



Development Support Document
Draft, May 2010
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Section 4.2 Carcinogenic Potential

Arsenic and Inorganic Arsenic Compounds

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

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3 **4.2 Carcinogenic Potential**

4 **4.2.1 Weight of Evidence (WOE) from Epidemiological Studies**

5 Several epidemiological studies have been reported in arsenic-exposed smelter workers that
6 indicate that inhalation exposure to inorganic arsenic increases the risk of lung cancer. In 2007,
7 ATSDR conducted a review of the WOE from many of the epidemiological studies and
8 concluded that chronic inhalation exposure to inorganic arsenic increases the risk of lung cancer.
9 In the following sections, the Toxicology Division (TD) staff have included selected portions of
10 Section 3.2.1.7 of ATSDR (2007), with table references removed. In addition to the ATSDR's
11 review of inorganic arsenic, the TD staff reviewed the individual journal articles referenced in
12 the ATSDR (2007) review and further conducted a thorough review of peer-reviewed articles of
13 inorganic arsenic in regards to inhalation exposure in smelters published after 2007 and included
14 a review of those studies.

15 Standard mortality rates (SMRs) are often reported in epidemiological studies. A SMR is
16 basically the number of observed deaths due to a particular disease (e.g., lung cancer) in a group
17 divided by the number that would be expected had the group developed the disease at the same
18 rate as a standard population (e.g., unexposed group, general population), taking into account the
19 number of person-years (PY) in each age group of a cohort and age group rates in the standard
20 population.

21 **4.2.1.1 WOE from Epidemiological Studies Included in ATSDR (2007)**

22 For the WOE from ATSDR (2007), section headings have been inserted by the TD to separate
23 the discussions of the separate studies. See ATSDR (2007) for the cited references.

24 **4.2.1.1.1 Overview**

25 "There is convincing evidence from a large number of epidemiological studies that
26 inhalation exposure to inorganic arsenic increases the risk of lung cancer. Most
27 studies involved workers exposed primarily to arsenic trioxide dust in air at copper
28 smelters (Axelson et al. 1978; Brown and Chu 1982, 1983a, 1983b; Enterline and
29 Marsh 1982; Enterline et al. 1987a, 1987b, 1995; Ferreccio et al. 1996; Järup and
30 Pershagen 1991; Järup et al. 1989; Lee and Fraumeni 1969; Lee-Feldstein 1983,
31 1986; Lubin et al. 2000; Mazumdar et al. 1989; Pinto et al. 1977, 1978; Sandstrom et
32 al. 1989; Viren and Silvers 1999; Wall 1980; Welch et al. 1982) and mines (Liu and
33 Chen 1996; Qiao et al. 1997; Taylor et al. 1989; Xuan et al. 1993), but increased
34 incidence of lung cancer has also been observed at chemical plants where exposure
35 was primarily to arsenate (Bulbulyan et al. 1996; Mabuchi et al. 1979; Ott et al.
36 1974; Sobel et al. 1988). In addition, several studies suggest that residents living near
37 smelters or arsenical chemical plants may also have increased risk of lung cancer
38 (Brown et al. 1984; Cordier et al. 1983; Matanoski et al. 1981; Pershagen 1985),
39 although the increases are small and are not clearly detectable in all cases (e.g., Frost

3 et al. 1987). The strongest evidence that arsenic is responsible for the observed lung
4 cancer comes from quantitative dose-response data relating specific arsenic exposure
5 levels to lung cancer risk. These data are available for arsenic-exposed workers at the
6 ASARCO copper smelter in Tacoma, Washington (Enterline and Marsh 1982;
7 Enterline et al. 1987a, 1995; Mazumdar et al. 1989), the Anaconda copper smelter in
8 Montana (Lee-Feldstein 1986; Welch et al. 1982), eight other U.S. copper smelters
9 (Enterline et al. 1987b), and the Ronnskar copper smelter in Sweden (Järup and
10 Pershagen 1991; Järup et al. 1989). A common limitation of these studies is
11 confounding exposure to other chemicals, such as sulfur dioxide, and cigarette
12 smoking.”

13 **4.2.1.1.2 ASARCO Copper Smelter in Tacoma, Washington**

14 “Enterline and Marsh (1982) reported a significant increase in respiratory cancer
15 mortality (standard mortality ratio [SMR]=189.4) based on 104 observed respiratory
16 cancer deaths and only 54.9 expected over the years 1941–1976 in a cohort of 2,802
17 male workers employed for ≥ 1 year between 1940 and 1964 at the ASARCO
18 smelter. When the cohort was separated into low and high arsenic exposure groups,
19 with mean estimated time-weighted average arsenic exposures of 0.054 and 0.157
20 mg As/m³, respectively (based on work history, historical urinary arsenic
21 measurements, and an experimentally derived relationship between urinary and
22 inhaled arsenic), respiratory cancer mortality was significantly increased in both
23 groups in a concentration-related fashion (SMR = 227.7 and 291.4 in the low and
24 high groups, respectively). Enterline et al. (1987a) re-analyzed these data using
25 improved exposure estimates that incorporated historical measurements of arsenic in
26 the ambient air and personal breathing zone of workers. Respiratory cancer mortality
27 was significantly increased in a concentration-related fashion in the low (SMR =
28 213.0), medium (SMR = 312.1), and high (SMR = 340.9) arsenic exposure groups,
29 which had mean estimated time-weighted average arsenic exposures of 0.213, 0.564,
30 and 1.487 mg As/m³, respectively. An alternative analysis of these data by
31 Mazumdar et al. (1989) produced similar results. Enterline et al. (1995) extended the
32 mortality follow-up from 1976 to 1986, but reported findings similar to the earlier
33 study in a less thorough analysis.”

34 **4.2.1.1.3 Anaconda Copper Smelter in Montana**

35 “Respiratory cancer mortality was significantly increased (SMR = 285) based on 302
36 observed respiratory deaths between 1938 and 1977 in a cohort of 8,045 white male
37 workers employed for at least 1 year between 1938 and 1956 at the Anaconda
38 smelter (Lee-Feldstein 1986). When workers were categorized according to
39 cumulative arsenic exposure and date of hire, lung cancer mortality was significantly
40 increased in all groups hired between 1925 and 1947. Workers in the lowest
41 cumulative exposure group (<10 mg-mo/m³) were reported to have had <2 years of
42 exposure at an average arsenic concentration of 0.38 mg/m³. An alternative analysis

3 of a subset of the Anaconda cohort (n=1,800, including all 277 employees with
4 heavy arsenic exposure and 20% of the others) that included information on smoking
5 and other occupational exposures was performed by Welch et al. (1982). This
6 analysis showed that lung cancer mortality increased with increasing time-weighted
7 average arsenic exposure, with a small nonsignificant increase in the low group
8 (SMR = 138) exposed to 0.05 mg/m³ and significant increases in the medium (SMR
9 = 303), high (SMR = 375), and very high (SMR = 704) groups exposed to 0.3, 2.75,
10 and 5.0 mg/m³, respectively. Cohort members were more likely to be smokers than
11 U.S. white males, but smoking did not differ among the arsenic exposure groups.
12 Exposure-response analysis of smokers was similar to the analysis based on the full
13 subcohort, while analysis of nonsmokers (limited by small group sizes) also showed
14 a similar pattern, but with lower SMRs. In a followup analysis of the same cohort,
15 Lubin et al. (2000) re-weighted the exposure concentrations based on duration and
16 time of exposure and re-evaluated the effects of exposure. Relative risks for
17 respiratory cancer increased with increasing duration in each arsenic exposure area
18 (light, medium, and heavy) after adjustment for duration in the other two exposure
19 areas. SMRs were significantly elevated following exposure to 0.58 mg/m³ (medium;
20 SMR = 3.01, 95% CI = 2.0–4.6) or 11.3 mg/m³ (high; SMR = 3.68, 95% CI = 2.1–
21 6.4) for 10 or more years, and following exposure to 0.29 mg/m³ (low; SMR = 1.86,
22 95% CI=1.2–2.9) for 25 or more years.”

23 **4.2.1.1.4 Eight U.S. Copper Smelters**

24 “Enterline et al. (1987b) studied the mortality experience from 1949 to 1980 of a
25 cohort of 6,078 white males who had worked for 3 years or more between 1946 and
26 1976 at one of eight U.S. copper smelters in Arizona, Utah, Tennessee, and Nevada.
27 Lung cancer mortality was significantly increased only in the Utah smelter (SMR =
28 226.7), which had the highest average arsenic exposure concentration (0.069 mg/m³
29 vs. 0.007–0.013 mg/m³ in the other smelters) and also contributed the largest number
30 of cohort members (n=2,288 vs. 189–965 from the other smelters). A nested case-
31 control study showed that arsenic exposure and cigarette smoking were significant
32 risk factors for lung cancer in the smelter workers. Smoking was lower in the Utah
33 smelter workers than in the other smelter workers, but still higher than in the referent
34 Utah population, suggesting that the risk attributable to arsenic in this study
35 population is somewhat lower than indicated by the SMR reported above.”

36 **4.2.1.1.5 Ronnskar Copper Smelter in Sweden**

37 “Järup et al. (1989) reported significantly increased lung cancer mortality (SMR =
38 372, 95% confidence interval [CI] = 304–450) based on 106 lung cancer deaths in a
39 cohort of 3,916 male workers employed for ≥ 3 months between 1928 and 1967 at
40 the Ronnskar smelter and followed for mortality through 1981. Workers were
41 separated into low, medium, and high arsenic exposure groups with mean time-
42 weighted average exposure estimates of 0.05, 0.2, and 0.4 mg/m³, respectively. Lung

3 cancer mortality was significantly increased in all three exposure groups in a
4 concentration-related fashion (SMR = 201, 353, and 480, respectively). A nested
5 case-control analysis of 102 lung cancer cases and 190 controls from the cohort
6 showed that lung cancer risk increased with increasing arsenic exposure in
7 nonsmokers, light smokers, and heavy smokers (Järup and Pershagen 1991). The
8 results demonstrated that arsenic is a risk factor for lung cancer in the smelter
9 workers, but also suggested a greater-than-additive interaction between smoking and
10 arsenic exposure. In this analysis, in contrast to the cohort study, lung cancer risk due
11 to arsenic was increased only in the higher arsenic-exposure groups. Potential
12 explanations for this difference between the cohort and case-control analyses include
13 a higher proportion of smokers in the smelter workers than in the regional referent
14 population in the cohort study, and limited power to detect increased risk in the case-
15 control study due to small group sizes in the dose-response analysis.”

16 4.2.1.1.6 Other Types of Nonrespiratory Cancer

17 “There have been occasional reports of other types of cancer (i.e., nonrespiratory
18 cancer) potentially associated with inhalation exposure to inorganic arsenic, but there
19 is no strong evidence for any of them. For example, Enterline et al. (1995) found
20 significantly increased mortality due to cancer of the large intestine and bone cancer
21 in the ASARCO cohort. However, neither cancer showed any relation to cumulative
22 arsenic exposure, and the purported increase in bone cancer risk was based on a very
23 small number of observations. Pesch et al. (2002) reported an increase in
24 nonmelanoma skin cancers resulting from exposure from a Slovakian coal-burning
25 power plant, but exposure levels associated with the lesions were not presented.
26 Bencko et al. (2005) also reported an increase in the incidence of nonmelanoma skin
27 cancer among workers of a power plant burning coal of a high arsenic content and in
28 the population living in the vicinity of the power plant. Bulbulyan et al. (1996)
29 reported an increase in risk of stomach cancer among workers exposed to the highest
30 average arsenic concentrations at a Russian fertilizer plant, but this finding, which
31 was based on a small number of observations and was only marginally statistically
32 significant, was confounded by exposure to nitrogen oxides, which were more
33 convincingly associated with stomach cancer in this study. Wingren and Axelson
34 (1993) reported an association between arsenic exposure and stomach and colon
35 cancer in Swedish glass workers, but this result was confounded by concomitant
36 exposure to other metals. Lee-Feldstein (1983) observed a small, marginally
37 significant increase in digestive tract cancer (SMR = 125) in one study of the
38 Anaconda cohort, but this was not found in other studies of this cohort (Lee and
39 Fraumeni 1969; Lee-Feldstein 1986; Welch et al. 1982). Wulff et al. (1996) observed
40 an apparent increase in the risk of childhood cancer (all types combined) in the
41 population living within 20 km of the Ronnskar smelter, but the apparent increase
42 was based on a small number of cases (13 observed vs. 6.7 expected) and was not
43 statistically significant, and exposure to arsenic was confounded by exposure to lead,

3 copper, cadmium, sulfur dioxide, and possibly other emissions such as arsenic and
4 selenium. A retrospective study of deaths due to unspecified types of malignancies
5 among workers of power plants found no significant differences in death rate
6 between two groups whose exposure levels to arsenic had a difference of one order
7 of magnitude (Bencko et al. 1980). However, the mean age of those deceased due to
8 cancer in the high-exposure group was 55.9 years compared to 61.2 years in the low-
9 exposure group, and this difference was statistically significant ($p < 0.05$). Also, when
10 the workers were stratified by exposure-duration, there was a significantly higher
11 frequency of tumors in the high-exposure group after shorter employment periods
12 (< 5 or $6-10$ years) than after a longer employment period (≥ 11 years). No
13 information was provided regarding specific types of cancer. Various case reports
14 have implicated occupational arsenic exposure as a potential contributing factor in
15 workers who developed sinonasal cancer (Battista et al. 1996), hepatic angiosarcoma
16 (Tsai et al. 1998a), and skin cancer (Cöl et al. 1999; Tsuruta et al. 1998), but provide
17 no proof that inhaled arsenic was involved in the etiology of the observed tumors.
18 Wong et al. (1992) found no evidence that environmental exposure to airborne
19 arsenic produced skin cancer in residents living near the Anaconda smelter or an
20 open pit copper mine.”

