1	0	50	2	1	-	-	1
2	0.26 ± 0.01	**50**	3	1	1	1	3
3	2.9 ± 0.04	50	7	1	2	5	4
4	28.5 ± 0.3	50	31*	14*	12	15	32*

*Significant difference from control ($p < 0.05$)

Table A2: Chromosome Aberrations in the Liver Cells of the Fetuses After Exposure of Pregnant Mice to Arsenic								
Group	**As_2O_3 (mg/m^3)**	**Number of Cells Observed**	**Number of Cells with Damage**	**Number of Abnormal Chromosomes**				
					Chromatid Type		Chromosome Type	
					Gaps	Breaks	Acentric Fragments	Breaks
1	0	200	6	1	3	-	1	1
2	0.26 ± 0.01	200	**10**	1	5	1	1	3
3	2.9 ± 0.04	200	13	1	7	1	1	4
4	28.5 ± 0.3	200	24*	2	9	2	4	12*

* Significant difference from control ($p < 0.05$)

Appendix B

```
=================================================================
       Power Model. (Version: 2.6; Date: 12/06/2005)
       Input Data File: F:\00_BMDS_AS\N_LINEAR_DATA.(d)
       Gnuplot Plotting File: F:\00_BMDS_AS\N_LINEAR_DATA.plt
                                        Tue May 13 11:06:45 2008
 =================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the response function is:

  Y[dose] = control + slope * dose^power


  Dependent variable = MEAN
  Independent variable = Dosemg/m3
  rho is set to 0
  The power is not restricted
  A constant variance model is fit

  Total number of dose groups = 4
  Total number of records with missing values = 0
  Maximum number of iterations = 250
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008



         Default Initial Parameter Values
             alpha =  0.0010129
              rho =      0  Specified
           control =    1.272
             slope =  -0.0792325
             power =   0.38835


      Asymptotic Correlation Matrix of Parameter Estimates

      ( *** The model parameter(s) -rho
        have been estimated at a boundary point, or have been specified by
the user,
        and do not appear in the correlation matrix )

         alpha   control    slope    power

   alpha      1   -1e-006   4.6e-007    5e-008

  control   -1e-006      1    -0.79    -0.66
```

slope	4.6e-007	-0.79	1	0.96
power	5e-008	-0.66	0.96	1

Parameter Estimates

Variable	Estimate	95.0% Wald Confidence Interval Std. Err.	Lower Conf. Limit	Upper Conf. Limit
alpha	0.000900332	0.000215221	0.000478507	0.00132216
control	1.27295	0.0102044	1.25295	1.29295
slope	-0.083801	0.0130598	-0.109398	-0.0582042
power	0.372968	0.0403298	0.293923	0.452013

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	1.27	1.27	0.02	0.03	-0.09
0.26	8	1.23	1.22	0.03	0.03	0.259
2.9	8	1.15	1.15	0.03	0.03	-0.217
28.5	11	0.981	0.981	0.04	0.03	0.0405