21 **4.2.1.2 WOE from Other Epidemiological Studies**

22 **4.2.1.2.1 United Kingdom (UK) Tin Smelter**

23 Binks et al. (2005) investigated whether there was any significant excess or deficits in mortality
24 among workers employed at a tin smelter complex in North Humberside, UK, at which
25 employees were potentially exposed to a number of substances, including lead, arsenic, cadmium
26 and natural series radionuclides. The cohort consisted of 1462 males employed for at least 1 year
27 between 1967 and 1995 and followed through the end of 2001. Mortality from lung cancer
28 showed a statistically significant excess with a SMR of 161 [CI = 124-206] ($P < 0.001$) and there
29 was evidence of a diminution of lung cancer risk with time since exposure. Mortality from
30 smoking-related diseases other than lung cancer showed a non-significant deficit and mortality
31 from all causes and all cancers did not differ from that expected. Jones et al. (2007) investigated
32 the relationship between lung cancer mortality and quantitative measures of exposure and
33 concluded the excess of lung cancer mortality in the cohort can most plausibly be explained if
34 arsenic is the principal occupational carcinogen. Refer to Section 4.2.4.4 for a more detailed
35 discussion of the Jones et al. (2007) study.

36 **4.2.1.2.1 China Mine Study**

37 A retrospective lung cancer mortality study of Chinese miners who had been exposed to
38 insoluble arsenic in four mines implicated arsenic to be the cause of lung cancer in the miners
39 (Tang and Zhen, 1996). The authors were able to demonstrate a dose-dependent decrease in the
40 incidence of lung cancer with a reduction in the concentration of insoluble arsenic in the air. The
41 main objective of the study was to determine whether the risk of mine workers developing lung

3 cancer was due to exposure to insoluble arsenic and/or radon exposures as both these are
4 chemicals of concern inside the mines.

5 While exposure to radon has been established to cause lung cancer, similar conclusions were
6 unavailable for arsenopyrite, an insoluble form of arsenic. Uncertainty regarding the
7 carcinogenic potential of arsenopyrite stemmed from the fact that arsenopyrite is an insoluble
8 form of arsenic. However, on finding that both arsenopyrite and arsenic trioxide form the same
9 metabolic products (i.e, arsenous acid, arsenic acid, methyl arsenate and diethyl arsenate) the
10 authors concluded arsenopyrite to be a carcinogen similar to arsenic trioxide.

11 The reported average arsenic concentrations and crude mortality rates (CMR) on exposure to the
12 arsenic concentrations were found to decrease in subsequent years which further confirm a good
13 dose-response relationship. The average arsenic air concentrations were reported as follows:

- 14 • 0.29 mg/m³ before 1950;
- 15 • 0.29 mg/m³ in the 1950's ;
- 16 • 0.022 mg/m³ in the 1960's;
- 17 • 0.015 mg/m³ in the 1970's; and
- 18 • 0.010 mg/m³ in the 1980's.

19 The CMR also showed a decrease as the concentration of arsenic decreased in the the mines in
20 the subsequent years. For exposures before 1950's, the CMR was 290/10⁵ as opposed to CMR of
21 150/10⁵ for exposures from 1950 to 1960's . Further, the CMR was 20/10⁵ if the arsenic
22 exposure took place in the beginning of 1960's.

23 While the study provided valuable WOE that indicated that the lung cancer among the mine
24 workers was because of exposure to arsenic as opposed to radon and other metals, the TD did not
25 use this study as a key study because of the following reasons:

- 26 • The study did not include adequate exposure data necessary for the TD staff to conduct a
27 dose response assessment and develop a URF;
- 28 • Although, the authors reported appropriate statistical parameters (i.e., "beta" slope value
29 and "S.E. on the beta"), the values were calculated based on a case control study of only
30 ~21 miners. The TD staff is of the opinion that the information to be inadequate to use
31 the study as a key study to determine a URF.
- 32 • Further, the cohort itself is small (only about 700 miners) and would be inadequate in
33 terms of sample size.

34 **4.2.1.3 WOE from Animal Studies**

35 The TD staff is of the opinion that animal models to be significantly limited in their usefulness in
36 regards to arsenic toxicity. Based on a review of the available literature on inorganic exposure in
37 animal models, the TD staff was unable to locate any animal inhalation studies for cancer. A
38 limited evidence from intratracheal instillation studies in hamsters supports the conclusions that
39 inhalation of arsenic may lead to lung cancer in humans. Further, humans differ from animals in

3 the pattern of metabolism as they excrete significantly more methylated forms of arsenic when
4 compared to other mammalian species (with the mouse and rabbit may be an exception). A
5 discussion on the carcinogenic potential of arsenic based on animal studies was taken from
6 ATSDR (2007). See ATSDR (2007) for the cited references.

7 No studies were located regarding cancer in animals after inhalation exposure to
8 inorganic arsenicals, although several intratracheal instillation studies in hamsters
9 have provided evidence that both arsenite and arsenate can increase the incidence of
10 lung adenomas and/or carcinomas (Ishinishi et al. 1983; Pershagen and Björklund
11 1985; Pershagen et al. 1984; Yamamoto et al. 1987). These data support the
12 conclusion that inhalation of arsenic may lead to lung cancer in humans.

13 **4.2.1.4 WOE Classifications**

14 The International Agency for Research on Cancer (IARC 2004) has classified arsenic and arsenic
15 compounds in Group 1, as chemicals and groups of chemicals which are casually associated with
16 cancer in humans. USEPA (1984) has classified inorganic arsenic as a Group A, human
17 carcinogen. Arsenic has also been classified in Group 1 (carcinogenic to humans) by Health
18 Canada (1994). According to guidance in the new cancer guidelines (USEPA 2005a), the TD
19 considers arsenic compounds as a group to be “Carcinogenic to Humans” via inhalation.

20 **4.2.2 Carcinogenic MOA**

21 While the mechanisms of arsenic-induced toxicity and carcinogenicity have not been clearly
22 identified, many studies have reported on the probable mechanisms of toxicity. Arsenic has been
23 reported to have multiple MOAs (genotoxic/mutagenic). Understanding the MOA will help
24 reduce uncertainty in risk assessments. Recently, Kitchin and Conolly (2010) presented a
25 thorough review of arsenic induced carcinogenesis in which they discuss oxidative stress as a
26 possible MOA. The summary report of the peer review meeting of the USEPA’s draft framework
27 for determining a mutagenic MOA for carcinogenicity (USEPA 2004) recommends the risk
28 assessment for arsenic to be conducted as a linear, no threshold dose-response curve because it’s
29 exact MOA has not yet been conclusively defined. The framework does not identify arsenic as a
30 carcinogen with a definitive mutagenic MOA. As the data on the MOA is yet to be elucidated,
31 the TD will use linear low-dose extrapolation to calculate unit risk factors (URFs) as a
32 conservative default assumption.

33 Due to the extremely large amount of mechanistic data for arsenic, it is not feasible to include all
34 pertinent primary studies that address issues concerning proposed mechanisms of arsenic toxicity
35 and carcinogenicity. It is generally agreed that multiple mechanisms are involved which could
36 also relate to the noncancer effects. The following sections include the description of the MOA
37 as described in ATSDR (2007).

38 **4.2.2.1 Oxidative Stress**

39 Various *in vivo* and *in vitro* mechanistic studies of arsenic toxicity have suggested reactive

3 oxygen species to be responsible for the toxicity of inorganic arsenic. The proposed mechanisms
4 for oxidative stress include: increased lipid peroxidation, superoxide production, hydroxyl
5 radical formation, blood nonprotein sulfhydryls, and/or oxidant-induced DNA damage. In
6 addition, reduction of cellular oxidant defense by treatment with glutathione-depleting agents
7 results in an increased sensitivity of cells to arsenic toxicity. Inhalation toxicity studies have
8 reported the mechanisms of toxicity that involve arsenic-induced oxidative stress include
9 findings that inhaled arsenic can predispose the lung to oxidative damage, chronic low-dose
10 arsenic alters genes and proteins that are associated with oxidative stress and inflammation, and
11 major transcriptional regulators of altered genes are redox sensitive.

12 **4.2.2.2 Altered Growth Factors→Cell Proliferation→Promotion of** 13 **Carcinogenesis**

14 There is general evidence that increased concentrations of growth factors can lead to increase in
15 cell proliferation and trigger carcinogenesis. Specifically, arsenic-induced cell death can also
16 lead to compensatory cell regeneration and carcinogenesis. Altered growth factors, cell
17 proliferation, and promotion of carcinogenesis have all been demonstrated *in vivo* experiments
18 exposed to arsenics. Altered growth factors and mitogenesis were noted in human keratinocytes.
19 Cell death was observed in human hepatocytes and rat bladder epithelium. Cell proliferation was
20 demonstrated in human keratinocytes and intact human skin and rodent bladder cells. Promotion
21 of carcinogenesis was noted in rat bladder, kidney, liver, and thyroid, and mouse skin and lung.

22 **4.2.2.3 Genotoxicity**

23 Several studies have indicated the genotoxic effects of arsenic. *In vitro* studies in human
24 fibroblasts, lymphocytes, and leukocytes, mouse lymphoma cells, Chinese hamster ovary cells
25 and Syrian hamster embryo cells indicate that inorganic arsenic can induce chromosomal
26 aberrations and sister chromatid exchange. A higher than average incidence in chromosomal
27 aberrations have been reported in human peripheral lymphocytes both after inhalation (Beckman
28 et al. 1977 and Nordenson et al. 1978) and oral exposure (Burgdorf et al. 1977) in occupational
29 workers. However USEPA recommends caution in interpreting these results because of small
30 sample sizes and because exposures from other pollutants were not accounted for (USEPA
31 1984). Inhaled arsenic is reported to be clastogenic and according to ATSDR (2007) workers
32 exposed to unspecified concentrations of arsenic trioxide at the Ronnskar copper smelter in
33 Sweden were reported to have a significant increase in the frequency of chromosomal
34 aberrations in peripheral lymphocytes (Beckman et al. 1977; Nordenson et al. 1978). Increased
35 chromosomal aberrations have also been reported in the fetuses of mice exposed to 22 mg/m³ of
36 inorganic arsenic on days 9 – 12 of gestation. However, lower concentrations of inorganic
37 arsenic (2.2 or 0.2 mg/m³) did not result in chromosomal aberrations. In addition, Vuyyuri et al.
38 (2006) reported a significantly increased frequency of micronuclei in buccal cells and increased
39 DNA damage in leukocytes compared to a control group in workers in the arsenic-based glass
40 making industry in Southern India. While the study did not report the exposure levels, it reported
41 blood concentrations in the workers to be approximately five times higher than in the reference
42 group.

3 Other studies have reported inorganic arsenic to cause chromatid gaps, chromosomal breaks, and
4 fragmentation in a dose-related fashion with the trivalent or arsenite forms being more toxic than
5 the pentavalent or arsenate forms. Also, the MMAIII and DMAIII forms are more directly
6 genotoxic and therefore more potent than the arsenite forms. Arsenic-induced genotoxicity can
7 also involve free-radical species and inorganic arsenic can also potentiate the mutagenicity
8 observed with other chemicals.

9 According to Jacobson-Kram and Montalbano (1985) (as cited in the IRIS document for
10 inorganic arsenic), inorganic arsenic is inactive or very weak for induction of gene mutations *in*
11 *vitro* but it is clastogenic with trivalent arsenic being an order of magnitude more potent than
12 pentavalent arsenic.

13 Arsenic compounds are very complex reagents which can generate oxygen radicals and cause
14 clastogenesis, and changes in DNA methylation. While arsenic is a carcinogen, its exact MOA
15 has not been conclusively defined. Arsenic has been reported to have multiple MOA
16 (genotoxic/mutagenic). The summary report of the Peer review meeting of the USEPA's draft
17 framework for determining a mutagenic MOA for carcinogenicity (USEPA 1984) recommends
18 the risk assessment for arsenic to be conducted as a linear, no threshold dose-response curve
19 because it's exact MOA has not yet been conclusively defined. The framework does not identify
20 arsenic as a carcinogen with a definitive mutagenic MOA.

21 **4.2.2.4 Additional Mechanisms of Toxicity**

22 According to ATSDR (2007), inorganic arsenic exposure has been shown to modify the
23 expression of a variety of genes related to cell growth and defense, including the tumor
24 suppressor gene p53, as well as to alter the binding of nuclear transcription factors. Carcinogenic
25 effects of arsenic may result from a cocarcinogenic effect. Whereas arsenic exposure alone did
26 not elicit skin tumors in mice, co-exposure to arsenic and ultraviolet light resulted in skin tumors
27 that were greater in number and larger in size than those produced by ultraviolet light alone.

28 **4.2.3 Epidemiological Studies used to Develop URFs**

29 USEPA developed a URF of 4.3×10^{-3} per $\mu\text{g}/\text{m}^3$ in 1984 (USEPA 1984) and it was reviewed by
30 IRIS in 2007. The URF was based on excess lung cancer mortality in workers at only two
31 smelters: The Asarco smelter in Tacoma, Washington (Enterline and Marsh 1982) and the
32 Anaconda smelter in Montana (Brown and Chu 1982, 1983a, 1983b; Lee-Feldstein 1983; and an
33 unpublished paper by Higgins and associates).

34 The Enterline et al. 1987 and 1995 updates of the Tacoma smelter, the Lubin et al. (2000, 2008)
35 updates of the Montana smelter studies, the Ronnskar Copper Smelter cohort study in Sweden
36 (Järup et al. 1989; Viren and Silvers 1994), and the UK tin smelter cohort study in Humberside,
37 UK (Binks et al. 2005; Jones et al. 2007) were not available in 1984. These four human
38 epidemiological studies contain adequate dose-response data for an updated assessment of the
39 carcinogenic potential of arsenic and the development of new inhalation unit risk factors (URFs).

3 The following updated and/or current studies will be used by TCEQ to develop a new inhalation
4 URF:

- 5 • The Asarco smelter in Tacoma, Washington (Enterline et al. 1995)
- 6 • Anaconda smelter in Montana (Lubin et al. 2000; 2008);
- 7 • Ronnskar Copper Smelter in Sweden (Järup et al. 1989; Viren and Silvers 1994); and
- 8 • United Kingdom (UK) tin smelter in Humberside, UK (Binks et al. 2005; Jones et al.
9 2007).

10 Historical information on all four studies has been discussed in Section 4.2.1.1 and 4.2.1.2 and
11 summary information is shown in Table 6.

DRAFT

3

Table 6. Epidemiological Studies with Adequate Dose-Response Data					
Occupational location and exposure period	Most Recent Dose-Response Data	Worker follow-up	No. of Workers Person-years (PY)	Cancer type SMR^a (p value)	Cumulative Arsenic Exposure (mg/m³-yr)^b
Tacoma, WA Asarco copper smelter (1940-64)	Enterline et al. (1995)	Through 1986	2802 84,916 PY	Respiratory 209.7 SMR (p < 0.01)	< 0.750 to 45+
Montana copper smelter (1938-1958)	Lubin et al. 2000; Lubin et al. 2008	Through 1989	8014 144,851 PY ^c (restricted cohort) 256,850 (full cohort)	Respiratory 187 SMR (restricted cohort) (p<0.001) 156 SMR (full cohort) (p<0.001)	1 to 26.2+
Ronnskar, Sweden copper smelter (1928-1967)	Järup et al. (1989); Viren and Silvers (1994)	Through 1981	3916 127,189 PY	Lung 372 SMR (p < 0.001)	< 0.25 to 100+
United Kingdom tin smelter (1937-1991)	Jones et al. 2007	Through 2001	1462 35,942 PY	Lung 161 SMR (p < 0.001)	<0.002 to 4.5+ ^d

4 ^a SMR, standardized mortality ratio; reported results from most recent study

5 ^b milligrams of arsenic per cubic meter per year (mg/m³-yr)

6 ^c For the Montana copper smelter, PY data were obtained from Table 1 of Lubin et al. 2008
7 because it is the most recent analysis of the data

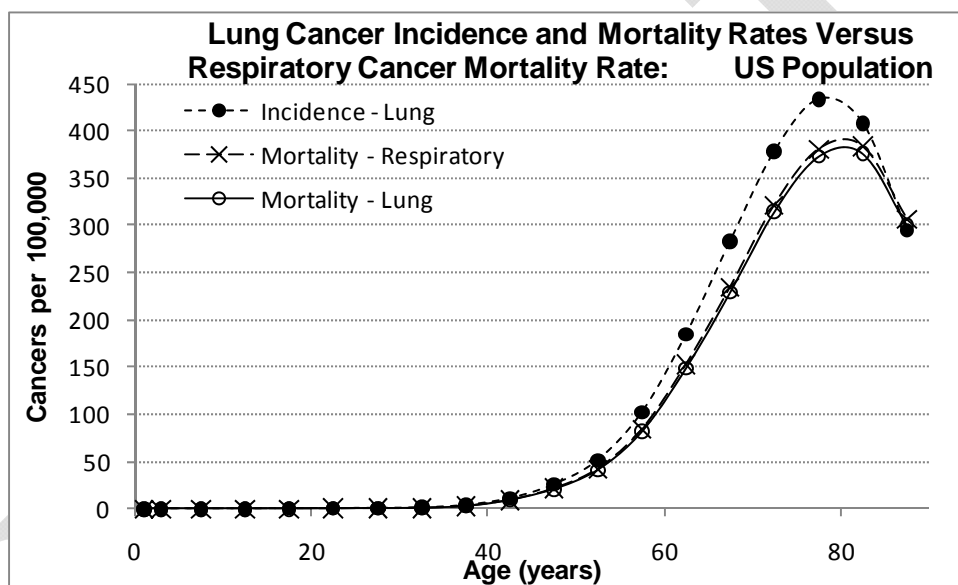
8 ^d For the UK smelter the distribution of the cumulative arsenic exposures are given in Table 2 of
9 Jones et al. (2008).

10 4.2.4 Dose Metric and Dose-Response Assessment

11 Enterline et al. (1995) and Lubin et al. (2000; 2008) examined *respiratory cancer mortality* (i.e.,
12 larynx, bronchus, trachea, lung, and other residual) by cumulative arsenic exposure level whereas
13 the other two epidemiology studies investigated lung cancer mortality (Järup et al. 1989; Jones et
14 al. 2007). Lung cancer mortality will be considered the cancer endpoint of interest for all four

3 studies for risk estimation purposes. The respiratory cancer mortality data from Enterline et al.
4 (1995) and Lubin et al. (2000; 2008) are a reasonable surrogate for lung cancer as most (96 %) of
5 the observed deaths (i.e., 182 out of 188 and 428 out of 446, respectively) were due to lung
6 cancer. As lung cancer mortality, and consequently respiratory cancer mortality, are reasonably
7 predictive of lung cancer incidence (i.e., five-year survival is only about 15% (American Cancer
8 Society 2005)), the TD considers the cancer potency estimates based on the two studies and the
9 resulting calculations as comparable (i.e., lung cancer incidence and mortality rates are
10 sufficiently similar to respiratory cancer mortality rates as to be comparable for purposes of this
11 assessment. Figure 1 includes lung cancer incidence rates, lung cancer mortality rates, and
12 respiratory cancer mortality rates. Lung cancer incidence and mortality rates are sufficiently
13 similar to the respiratory cancer mortality rates as to be comparable for purposes of this
14 assessment.

15 **Figure 1. Lung Cancer Incidence and Mortality Rates versus Respiratory Cancer Mortality**
16 **Rates^a**



17
18 ^a Based on US lung cancer mortality, respiratory cancer mortality, and incidence rates in
19 Appendix A

20 The dose metric used for the dose-response assessments is typically cumulative arsenic exposure
21 ($\mu\text{g}/\text{m}^3\text{-yr}$) because it is the only measure available from all cohort studies and because there are
22 no biological/mechanistic data or statistical evidence which indicates that another dose metric is
23 more appropriate, except for Lubin et al. (2008). Lubin et al. (2008) investigated a dose metric of
24 cumulative arsenic exposure modified by the concentration, as discussed in Section 4.2.4.2.1.2).

25 Standard regression analysis approaches for survival data (Poisson regression and Cox
26 regression) are considered more reliable and less restricted to calculate the maximum likelihood
27 estimates of β and corresponding variance when the necessary detailed data are available (e.g.,

3 can adjust for covariate effects and use internally-derived background hazard rates). While
4 results of the standard Poisson regression analysis were available for Lubin et al. (2000; 2008)
5 and Jones et al. (2007), only summary data (i.e., observed and expected deaths versus cumulative
6 arsenic exposure levels) were available for Enterline et al. (1995) and Järup et al. (1989). For
7 these two studies with the summary data, the TD used the linear multiplicative relative risk
8 model and Poisson regression modeling (Appendix B) to obtain maximum likelihood estimates
9 of β (Section B.2, Appendix B) and the asymptotic variance for β (Section B.3, Appendix B). In
10 addition to the more plausible assumptions regarding the amount of increase in risk with age, the
11 linear multiplicative relative risk model naturally results from the Poisson regression and Cox
12 proportional hazards models when only summary data are available.

13 The linear multiplicative relative risk model, as opposed to the additive risk model, was used to
14 calculate β estimates. The multiplicative relative risk model is preferred over the additive risk
15 model for lung cancer because of more plausible assumptions concerning the increase in risk
16 with age. For lung cancer, risk increases rapidly with age, which is better captured by the
17 multiplicative relative risk model where risk increases over background rates multiplicatively.
18 By contrast, the additive risk model assumes that cumulative exposure causes the same absolute
19 increase in risk regardless of the age at which the risk is calculated which is less plausible
20 relative to actual observed age-related increases in lung cancer mortality and overall mortality.
21 Lubin et al. (2000) investigated the absolute or additive risk model but found that it provided
22 poorer fits to the data than the multiplicative relative risk model.

23 ***4.2.4.1 Enterline et al. (1982, 1987a, 1987b, and 1995)***

24 **Asarco Smelter, Tacoma, Washington**

25 The aim of Enterline et al.(1995) was to investigate the risks of cumulative arsenic exposure on
26 updated worker respiratory cancer mortality information. An earlier study of 2802 men who
27 worked at a copper smelter at Tacoma, WA for a year or more during the period of 1940-1964
28 and were followed up for deaths during the period 1941-1976 was updated until 1986. Estimates
29 of exposure for the period 1977-1984 were added. Exposure to arsenic air concentrations were
30 estimated from departmental air arsenic and workers urinary arsenic measurements. Information
31 on smoking was not available. The SMR for respiratory cancer was 209.7 for the total cohort (p
32 < 0.01). There were 1583 deaths observed in the updated study versus 1061 deaths (Enterline et
33 al. 1982; 1987) and 188 versus 104 respiratory cancers (Enterline et al. 1982; 1987). Refer to
34 Section 4.2.1.1.2 for additional information on Enterline et al. (1982; 1987) and Table 6 for
35 summary information.

36 Arsenic concentrations in air were estimated for each department starting from 1938 and urinary
37 arsenic measurements were estimated from each department and worker starting from 1948.
38 While the measurements of arsenic in air were confined mostly to the departments in which
39 arsenic was thought to be a problem, arsenic in urine was measured for all workers. Enterline et
40 al. (1995) reported that the conversion of data of urinary arsenic to air arsenic was made by the
41 identification of departments and years for which data from both air and urinary arsenic

3 concentrations were available and by the determination of the mathematical relation between the
4 two.

5 In order to estimate actual worker exposure concentrations, the average concentrations of arsenic
6 in air were weighted by hours per shift at the sample location, number of men at the location per
7 shift, and frequency of operation for samples. While prior to 1971 arsenic data was obtained by
8 tape and spot samples, starting in 1971, personal air measurements were available. The authors
9 then constructed an exposure matrix for arsenic in air by department and year from 1938 up to
10 the time the smelter closed in 1984. The exposure estimates from 1938 were used for years before
11 1938. Finally, the cumulative exposure was calculated and reported as $\mu\text{g}/\text{m}^3\text{-yr}$.