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

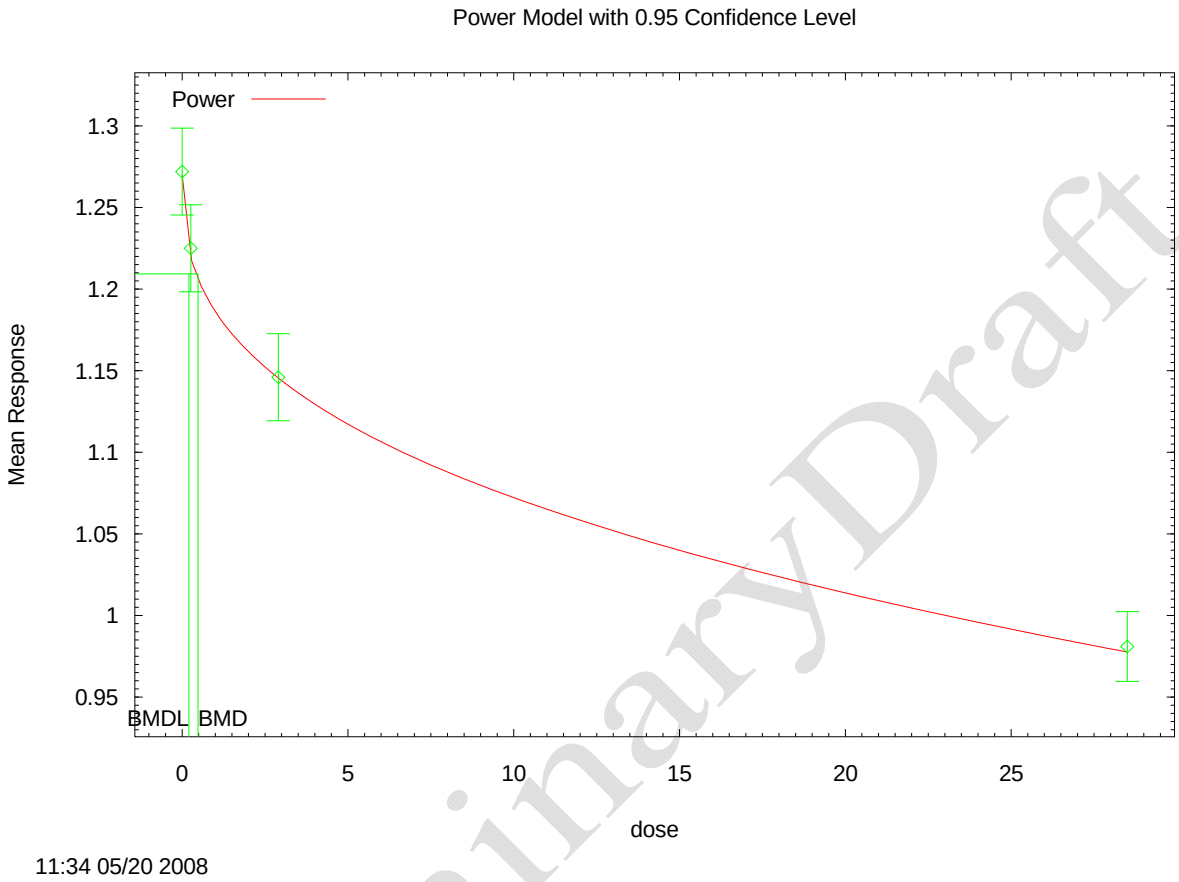
Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = alpha*(Mu(i))^rho

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	105.785170	5	-201.570341
A2	107.435327	8	-198.870654
A3	105.785170	5	-201.570341

```
     fitted     105.223078      4  -202.446157
       R      56.600293      2  -109.200586


          Explanation of Tests

 Test 1: Do responses and/or variances differ among Dose levels?
     (A2 vs. R)
 Test 2: Are Variances Homogeneous? (A1 vs A2)
 Test 3: Are variances adequately modeled? (A2 vs. A3)
 Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

           Tests of Interest

  Test  -2*log(Likelihood Ratio) Test df    p-value

  Test 1        101.67     6     <.0001
  Test 2       3.30031     3     0.3476
  Test 3       3.30031     3     0.3476
  Test 4       1.12418     1      0.289

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1. The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =     0.05

Risk Type    =   Relative risk

Confidence level =     0.95

       BMD = 0.478286


      BMDL = 0.204976
```



APPENDIX C

Table C1: RDDR Model Run Output

Regional deposited dose ratios

SPECIES	Body weight(g)	Extrathoracic VE(ml)	Extrathoracic SA(cm^2)	Extrathoracic dep	Tracheobronchial SA(cm^2)	Tracheobronchial dep	Pulmonary SA(m^2)	Pulmonary dep
mouse	23	25.8	3.000	0.302	3.500	0.093	0.050	0.111
human	70000	13800.0	200.000	0.161	3200.000	0.041	54.000	0.288
RATIO	0.000	0.002	0.015	1.871	0.001	2.280	0.001	0.383

RDDR	0.233	3.901	0.775

	Thoracic SA(m^2)	Thoracic dep	**Total RT** SA(m^2)	**Total RT** dep	Extrarespiratory BW(g)	Extrarespiratory dep
mouse	0.050	0.203	0.051	0.505	23	0.505
human	54.320	0.125	54.340	0.490	70000	0.490
RATIO	0.001	1.622	0.001	1.030	0.000	1.030

RDDR	1.246	**2.067**	5.995

V. 2.3

Note:
MMAD = 1.00 µm (ATSDR 2007)
σ_g = 1.74 (Holson 1999, used the σ_g from the 300 µg/m^3 group
Body weight (g) = 22.5 g (Round to 2 significant figures and is the average of body weight of female mice from Table 4-5 of EPA 1994)