12 Enterline et al. (1995) reported significant excesses for all malignant neoplasms taken together
13 (i.e., cancers of the large intestine, respiratory system, and bone). For < 20 years since first
14 exposure, only respiratory cancer was significant. However, for ≥ 20 years since first exposure
15 SMRs were generally higher but those that were significant were the same as for the total cohort.
16 Enterline et al. (1995) reported the relation between cumulative exposure to arsenic in air
17 expressed as $\mu\text{g}/\text{m}^3/\text{yr}$ and cancer of the respiratory system for the entire cohort, for the cohort
18 hired before 1940, and for the cohort hired in 1940 or later. This stratification helped separate
19 workers before 1940 who were estimated to have had relatively high exposure concentrations
20 coupled with poor respiratory protection from workers with relatively lower exposure
21 concentrations coupled with better respiratory protection.

22 USEPA developed a URF from the Enterline and Marsh (1982) study which was based on the
23 results from the Pinto et al. (1976) study. The Pinto et al. (1976) study reported an association
24 between airborne arsenic concentrations and urinary arsenic concentrations. The basis of this
25 relationship was that the urinary arsenic concentration could be used as a biomarker for airborne
26 exposure, and the dose response for arsenic-related lung cancer mortality could be expressed in
27 terms of cumulative urinary arsenic exposure ($\mu\text{g}/\text{As}/\text{liter urine years}$). This relationship was
28 expressed with the following formula:

$$29 \quad \text{As}_{\text{air}} = 0.304 \text{As}_{\text{urine}}$$

30 where As_{air} is measured as $\mu\text{g}/\text{m}^3$ and As_{urine} is measured as $\mu\text{g}/\text{liter}$

31 Enterline and Marsh (1982) used this relation and estimated cumulative air exposure by
32 multiplying the 1982 cumulative urinary arsenic exposure by 0.304. However, Enterline et al.
33 (1987) indicated limitations in the Pinto et al. (1976) study, conducted a re-analysis, and reported
34 an updated relationship between airborne arsenic exposure and respiratory cancer mortality
35 among workers from the Tacoma smelter in the following formula:

$$36 \quad \text{As}_{\text{air}} = 0.0064 (\text{As}_{\text{urine}})^{1.942}$$

37 Where As_{air} is measured as $\mu\text{g}/\text{m}^3$ and As_{urine} is measured as $\mu\text{g}/\text{liter}$.

3 Enterline et al. (1987) reported that in the Pinto et al. (1976) study the authors did not take into
4 account prior arsenic exposure through diet. This resulted in high baseline levels of urinary
5 arsenic (about 150 µg/liter). As such, Enterline et al. (1987) indicated that the Pinto et al. (1976)
6 study did not depict the true relationship between urinary arsenic measurements and airborne
7 arsenic levels.

8 **4.2.4.1.1 Slope Parameter (β) Estimates**

9 **4.2.4.1.1.1 Enterline et al. (1995) Dose-Response**

10 When Enterline et al. (1995) investigated the dose-response relationship for the entire cohort
11 using standard regression analysis, they found the linear correlation between log dose and SMRs
12 was highly significant ($p < 0.001$). The fitted regression equation between dose and SMRs was
13 best described as a power function:

$$14 \quad \text{SMR} = 100 + 10.5 (\text{cumulative exposure})^{0.279}$$

15 If the dose-response relationship is described by the above power function, it indicates a
16 relatively large increment in respiratory cancer risk at low exposures. Using the Tacoma cohort,
17 Health and Welfare Canada (NHW 1993 as reported in Viren and Silver 1999) has strongly
18 challenged strict linearity and preferred a curvilinear model. A curvilinear relationship may have
19 been observed by Enterline et al. (1995) and NHW (1993) for the following reasons:

- 20 • Enterline et al. (1995) fit the data so that the SMR was fixed at 100 for the person years
21 with zero cumulative exposure, which may have contributed to the curvilinear dose-
22 response relationship;
- 23 • Viren and Silvers (1999) investigated whether the dose-response relationship in the
24 Tacoma cohort was linear or curvilinear and found that the nonlinearity in the dose-
25 response was strongly influenced by date of initial hire. A curvilinear relationship was
26 evident only among workers hired prior to 1940 and was strongly related to the
27 artifactually low lung cancer mortality seen among workers hired between 1930 and
28 1939; and
- 29 • Lubin et al. (2000) have also questioned the concave relationship found by Enterline et al.
30 (1995) and stated it may be due to an artifact of the exposure assessment procedure.

31 Therefore, the β estimate derived by Enterline et al. (1995) using the power model was not
32 considered appropriate.

33 **4.2.4.1.1.2 Viren and Silvers (1999) Dose-Response**

34 Viren and Silvers (1999) examined the updated results from the Asarco smelter in Tacoma, WA
35 and also updated results from a Swedish cohort of smelter workers. In this section, TD will
36 discuss the Tacoma smelter results and the Swedish results will be discussed in Section 4.2.4.3.

37 Viren and Silvers (1999) used the following model equations and symbols to calculate the
38 intercept and potency estimates:

3
$$\lambda_t = E_t \times (b_1 + b_2 \times d_j)$$

4 The following standard parameterization of the multiplicative relative risk linear model with
5 intercept (Crump and Allen 1985), is used more often and readily usable for excess risk
6 estimation, as discussed in Appendix B:

7
$$E(O_j) = \alpha \times E_{oj} \times (1 + \beta \times d_j)$$

8 where $\lambda_t = E(O_j)$ and $E_t = E_{oj}$. Thus, the α in the standard multiplicative relative risk linear model
9 with intercept is equal to b_1 in the Viren and Silvers' linear – with intercept ($\beta_1\beta_2$) model.
10 Similarly, the β in the standard multiplicative relative risk linear model with intercept is equal to
11 b_2/b_1 in the Viren and Silvers' linear – with intercept ($\beta_1\beta_2$) model. By replacing $\alpha \times E_{oj}$ by a
12 target population's background risk, the standard multiplicative relative risk linear model can be
13 used to estimate excess risks for a target population with background risks different than those of
14 the cohort. This may account for potential issues such as the healthy worker effect and any
15 differences between internally- and externally-derived background rates.

16 As discussed in Appendix B, incorporation of the term α into the relative risk model yields:

17
$$E(O_j) = \alpha \times E_{oj} \times (1 + \beta \times d_j)$$

18 Where:

- 19 $E(O_j)$ = expected number of lung cancer cases for exposure group j
20 E_{oj} = expected number of background lung cancer cases for exposure group j
21 β = multiplicative factor by which background risk increases with cumulative
22 exposure
23 d_j = cumulative exposure for exposure group j
24 α = accounts for differences in lung cancer background rates between the study
25 population and the reference population

26 Viren and Silvers (1999) analyzed the dose-response relationship of the Enterline et al. (1995)
27 data using four different models:

- 28 • the Canadian ($\beta_1 \beta_2 \beta_3$) model;
29 • the linear ($\beta_1 \beta_2$) with intercept model;
30 • the linear ($1 + \beta_2$) model; and
31 • a null (β_0) model.

32 Refer to Viren and Silvers (1999) for model equations and additional details. They found the
33 linear two-parameter model with intercept ($\beta_1 \beta_2$) was preferred, showing strong statistical
34 evidence supporting the association between excess respiratory cancer risk and arsenic exposure
35 and having the smaller Akaike information criterion (AIC). Viren and Silvers (1999) also
36 provided the following intercept and potency estimates for the total cohort, workers initially
37 hired < 1940, and workers initially hired \geq 1940:

- 3 • Total cohort: intercept 1.681, potency 3.59E-05, *potency/intercept* = 2.14E-05 (β
4 *parameter estimate to use for BEIR IV*)
- 5 • workers initially hired < 1940: intercept 1.43, potency 4.92E-05, *potency/intercept* =
6 3.44E-05 (β *parameter estimate to use for BEIR IV*)
- 7 • workers initially hired \geq 1940: intercept 2.05, potency 5.49E-05, *potency/intercept* =
8 2.68E-05 (β *parameter estimate to use for BEIR IV*) (no association, regression didn't
9 achieve statistical significance at $P < 0.01$ based on the corresponding likelihood ratio
10 statistic).

11 4.2.4.1.1.3 Adjusting for Year of Hire as a Nonparametric Function

12 Table 7 provides the summary information used to calculate intercepts and β parameter estimates
13 (Table 2 from Enterline et al. 1995). For the data presented in Table 7, maximum likelihood
14 estimation procedures with Poisson regression modeling were used to calculate the maximum
15 likelihood estimate (MLE) β and standard error (SE) using procedures described in Appendix B
16 for the total cohort, for the cohort of workers hired before 1940, and for the cohort of workers
17 hired after 1939. In addition, a separate dose-response analysis was conducted using the
18 summary data from Enterline et al. (1995) and adjusting for year of hire as a nonparametric
19 function (Sielken et al. 2009, Appendix C):

20 The linear model with **no** adjustment for year of first hire is

$$21 E(O_j) = \alpha \times E_{oj} \times (1 + \beta \times d_j),$$

22 While the linear model **with adjustment** for year of first hire is given by

$$23 E(O_j) = h \times \alpha \times E_{oj} \times (1 + \beta \times d_j),$$

24 where h equals one if hired before 1940 and h is estimated if hired 1940 or later.
25

3

Cumulative exposure (µg/m ³ -yr)	Mean Exposure (Total Cohort)	Total cohort			Hired < 1940			Hired ≥ 1940		
		O	E	SMR	O	E	SMR	O	E	SMR
< 750	405	22	14.29	154.0	2	3.08	65.0	20	11.21	178.4*
750 - <2,000	1,305	30	17.10	175.5**	5	7.33	68.2	25	9.77	256.0**
2,000 - <4,000	2,925	36	17.17	209.7**	22	8.93	246.2**	14	8.23	170.1
4,000 - <8,000	5,708	36	17.00	211.7**	15	10.01	149.9	21	7.00	300.2**
8,000 - <20,000	12,334	39	15.48	252.0**	28	10.98	255.1**	11	4.50	244.4*
20,000 - <45,000	28,336	20	7.04	284.0**	14	5.56	251.7**	6	1.48	405.5**
≥45,000	58,957	5	1.58	315.7*	5	1.48	338.7*	0	0.11	---

4 * P < 0.05 ; ** P < 0.01

5 The respiratory cancer data from Table 7 was fit and β values were estimated using Poisson
6 regression, external background lung cancer rates, and assuming a linear dose-response model
7 adjusting, when appropriate, for the year of hire with a nonparametric model (Sielken et al.,
8 Appendix C). Poisson regression with externally derived background cancer rates implicitly
9 adjusts for age when the reference population background rates are calculated using age-
10 dependent background cancer rates. Estimates for all workers with no adjustments, workers hired
11 < 1940, and workers hired ≥ 1940 are shown for comparison. The MLE, standard error (SE),
12 95% lower confidence limit on the β (95%LCL), and 95% upper confidence limit on the β
13 (95%UCL) were also calculated and are presented in Table 8. The TD was able to reproduce the
14 intercept and β parameter estimates based on Viren and Silvers (1994) for the workers initially
15 hired < 1940 and 1940+ (refer to Table 8 and footnotes).
16

3

Table 8. Beta (β), Standard Error (SE), and 95% Lower Confidence Limit (LCL) and Upper Confidence Limit (UCL) β Values (Enterline et al. 1995)^a				
Data Analyzed	Sielken et al. (2009) (Appendices B and C) $E(O) = \alpha \times E \times (1 + \beta \times d)$ or $E(O) = h \times \alpha \times E \times (1 + \beta \times d)$			
	Intercept (α)	β (MLE) \pm SE	β (95% LCL)_c	β (95% UCL)_d
All workers adjusting for year of hire ($h = 1.38$ ^b)	1.46	3.15E-05 $\pm 1.48E-05$	7.17E-06	5.59E-05
All workers with no adjustment	1.81 ^e	2.13E-05 ^e $\pm 1.13E-05$	2.64E-06	3.99E-05
Workers hired < 1940	1.43 ^f	3.44E-05 ^f $\pm 1.89E-05$	3.29E-06	6.56E-05
Workers hired 1940+	2.05 ^g	2.67E-05 ^g $\pm 2.33E-05$	-1.17E-05	6.51E-05

4 ^a Units are in excess relative risk (ERR) per $\mu\text{g}/\text{m}^3\text{-yr}$

5 ^b the background lung cancer mortality rate for workers hired 1940+ is 1.38-fold higher than the
6 background lung cancer mortality rate for workers first hired < 1940 (Sielken et al.
7 Appendix C)

8 ^c 95% LCL = $\beta - (1.645 \times \text{SE})$ for a standard normal distribution

9 ^d 95% UCL = $\beta + (1.645 \times \text{SE})$ for a standard normal distribution

10 ^e intercept = 1.68 and potency/intercept = $2.14E-05$ (Table 3 in Viren and Silvers 1999)

11 ^f intercept = 1.43 and potency/intercept = $3.44E-05$ (Table 5 in Viren and Silvers 1999)

12 ^g intercept = 2.05 and potency/intercept = $2.68E-05$ (no association, regression didn't achieve
13 statistical significance at $P < 0.01$ based on the corresponding likelihood ratio statistic
14 (Table 5 in Viren and Silvers 1999))

15 4.2.4.1.2 Dosimetric Adjustments

16 Consistent with TCEQ (2006), occupational concentrations ($\text{Concentration}_{\text{OC}}$) were converted to
17 environmental concentrations for the general population ($\text{Concentration}_{\text{HEC}}$) using the following
18 equation:

19
$$\text{Concentration}_{\text{HEC}} = \text{Concentration}_{\text{OC}} \times (\text{VE}_{\text{ho}}/\text{VE}_{\text{h}}) \times (\text{days per week}_{\text{oc}}/\text{days per week}_{\text{res}})$$

20 where: VE_{ho} = occupational ventilation rate for an 8-h day ($10 \text{ m}^3/\text{day}$)

21 VE_{h} = non-occupational ventilation rate for a 24-h day ($20 \text{ m}^3/\text{day}$)

22 $\text{days per week}_{\text{oc}}$ = occupational weekly exposure frequency (default of 5 days per
23 week)

24 $\text{days per week}_{\text{res}}$ = residential weekly exposure frequency (7 days per week)

4.2.4.1.3 Unit Risk Factors (URFs) and Air Concentrations at 1 in 100,000 Excess Lung Cancer Mortality

URFs express cancer potency in units of risk per air concentration (e.g., risk per $\mu\text{g}/\text{m}^3$) assuming continuous environmental lifetime exposure. They are calculated using linear low-dose extrapolation when the carcinogenic MOA is unknown, which is the case for arsenic (Section 4.2.2). Where a dose-response curve is modeled for tumor or cancer mortality data (Figure 2), the URF is the slope of a straight line from the POD to the origin, with the POD being the lowest tumor response or cancer mortality response supported by the study data.

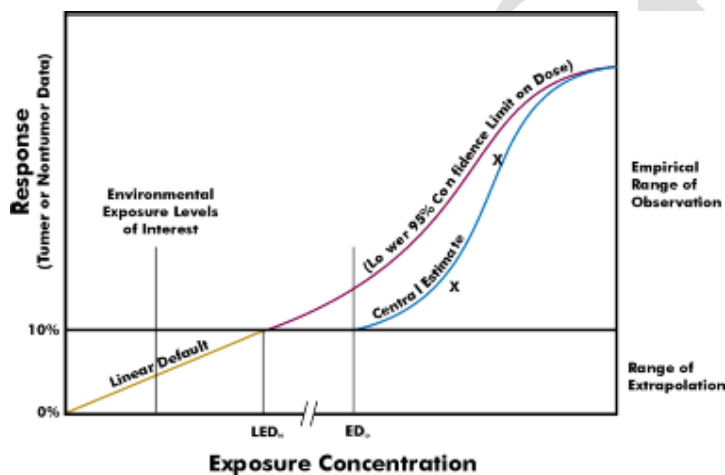


Figure 2. Example of a linear approach to extrapolate to lower exposures

The terms “ED10 and LED10” refer to dose but are analogous to the terms “EC10 and LEC10”, respectively (Exhibit 12-3A of USEPA 2004a).

Frequently in animal-based risk estimates, the lower statistical bounds on the concentration producing a 10% excess tumor response (LEC_{10}) is used as the POD for linear low-dose extrapolation and calculation of the URF, since the limit of detection of tumor studies is often around 10%, and the resulting equation is:

$$\text{URF} = \text{risk per } \mu\text{g}/\text{m}^3 = 0.10 / \text{LEC}_{10} \text{ (where } \text{LEC}_{10} \text{ is expressed in } \mu\text{g}/\text{m}^3\text{)}$$

However, for this cancer assessment, the response data are based on humans and have already been fit to a linear equation (linear multiplicative relative risk model) for use with the BEIR IV methodology (NRC 1988). Therefore, an extrapolated URF using a high POD and a URF estimated using a small POD are approximately equal.

Air concentrations were solved iteratively with life-table analyses using the BEIR IV approach (NRC 1988). Air concentrations based on extra risk were calculated as opposed to added risk. Mortality and survival rates were used to calculate air concentrations based on a lifetime

3 exposure of 70 years, the default used by TCEQ for exposure analysis (TCEQ 2006). The
4 following Texas-specific lung cancer mortality rates and survival rates were used:

- 5 • Texas-specific mortality rates for 2001-2005 for lung cancer and Texas-specific survival
6 rates for 2005 were kindly provided by the Texas Department of State Health Services,
7 Cancer Epidemiology and Surveillance Branch, Texas Cancer Registry (Appendix A).

8 For comparison, results are shown in Table D-1 using the following United States (US) mortality
9 and survival rates:

- 10 • US mortality rates for 1975-2005 for lung cancer (Surveillance, Epidemiology, and End
11 Results database (Appendix A);
- 12 • US survival rates for 2004 (Arias 2007) (Appendix A).

13 Table 9 shows estimates of URFs and air concentrations at 1 in 100,000 excess lung cancer
14 mortality risk (10^{-5} -risk air concentrations) based on β (MLE), β (95% LCLs) and β (95% UCLs)
15 from Table 8 and using Texas mortality and survival rates. URFs and arsenic 10^{-5} -risk air
16 concentrations were calculated using β values for all workers adjusting for year of hire, all
17 workers with no adjustment, and workers hired <1940. URFs were not calculated for workers
18 hired 1940+ because Viren and Silvers (1999) found no association for those workers, (i.e.,
19 regression didn't achieve statistical significance at $P < 0.01$ based on the corresponding
20 likelihood ratio statistic).

21

3

Table 9. URFs and 10⁻⁵ Risk Air Concentrations (Enterline et al. 1995)					
Data Analyzed	Back-ground Rates	β (MLE) URF 10⁻⁵-Risk Air Concentrations	β (95% LCL) URF 10⁻⁵-Risk Air Concentrations	β (95% UCL) URF 10⁻⁵-Risk Air Concentrations	Ratio: URF (95% UCL) to URF (MLE)
All workers adjusting for year of hire	Texas	1.19E-04/ μg/m ³ 0.0837 μg/m ³	2.72E-05/ μg/m ³ 0.367 μg/m ³	2.12E-04/ μg/m ³ 0.0471 μg/m ³	1.8
All workers with no adjustment	Texas	8.08E-05/ μg/m ³ 0.124 μg/m ³	1.00E-05/ μg/m ³ 0.998 μg/m ³	1.51E-04/ μg/m ³ 0.0660 μg/m ³	1.9
Workers hired < 1940	Texas	1.30E-04/ μg/m ³ 0.0766 μg/m ³	1.25E-05/ μg/m ³ 0.801 μg/m ³	2.49E-04/ μg/m ³ 0.0402 μg/m ³	1.9
Ratio: high to low URFs (MLE)		1.6			

4 **4.2.4.1.4 Preferred β and URF Potency Estimate (Enterline et al. 1995)**

5 As shown in Table 9, the URFs for the different groups ranged from 8.08E-05 per (μg/m³) for all
6 workers with no adjustment to 1.30E-04 per (μg/m³) for workers hired < 1940, approximately a
7 factor of 1.6. There was approximately a two-fold factor between the URF (MLE) compared to
8 the URF (95% UCL) for all URFs, which supports the good fit of the Enterline et al. (1995) data.
9 The confidence limits are indicators of the variability, and to some extent the uncertainty, in the
10 dose-response curve for mortality.

11 TD used the following considerations in selecting the preferred URF potency values to represent
12 the carcinogenic potency of inorganic arsenic based on this study:

- 13 • The URF (MLE) of 1.19E-04 per μg/m³ for all workers adjusting for year of hire is
14 preferred because it adjusts for year of hire as a nonparametric function and uses the
15 entire cohort with a larger number of evaluated PY.
- 16 • The MLE estimate is preferred because it is, by definition, the estimate that maximizes
17 the likelihood of the observed data, and, therefore, the best estimate to be used when

3 combining URFs from the other cohorts (Lubin et al. 2008; Järup et al. 1989; Jones et al.
4 2007) as discussed in Section 4.2.5.

5 The preferred URF estimates range from 2.72E-05 per $\mu\text{g}/\text{m}^3$ (95% LCL) to 2.12E-04 per $\mu\text{g}/\text{m}^3$
6 (95% UCL).

7 **4.2.4.1.5 Comparison of TCEQ's URF from Enterline et al. (1995) to USEPA's URF**

8 The preferred URF of 1.19E-04 per $\mu\text{g}/\text{m}^3$ is less conservative than the range of URFs of 6.81E-
9 03 per $\mu\text{g}/\text{m}^3$ to 7.60E-03 per $\mu\text{g}/\text{m}^3$ and the geometric mean URF of 7.19E-03 per $\mu\text{g}/\text{m}^3$,
10 calculated by USEPA (1984) for this cohort based on Enterline and Marsh (1982). Consequently,
11 the 10^{-5} -risk air concentration of 0.0837 $\mu\text{g}/\text{m}^3$ is higher than the air concentration of 0.0014
12 $\mu\text{g}/\text{m}^3$ based on the USEPA (1986) geometric mean URF for this cohort. The difference in the
13 URFs calculated by the TD and USEPA (1986) are as follows:

- 14 • the availability of an updated epidemiological study with additional years of follow-up
15 and number of deaths;
- 16 • the use of a multiplicative relative rate model with a factor that adjusts for background
17 compared to USEPA (1984) who used an absolute risk model (Viren and Silvers, 1994)
- 18 • more refined exposure estimates (Enterline et al. 1995);
- 19 • the use of a model that corrected for year of hire as a nonparametric function; and
- 20 • the use of a 70-year default lifetime exposure (TCEQ 2006) versus 76.5 years (USEPA
21 1984).
- 22 • the use of 2005 Texas-specific lung cancer mortality rates and survival probabilities
23 compared to USEPA (1984) use of US 1976 lung cancer mortality rates and survival
24 probabilities.

25 **4.2.4.2 Lubin et al. (2000, 2008)**

26 The aim of Lubin et al. (2000) was to investigate the shape of the exposure-response curve in an
27 updated study in workers at the Anaconda copper smelter in Montana initially investigated by
28 Brown and Chu (1982, 1983a, 1983b) and Lee-Feldstein (1986). An earlier study of 8,047 men
29 who worked at the Montana smelter for a year or more from 1938 to 1957 and were followed for
30 deaths during the period 1938-1977 was updated until the end of 1989. Significantly increased
31 SMRs of 156 and 187 were found for respiratory cancer in a restricted subcohort and in the full
32 cohort, respectively.. Refer to Section 4.2.1.1.3 (Lee-Feldstein 1986; Welch et al. 1982; Lubin et
33 al. 2008) and Table 6 for summary information on the Montana cohort.

34 **Cumulative Exposures**

35 Cumulative exposure estimates in $\text{mg}/\text{m}^3\text{-yr}$ were based on employment records of workers in
36 jobs with light (L), medium (M), and heavy (H) arsenic exposure and measurements of airborne
37 arsenic concentration between 1943 and 1958. The cumulative exposure to arsenic was
38 calculated as

3 Cumulative Exposure = 0.29 L + 0.58 M + (γ × 11.3) H

4 where L, M and H are the lengths of time in years that the worker was in jobs with low, medium
5 and high exposure concentrations, respectively, and 0.29, 0.58 and 11.3 are the arsenic air
6 concentrations in jobs with low, medium and high exposures. The weighting factor, γ , is a
7 fraction that measures the proportion of exposure reduction in high-concentration jobs due to the
8 use of protective equipment.

9 The cumulative exposure estimates calculated by Lubin et al. (2000) based on duration in jobs
10 with low and medium exposure concentrations and time of exposure in areas of heavy exposure
11 were re-calculated using a weighting factor γ of 0.1 to take into account the reduction in
12 exposure due to the use of air filtration masks in heavy-exposure jobs. This resulted in more
13 representative arsenic cumulative exposure estimates that were lower than the estimates using a
14 weighting factor γ of 1.0 used previously, particularly at the highest cumulative exposures.
15 Furthermore, using the weight of 0.1 on high-exposure jobs resulted in: 1) rate ratios that
16 conformed to a linear dose-response relationship with cumulative exposure to arsenic and 2)
17 steeper estimates of the slopes, which imply more health-protective excess risks of respiratory
18 cancer deaths.

19 **Restricted Cohort**

20 Approximately 40% of the 8,014 workers in the Montana cohort quit work at the smelter early:
21 1,616 (20%) were under age 30 years, and 1,565 (20%) were between ages 30-39. In order to
22 minimize the impact of unmeasured exposures on workers that quit working at the smelter,
23 Lubin et al. (2000) performed analyses both on the full cohort and on data restricted to current
24 workers and to former workers who stopped working at the smelter at age 50 years or older.

25 **4.2.4.2.1 Slope Parameter (β) Estimates**

26 **4.2.4.2.1.1 Lubin et al. 2000**

27 Lubin et al. (2000) modeled the data using a relative risk of disease mortality. He evaluated the
28 following covariates: age, year of follow-up, age at start of employment, and years in work areas
29 with either light, medium, or high concentration of arsenic. Although there were some data
30 provided using the total cohort, *the majority of results are based on the restricted cohort*. He
31 obtained the following results:

- 32 • additive (absolute) excess risk models generally provided poorer fits to the data;
- 33 • lagged exposures did not improve the fit of the models;
- 34 • there was a linearity of risk ratios with cumulative arsenic exposure when a weight of 0.1
35 was used for heavy exposure areas;

- 3 • an exponential relative risk function (often called a “power” model) did not significantly
4 improve the fit compared with a linear ERR model when a weight of 0.1 was used for
5 heavy exposure areas; and
- 6 • there was a linear association of the rate ratio of lung cancer and duration of exposure in
7 work areas with light, medium and heavy exposure and there was a similarity of
8 estimated risk ratios for duration of exposure in the medium and heavy exposure areas.

9 Lubin et al. (2000) calculated a slope parameter β estimate of $2.1E-04$ per $\mu\text{g}/\text{m}^3\text{-yr}$ (95%
10 confidence interval: $1.0E-04$, $4.6E-04$) for cumulative exposure estimates with a weight of 0.1
11 for heavy exposure areas. Risk of disease, h , was the product of the background mortality rate,
12 h_0 , and a relative risk (RR) function: $h = h_0 \times \text{RR}(x)$, where x was a vector of covariates and
13 $\text{RR}(\cdot)$ was a relative risk function. The background rate, h_0 , was modeled using stratum
14 parameters for categories of attained age and calendar year of follow-up. The β estimate declined
15 with increasing attained age, time since last exposure, and year of follow-up, but these factors
16 were highly correlated, and analyses could not adequately separate their effects. The β estimate
17 did not vary significantly with year first exposed, age first exposed, year of birth, or place of
18 birth.

19 **4.2.4.2.1.2 Lubin et al. 2008**

20 Lubin et al. (2008) employed a novel methodology using a linear-exponential model used
21 previously in a study of smoking-related lung cancer (Lubin and Caporaso 2006) to evaluate the
22 shape of the dose- response relationship between respiratory cancer mortality and cumulative
23 exposure to arsenic and the modification of this relationship by the average exposure
24 concentration. They evaluated the modification of that relationship by arsenic concentration or
25 exposure “delivery”. In this paper, Lubin et al. (2008) explored the effect of arsenic
26 concentration and exposure duration on the dose-response relationship between rate ratios and
27 the cumulative exposures to arsenic. Lubin et al. (2008) concluded that the ERR for a fixed
28 cumulative exposure was greater when the exposure was accumulated from exposures of shorter
29 duration at higher concentrations than when the exposure was accumulated from exposures of
30 longer duration at lower concentrations (i.e., there was a concentration-rate effect).

31 **4.2.4.2.1.2.1 Concentration as an Effect-Modification Factor**

32 The dose-response relationship used by Lubin et al. (2008) uses concentration as an effect-
33 modification factor rather than as a covariate. A covariate effect is generally used to account for
34 differences in background hazard rates of different groups of PY. An effect-modification factor,
35 on the other hand, is used to model how the excess hazard rate changes due to the effect-
36 modification factor. The covariate effects are normally excluded in the estimation of excess risks
37 and the background risks of a target population are used instead. The effect-modification factors,
38 on the other hand, are kept in the estimation of excess risks because they describe how the risk
39 changes with these factors. One can think of these effect-modifying factors as part of the dose
40 metric. The usual dose metric in dose-response models for epidemiological data is cumulative

3 exposure. Lubin et al. (2008), however, used a dose metric that is equal to the cumulative
4 exposure multiplied by the average concentration over the exposure period raised to a power, as
5 discussed in the next section.

6 4.2.4.2.1.2.2 Models in Lubin et al. (2008)

7 There are two ways of interpreting Lubin et al. (2008) models as outlined in Appendix E:

8 **Interpretation 1:** Lubin et al. (2008) estimated the multiplicative relative risk linear model but
9 instead of assuming a slope (β) that is a constant, they assumed that the slope is a function of the
10 average arsenic concentration (c). The function of the average arsenic concentration for the slope
11 of the linear relative risk model that Lubin et al. used is:

$$12 \quad \beta(c) = \beta \times c^\phi$$

13 where ϕ models the effect that the concentration has on the excess risk per unit of cumulative
14 exposure and is estimated from the data. That is, the relative risk is given by the following

$$15 \quad RR = 1 + \beta \times c^\phi \times \text{CumExp}$$

16 where CumExp is the cumulative exposure to arsenic.

17 **Interpretation 2:** Lubin et al. (2008) estimated the multiplicative relative risk linear model
18 assuming a constant slope (β) but the dose metric was the product of the cumulative exposure
19 and the average arsenic concentration (c) raised to a power. That is, the dose metric is given by
20 the following relation

$$21 \quad \text{Dose Metric} = \text{CumExp} \times c^\phi$$

22 where CumExp is the cumulative exposure to arsenic and ϕ models the effect that the
23 concentration has on the cumulative exposure and is estimated from the data. That is, the relative
24 risk is given by the following

$$25 \quad RR = 1 + \beta \times c^\phi \times \text{CumExp}$$

26 The second interpretation of the Lubin et al. (2008) model is how BEIR VI (NRC 1999) and
27 Jones et al. (2007) applied these models for exposures to radon and arsenic, respectively.

28 The objective of the Lubin et al. (2008) paper was to evaluate the shape of the dose response
29 relationship between respiratory cancer mortality and cumulative exposure to arsenic and the
30 modification of this relationship by the average exposure concentration. When the effects of the
31 average exposure concentration were investigated (refer to Figure 1 from Lubin et al. 2008,
32 which is reproduced in Appendix E), the following was observed:

- 3 • Within each average arsenic exposure concentration category (0.29 mg/m³, 0.30-0.39
4 mg/m³, 0.40-0.49 mg/m³, and >0.5 mg/m³), the relative rates (RRs) increased with
5 cumulative arsenic exposure (i.e., a direct concentration effect) and were consistent with
6 linearity within each average concentration category.
- 7 • Estimates of the β slope parameters varied significantly, and generally increased, with
8 increasing average arsenic exposure concentration category (0.29 mg/m³, 0.30-0.39
9 mg/m³, 0.40-0.49 mg/m³, and >0.5 mg/m³), suggesting a greater exposure-response
10 relationship with increasing arsenic concentration.

11 4.2.4.2.1.2.3 Nonparametric Effects of Time since Last Exposure and Age

12 Lubin et al. (2008) went beyond defining the dose metric by the functional form shown above
13 and also considered nonparametric effects of time since last exposure (TSLE) and age modifying
14 the cumulative exposure. When the effects of TSLE were investigated, the β for the restricted
15 cohort decreased with time since last arsenic exposure by factors of 1.0, 0.8, and 0.2 for < 5, 5-
16 14, and > 15 years, although variations were not statistically significant. In the restricted cohort,
17 there was a suggestion of declining arsenic effect with attained age (< 60, 60-69, and \geq 70 years),
18 but no preference for effect modification of age with either cumulative arsenic exposure or
19 arsenic concentration. That is, the introduction of TSLE or age as effect-modification factors did
20 not improve the model fit to the observed data.

21 4.2.4.2.1.2.4 Maximum Likelihood Estimates of the Slope with the Linear-Exponential Model

22 Table 3 of Lubin et al. (2008) lists the slopes of the linear-exponential model used previously in
23 a study of smoking-related lung cancer (Lubin and Caporaso 2006) as a function of the exposure
24 concentration for both the full cohort and the restricted sub-cohort. The results are as follows:

25 1) full cohort

$$26 \quad \beta(c) = 0.115 \times c^{1.123} \text{ per mg/m}^3\text{-yr}$$

27 MLE and 95% CI: 0.115 (0.07-0.19) and 1.123 (0.41-1.84)

28 2) restricted sub-cohort

$$29 \quad \beta(c) = 0.083 \times c^{0.822} \text{ per mg/m}^3\text{-yr}$$

30 MLE and 95% CI: 0.083 (0.04-0.15) and 0.822 (0.01-1.63) (note: footnote c in Table 3 of
31 Lubin et al. 2008 incorrectly lists 0.63 instead of 1.63)

32 The slopes, $\beta(c)$, are rate of increase in the relative risk per mg/m³-yr and the concentration c is
33 in units of mg/m³. Even though the variance for β and ϕ could be inferred from their confidence
34 intervals, upper and lower confidence limits on the slope $\beta(c)$ cannot be estimated without
35 knowing the covariance between β and ϕ .

3 The effect-modification factor (exposure concentration) can be used to provide a measure of
4 uncertainty by fixing the concentration at levels well above the average environmental exposures
5 – i.e., assuming that the dose metric is cumulative exposure and that the modification-factor
6 affects the slope of the relative risk model. Assuming average concentration larger than the
7 environmental concentrations in the estimation of excess risks results in an overestimation of the
8 slope and, therefore, in health protective risk estimates (see sensitivity study discussed in Section
9 4.2.4.2.1.2.5 and Appendix E). Conversely, assuming average concentration less than the
10 environmental concentrations in the estimation of excess risks results in an underestimation of
11 the slope and, therefore, in less health protective risk estimates.

12 ATSDR (2007) reported atmospheric levels of arsenic to range from 0.001 - 0.003 $\mu\text{g}/\text{m}^3$ in rural
13 areas to 0.02 - 0.010 $\mu\text{g}/\text{m}^3$ for urban areas. If the environmental concentrations that the general
14 public is exposed to are used to calculate the $\beta(c)$ parameter estimate, it would result in a slope
15 estimate near zero. As TCEQ wishes to protect public health and utilizing an environmentally
16 representative concentration would result in a slope near zero, the TD has decided that the slope β
17 parameter estimate will be determined using the multiplicative relative risk model, as discussed
18 in the following section.

19 **4.2.4.2.1.2.5 Maximum Likelihood Estimates of the Slope with the Linear Multiplicative Model**

20 In Lubin et al. (2000), the results were focused mainly on the restricted sub-cohort as opposed to
21 the results based on the full cohort. The main reason for focusing on the restricted sub-cohort
22 was to minimize the effects of unmeasured exposures “because there was no information on
23 exposures after the workers left the smelter.” In generating the cumulative exposures for the full
24 cohort, Lubin et al. (2008) assumed that workers were not exposed to arsenic after they left the
25 smelter. This is a standard assumption made in epidemiological studies. Assuming zero exposure
26 when there might have been non-zero exposures may result in an underestimation of cumulative
27 exposures. *Underestimation of actual cumulative exposures results in overestimation of the slope*
28 *in a multiplicative relative risk model and, consequently, in more health-protective risk*
29 *estimates.* Thus, the slope for the multiplicative relative risk model based on the full cohort
30 derived here is probably greater than the slope that would have been obtained if exposures for
31 workers that had left the smelter were assumed to be greater than zero. In order to be health
32 protective and to use information from the full cohort (the Lubin et al. 2008 restricted sub-cohort
33 excludes approximately 44% of the PY and 185 or 41% of the respiratory cancer deaths), the TD
34 will calculate the β parameter estimate using data from the full cohort with 256,900 PY.

35 Table 2 in Lubin et al. (2008) lists the mean cumulative exposure to arsenic ($\text{mg}/\text{m}^3\text{-yr}$), the
36 number of respiratory cancers and the standardized mortality ratios (SMRs) for six cumulative
37 exposure intervals for the full cohort unadjusted and adjusted for calendar period and country of
38 birth. The SMRs for respiratory cancers adjusted for calendar period and country of birth are
39 more appropriate than the unadjusted SMRs also listed in Table 2. The adjusted SMRs include
40 the effects of possible fluctuations of background respiratory cancer mortality rates in different

3 calendar years and different countries of birth. The relevant data extracted from Table 2 of the
4 Lubin et al. (2008) paper are shown in Table 10.

Table 10. Observed, Expected and Standard Mortality Rates (SMRs) from Table 2 in Lubin et al. (2008)

Cumulative exposure interval ($\mu\text{g}/\text{m}^3\text{-yr}$)	Mean Exposure ($\mu\text{g}/\text{m}^3\text{-yr}$)	Observed number of respiratory cancer deaths	Expected * number of respiratory cancer deaths	SMR
< 750	470	62	73.81	0.84
750-2,000	1,240	96	75.00	1.28
2,000-5,000	3,430	74	68.52	1.08
5,000-10,000	7,270	83	74.77	1.11
10,000-15,000	11,900	84	50.00	1.68
$\geq 15,000$	21,900	47	20.00	2.35

5 * Expected = Observed / SMR

6 Using the data in the table above, Poisson regression modeling with a factor that accounts for the
7 possibility of different background rates in an epidemiological cohort and its reference
8 population can be used (Crump and Allen 1985), as outlined in Appendix B. That is, the same
9 model used in the Tacoma study. The slope parameter β estimate, SE, β (95% LCL), and β (95%
10 UCL) for the full cohort using the data in Table 10 were calculated and are presented in Table
11 11. Results using the Lubin et al. (2000) restricted cohort are also presented for comparison as
12 well as slope parameter estimates by categories of cumulative arsenic exposure ($\mu\text{g}/\text{m}^3\text{-year}$)
13 (from Model 1, Figure 1 of Lubin et al. 2008 which is reproduced in Appendix E).

14

3

Table 11. Estimates of β (MLE), SE, β (95% LCL) and β (95% UCL) (Lubin et al. 2000; 2008) ^a			
Data Analyzed	β (MLE) \pm SE	β (95% LCL) ^b	β (95% UCL) ^b
Lubin et al. (2000) ^c (restricted sub-cohort)	2.03E-04 \pm 9.48E-05	2.64E-05	3.79E-04
Lubin et al. (2008) ^d (full cohort)	5.75E-05 \pm 1.61E-05	3.10E-05	8.40E-05
Lubin et al. (2008) ^e 290 $\mu\text{g}/\text{m}^3$	1.6E-05 \pm 1.17E-05 ^f	-3.23E-06	3.52E-05
Lubin et al. (2008) ^e 300-390 $\mu\text{g}/\text{m}^3$	6.7E-05 \pm 2.41E-05 ^g	2.73E-05	1.07E-04
Lubin et al. (2008) ^e 400-490 $\mu\text{g}/\text{m}^3$	7.7E-05 \pm 3.58E-05 ^h	1.81E-05	1.36E-04
Lubin et al. (2008) ^e >500 $\mu\text{g}/\text{m}^3$	7.2E-05 \pm 1.63E-05 ⁱ	4.53E-05	9.87E-05

- 4 ^a Units are in ERR per $\mu\text{g}/\text{m}^3$ -yr and cumulative exposure estimates with a weight of 0.1 in
5 heavy exposure areas
- 6 ^b 95% LCL = $\beta - (1.645 \times \text{SE})$ for a standard normal distribution; 95% UCL = $\beta + (1.645 \times \text{SE})$
7 for a standard normal distribution
- 8 ^c Linear model fit to the rate ratios in Table 4 of Lubin et al. (2000) with weight $\lambda=0.1$ using least
9 squares regression with a multiplicative intercept. Lubin et al. (2000) estimates are 2.1E-
10 04 (95% CI: 1.0E-05, 4.6E-04) – page 558.
- 11 ^d Maximum likelihood estimate of the slope and its SE for the multiplicative linear relative risk
12 model based on the full cohort data in Table 10
- 13 ^e Estimates of the ERR per $\mu\text{g}/\text{m}^3$ -yr of respiratory cancer mortality by categories of cumulative
14 arsenic exposure ($\mu\text{g}/\text{m}^3$ -yr) based on the full cohort, (from Model 1, Figure 1 of Lubin et
15 al. 2008, reproduced in Appendix E)
- 16 ^f The average SE was back-calculated from 95% confidence intervals of -5.00E-06, 4.10E-05 per
17 $\mu\text{g}/\text{m}^3$ -yr based on the following equation: confidence interval = $\beta \pm (1.96 \times \text{SE})$
- 18 ^g The average SE was back-calculated from 95% confidence intervals of 2.40E-05, 1.19E-04 per
19 $\mu\text{g}/\text{m}^3$ -yr based on the following equation: confidence interval = $\beta \pm (1.96 \times \text{SE})$
- 20 ^h The average SE was back-calculated from 95% confidence intervals of 1.70E-05, 1.59E-04 per
21 $\mu\text{g}/\text{m}^3$ -yr based on the following equation: confidence interval = $\beta \pm (1.96 \times \text{SE})$
- 22 ⁱ The average SE was back-calculated from 95% confidence intervals of 4.30E-05, 1.07E-04 per
23 $\mu\text{g}/\text{m}^3$ -yr based on the following equation: confidence interval = $\beta \pm (1.96 \times \text{SE})$

24 Sielken and Associates (Appendix E.5) conducted sensitivity analyses comparing slope
25 parameter estimates from the linear-exponential model to slope parameter estimates from the
26 multiplicative relative risk model. Since the slope for the cumulative exposure of the
27 multiplicative relative risk model is dependent on the exposure concentration, the slopes at some

3 specific concentrations are of interest:

- 4 1. slope for the full cohort at the mean airborne arsenic concentration for the full cohort
5 (0.35 mg/m³ in Table 1 of Lubin et al. 2008) = 3.54E-05 per µg/m³-yr
- 6 2. slope for the restricted sub-cohort at the mean airborne arsenic concentration for the
7 restricted sub-cohort (0.36 mg/m³ in Table 1 of Lubin et al. 2008) = 3.58E-05 per µg/m³-
8 yr.

9 In both cases, the slope parameter estimate from the linear-exponential model was lower (i.e.,
10 less conservative) than the slope parameter estimate for the Lubin et al. (2008) full cohort
11 calculated by the TD (5.75E-05 per µg/m³-yr), which indicates that this value is conservative and
12 health-protective.

13 In Figure 2 of Lubin et al. (2008) (and reproduced in Appendix E), the dotted line is the slope of
14 the standard multiplicative relative risk model for the full cohort. The slope (β) is equal to

15 4.756E-05 per µg/m³-yr (reported in the figure legend)

16 The slope estimated by Lubin et al. (2008) for the full cohort and using the standard
17 multiplicative relative risk model with cumulative exposure as the dose metric (4.756E-05 per
18 µg/m³-yr) is different than the slope the TD estimated from the data in Table 2 of Lubin et al.
19 (2008) (5.75E-05 per µg/m³-yr) (Appendix E). This difference is because the slope estimated by
20 TD using the data in Table 2 is adjusted using external background hazard rates (i.e., SMRs)
21 whereas Lubin et al. (2008) adjusted the slope using cohort-specific background rates that can be
22 obtained only when the data are available (which are preferable). However, Lubin et al. (2008)
23 report neither a confidence interval nor a standard error for the estimate of the slope. Since it was
24 possible to calculate the SE of the slope β parameter using data from Table 10, and the slope β
25 parameter estimate is slightly more conservative than the slope calculated by Lubin et al. (2008),
26 the TD will use the β and SE values from Table 11 for the full cohort based on data from Lubin
27 et al. (2008).

28 4.2.4.2.2 Dosimetric Adjustments

29 Occupational concentrations were converted to environmental concentrations for the general
30 population using the equation in Section 4.2.4.1.2.

31 4.2.4.2.3 URFs and 10⁻⁵-Risk Air Concentrations

32 URFs and 10⁻⁵-risk air concentrations were calculated using procedures discussed in Section
33 4.2.4.1.3. Table 12 shows estimates of URFs and 10⁻⁵-risk air concentrations for excess lung
34 cancer mortality for the Lubin et al. (2000) restricted cohort, for the full cohort (Lubin et al.
35 2008), as well as estimates by categories of cumulative arsenic exposure based on β (MLE), β
36 (95% LCLs) and β (95% UCLs) from Table 11 using Texas mortality and survival rates from

3 Appendix A. For comparison, results are shown in Table D-2 of Appendix D using US mortality
4 and survival rates from Appendix A.

Table 12. URFs and 10⁻⁵-Risk Air Concentrations (Lubin et al. 2000; 2008)					
Data Analyzed	Back-ground Rates	β (MLE) URF 10⁻⁵-Risk Air Concentration	β (95% LCL) URF 10⁻⁵-Risk Air Concentration	β (95% UCL) URF 10⁻⁵-Risk Air Concentration	Ratio: URF (95% UCL) to URF (MLE)
Lubin et al. (2000) (restricted subcohort)	Texas	7.70E-04 / μg/m ³ 0.0130 μg/m ³	1.00E-04 / μg/m ³ 0.0998 μg/m ³	1.44E-03 / μg/m ³ 0.00695 μg/m ³	1.9
Lubin et al. (2008) (full cohort)	Texas	2.18E-04 / μg/m ³ 0.046 μg/m ³	1.18E-04 / μg/m ³ 0.0850 μg/m ³	3.19E-04 / μg/m ³ 0.0313 μg/m ³	1.5
Lubin et al. (2008) * 290 μg/m³	Texas	6.07E-05 / μg/m ³ 0.165 μg/m ³	NA	1.33E-04 / μg/m ³ 0.075 μg/m ³	2.2
Lubin et al. (2008) * 300 - 390 μg/m³	Texas	2.54E-04 / μg/m ³ 0.0393 μg/m ³	1.03E-04 / μg/m ³ 0.0965 μg/m ³	4.06E-04 / μg/m ³ 0.0246 μg/m ³	1.6
Lubin et al. (2008) * 400 - 490 μg/m³	Texas	2.92E-04 / μg/m ³ 0.0342 μg/m ³	6.87E-05 / μg/m ³ 0.146 μg/m ³	5.16E-04 / μg/m ³ 0.0194 μg/m ³	1.8
Lubin et al. (2008) * > 500 μg/m³	Texas	2.73E-04 / μg/m ³ 0.0366 μg/m ³	1.72E-04 / μg/m ³ 0.0582 μg/m ³	3.74E-04 / μg/m ³ 0.0267 μg/m ³	1.4
Ratio: high to low URFs (MLE)		13			

5 NA = as the 95% LCL β value was negative, suggesting zero risk, calculation of an air
6 concentration at 1 in 100,000 excess risk was not possible.

7 * categories of average arsenic exposure concentration (μg/m³) based on the full cohort

8 **4.2.4.2.4 Preferred β and URF Potency Estimate (Lubin et al. 2000, 2008)**

9 The URF of 7.70E-04 per μg/m³ obtained from Lubin et al. (2000) restricted subcohort is
10 approximately 3.5-fold higher (i.e., more conservative) than the URF of 2.18E-04 per μg/m³
11 obtained from Lubin et al. (2008) full cohort. The URF based on the full cohort is preferred

3 because it includes more deaths and PY in the analyses. There was approximately a 1.5-fold ratio
4 between the URF (MLE) compared to the URF (95% UCL) from the Lubin et al. (2008) full
5 cohort study as compared to a 1.8-fold ratio for the restricted sub-cohort, which indicates that the
6 estimate based on the full cohort is better because it is less uncertain.

7 The URF of $2.18\text{E-}04$ per $\mu\text{g}/\text{m}^3$ obtained from Lubin et al. (2008) full cohort (256,900 PY) is
8 approximately 3.6-fold higher (i.e., more conservative) than the URF of $6.07\text{E-}05$ per $\mu\text{g}/\text{m}^3$
9 from Lubin et al. (2008) using the 0.29 mg/m^3 category of average arsenic exposure
10 concentration based on the full cohort (167,583 PY). This later estimate is based on low arsenic
11 occupational concentration exposures which are more similar to the environmental concentration
12 exposures of the general population. However, the URF calculated using the full cohort (2.18E-
13 04 per $\mu\text{g}/\text{m}^3$) is preferred because it includes more deaths and PY in the analyses and is slightly
14 more conservative. There was approximately a 1.5-fold difference between the URF (MLE)
15 compared to the URF (95% UCL) from the Lubin et al. (2008) full cohort study as compared to a
16 2.2-fold ratio difference for the full cohort with average arsenic concentrations of 0.29 mg/m^3 ,
17 which indicates that the estimate based on the full cohort is better because it is less uncertain.

18 The MLE estimate is preferred over upper confidence limits because it is, by definition, the best
19 estimate to be used when combining URFs from the other cohorts (Enterline et al. 1995; Järup et
20 al. 1989; Jones et al. 2007) as discussed in Section 4.2.5. URF estimates obtained from Lubin et
21 al. (2008) full cohort range from $1.18\text{E-}04$ per $\mu\text{g}/\text{m}^3$ (95% LCL) to $3.19\text{E-}04$ per $\mu\text{g}/\text{m}^3$ (95%
22 UCL).

23 **4.2.4.2.5 Comparison of TCEQ's URF to USEPA's URF (Lubin 2000, Lubin 2008)**

24 The preferred URF of $2.18\text{E-}04$ per $\mu\text{g}/\text{m}^3$ is less conservative than the range of URFs of 1.25E-
25 03 to $4.90\text{E-}03$ per $\mu\text{g}/\text{m}^3$ and the geometric mean of $2.56\text{E-}03$ per $\mu\text{g}/\text{m}^3$ calculated by USEPA
26 (1986) for this cohort based on Brown and Chu (1983a,b,c), Lee-Feldstein (1983), and Higgins et
27 al. (1982). Consequently, the resulting 10^{-5} -risk air concentration for excess lung cancer
28 mortality of 0.046 $\mu\text{g}/\text{m}^3$ based on the selected URF is approximately 12 times higher than the
29 10^{-5} -risk air concentration of 0.0039 $\mu\text{g}/\text{m}^3$ based on the geometric mean URF (USEPA 1986)
30 for this cohort. The difference in the URFs calculated by the TCEQ and USEPA are due to
31 various factors, including the following:

- 32 • the availability of an updated epidemiological study with more PY and deaths (Lubin et
33 al. 2000; 2008);
- 34 • more realistic exposure estimates (i.e., cumulative exposure estimates with a weight of
35 0.1 for heavy exposure areas) (Lubin et al. 2000; 2008);
- 36 • The TD used the Lubin et al. (2008) data and conducted standard Poisson regression
37 analysis, a multiplicative model, and SMR data adjusted for calendar period and country
38 of birth as opposed to USEPA (1986) who used an absolute risk model and did not
39 include any covariates; and
- 40 • The TCEQ used default lifetime exposure duration of 70 years whereas USEPA (1986)
41 used 76.5 years.

- the use of 2005 Texas-specific lung cancer mortality rates and survival probabilities compared to USEPA (1984) use of US 1976 lung cancer mortality rates and survival probabilities.

4.2.4.3 Järup et al. (1989); Viren and Silvers (1994)

Järup et al. (1989) investigated lung cancer mortality in a cohort of 3,916 male Swedish smelter workers employed for at least three months from 1928 to 1967, and followed through 1981. Lung cancer mortality was related to the estimated average intensity of exposure to arsenic but not to duration. There was also no evident dose-response relationship between estimated exposure to sulfur dioxide and lung cancer. Section 4.2.1.1.5 *Ronnskar Copper Smelter in Sweden* and Table 6 provide additional information about the Ronnskar, Sweden copper smelter workers.

Järup et al. (1989) indicate that, “data suggest that arsenic concentration is more important than duration of exposure for the risk of developing lung cancer.” In addition, Järup et al. (1989) indicate that they, “did not find a clear dose-response relationship in the low exposure categories.” These two statements in Järup et al. (1989) are consistent with Lubin et al. (2008) conclusions that their results suggested a “direct concentration effect on the exposure-response relationship, indicating that for a fixed level of cumulative arsenic exposure, inhalation of higher concentrations of arsenic over shorter durations was more deleterious than inhalation of lower concentrations over longer durations.”

Viren and Silvers (1994) used summary data from Järup et al. (1989) and calculated β estimates using an absolute risk model, but did not provide variance estimates. The TD used summary data in Järup et al. (1989) and Viren and Silvers (1994) to calculate β estimates and variance estimates using Poisson regression and a multiplicative relative risk model.

Table 13 contains the summary data from Järup et al. (1989) and Viren and Silvers (1994) that were used to estimate β parameter values. Ranges of dose categories in ($\text{mg}/\text{m}^3\text{-yr}$) were provided by Järup et al. (1989) and Viren and Silvers (1994) used the midpoint of each cumulative exposure level as a measure of dose. For cumulative exposure exceeding $100 \text{ mg}/\text{m}^3\text{-yr}$, an interval that was open ended, Viren and Silvers (1994) assumed that the median exposure in this group was 25% greater than the lower bound of the given interval.

3

Dose category ($\mu\text{g}/\text{m}^3\text{-yr}$)	Range midpoint ^a ($\mu\text{g}/\text{m}^3\text{-yr}$)	Total cohort ^b			First hired < 1940 ^b			First hired 1940+ ^a		
		O	SMR ^c	E ^d	O	SMR ^c	E ^d	O	SMR ^c	E ^d
< 250	125	14	271	5.17	3	284	1.06	11	267	4.12
250 - < 1,000	625	13	360	3.61	3	603	0.50	10	319	3.13
1,000 - < 5,000	3,000	17	238	7.14	6	223	2.69	11	247	4.45
5,000 - < 15,000	10,000	15	338	4.44	10	285	3.51	5	537	0.93
15,000 - < 50,000	32,500	29	461	6.29	27	448	6.03	2	757	0.26
50,000 - < 100,000	75,000	6	728	0.82	6	728	0.82	---	---	---
100,000 +	125,000	12	1,137	1.06	12	1,137	1.06	---	---	---

4 ^a Data from Viren and Silvers (1994)

5 ^b Data from Table IV and V (Järup et al. 1989)

6 ^c SMR, no latency period

7 ^d E was not provided, but was calculated based on $E = O/\text{SMR}$

8 4.2.4.3.1 Slope Parameter (β) Estimates

9 The lung cancer data from Table 13 was fit and a β (MLE) value was estimated using the linear
10 multiplicative relative risk model with maximum likelihood estimation procedures (Crump and
11 Allen 1985, Appendix B). The slope of the multiplicative relative risk linear model for the total
12 cohort but adjusting for the first year of hire was also conducted, when appropriate. The relative
13 risk model used to calculate the β value included a term (α) to account for different background
14 rates in the epidemiological cohort and the reference population group. This analysis parallels the
15 analyses done for the Tacoma cohort (see Appendix C). In fact, the data structure for the
16 Ronnskar cohort is so similar to the data structure of the Tacoma cohort that the model
17 descriptions are essentially the same. The results for the entire cohort adjusting for the year of
18 first hire is the most defensible result because it is based on more data than the separate analyses
19 based on subsets of the cohort and adjusts for the effect of potential differences in exposure
20 concentrations with calendar year by using a nonparametric estimate for the effect of year of
21 hire.

22 Estimates for the total cohort unadjusted for year of first hire, workers first hired < 1940, and
23 workers hired 1940+ are also shown. A majority of workers were hired 1940+ and were exposed
24 to lower concentrations of arsenic than those hired before 1940. The intercept α , SE, β
25 (95%LCL), and β (95%UCL) were also calculated and presented in Table 14.

Table 14. Estimates of β (MLE), SE, β (95% LCL) and β (95% UCL) (Järup et al. 1989)^a

Data Analyzed	Intercept (α)	β (MLE) \pm SE	β (95% LCL) _b	β (95% UCL) _c
All workers adjusting for year of hire (h = 1.19 ^d)	2.37	2.92E-05 \pm 1.63E-05	2.31E-06	5.61E-05
All workers with no adjustment	2.67	2.38E-05 \pm 9.14E-06	8.79E-06	3.89E-05
Workers hired < 1940	2.48	2.62E-05 \pm 1.35E-05	4.00E-06	4.84E-05
Workers hired 1940+	2.60	6.17E-05 \pm 5.92E-05	-3.57E-05	1.59E-04

3 ^a Units are in ERR per $\mu\text{g}/\text{m}^3\text{-yr}$

4 ^b 95% LCL = $\beta - (1.645 \times \text{SE})$ for a standard normal distribution

5 ^c 95% UCL = $\beta + (1.645 \times \text{SE})$ for a standard normal distribution

6 ^d the background lung cancer mortality rate for workers hired 1940+ is 1.19-fold higher than the
7 background lung cancer mortality rate for workers first hired < 1940

8 4.2.4.3.2 Sensitivity Analyses

9 The data in Järup et al. do not include the average cumulative exposure for each of the
10 cumulative dose categories. Viren and Silvers (1994) used the midpoints of the dose ranges in
11 fitting the models to the Järup et al. data. Here, the TD also used the midpoints of the dose ranges
12 in fitting the models. The midpoints of the dose ranges are good approximations to the average
13 cumulative exposure for the PY in the dose ranges. However, the last dose range (cumulative
14 exposures greater than $100 \text{ mg}/\text{m}^3\text{-yr}$) is unbounded and Viren and Silvers, “assumed that the
15 median exposure in this group was 25% greater than the lower bound of the given interval.” The
16 estimation of the midpoint for the highest, unbounded, cumulative exposure range is always
17 associated with some uncertainty, unless it is based on actual data. Oftentimes reviewers are
18 uncertain of the influence that the value of the midpoint for the highest dose range may have on
19 estimates of the model parameters. One analysis that helps in assessing the uncertainty that the
20 specific value for the highest dose range may have introduced in the estimates of the parameters
21 is to evaluate the same dose response model without the data on the highest dose range (Sielken
22 and Associates, Appendix F.3). The likelihood of observing the data that excludes the highest
23 cumulative exposure range using the models fit to the data that excludes the highest cumulative
24 exposure range was compared to the likelihood of observing the data that excludes the highest
25 cumulative exposure range using the models fit to the data that include all dose ranges. They are
26 essentially equal; indicating that the model fit to the data that includes all the dose ranges is as
27 good as the model fit to the data that excludes the highest dose range (Table F-3) (i.e., the impact
28 of the observed and expected number of lung cancer deaths and the estimated mid-point for the
29 highest cumulative exposure group on the magnitude of the estimated β parameter is negligible).

3 **4.2.4.3.3 Dosimetric Adjustments**

4 Occupational concentrations were converted to environmental concentrations for the general
5 population using the equation in Section 4.2.4.1.2.

6 **4.2.4.3.4 URFs and 10⁻⁵-Risk Air Concentrations**

7 URFs and 10⁻⁵-risk air concentrations were calculated using procedures discussed in Section
8 4.2.4.1.3. Table 15 shows estimates of URFs and 10⁻⁵-risk air concentrations for excess lung
9 cancer mortality for all workers adjusting for year of hire, all workers with no adjustment for
10 year of hire, workers first hired < 1940, and workers hired 1940+ based on β (MLE), β (95%
11 LCLs) and β (95% UCLs) from Table 14 using Texas mortality and survival rates. Results using
12 US mortality and survival rates are in Table D-3 of Appendix D for comparison.

Table 15. URFs and 10⁻⁵ Risk Air Concentrations (Järup et al. 1989)					
Data Analyzed	Back-ground Rates	β (MLE) URF 10⁻⁵-Risk Air Concentration	β (95% LCL) URF 10⁻⁵-Risk Air Concentration	β (95% UCL) URF 10⁻⁵-Risk Air Concentration	Ratio: URF (95% UCL) to URF (MLE)
All Workers adjusting for year of hire	Texas	1.11E-04/μg/m ³ 0.0902 μg/m ³	8.76E-04/ μg/m ³ 1.14 μg/m ³	2.13E-04 μg/m ³ 0.0470 μg/m ³	1.9
All workers with no adjustment	Texas	9.03E-05/ μg/m ³ 0.111 μg/m ³	3.33E-05/ μg/m ³ 0.300 μg/m ³	1.48E-04/ μg/m ³ 0.0677 μg/m ³	1.6
First hired < 1940	Texas	1.00E-04/ μg/m ³ 0.100 μg/m ³	1.52E-05/ μg/m ³ 0.659 μg/m ³	1.84E-04/ μg/m ³ 0.0544 μg/m ³	1.8
First hired 1940+	Texas	2.34E-04/ μg/m ³ 0.0427 μg/m ³	NA	6.03E-04/ μg/m ³ 0.0166 μg/m ³	2.6
Ratio: high to low URFs (MLE)		2.6			

13 NA = as the 95%LCL β value was negative, suggesting zero risk, calculation of an air
14 concentration at 1 in 100,000 excess risk was not possible.

15

3

4 **4.2.4.3.5 Preferred β and URF Potency Estimate (Järup et al. 1989)**

5 As shown in Table 15, the URF (MLE) for the different groups ranged from 9.03E-05 per $\mu\text{g}/\text{m}^3$
6 to 2.34E-04 per $\mu\text{g}/\text{m}^3$, approximately a factor of 2.6.

7 The URF (MLE) of 1.11E-04 per $\mu\text{g}/\text{m}^3$ with a corresponding 10^{-5} -risk air concentration of
8 0.0902 $\mu\text{g}/\text{m}^3$ for all workers adjusting for year of hire is preferred because it uses the entire
9 cohort with a larger number of evaluated PY and adjusts for the effect of potential differences in
10 exposure concentrations with calendar year by using a nonparametric estimate for the effect of
11 year of hire. There was less than a two-fold difference between URF estimates using the MLE
12 compared to the 95% UCL for the all workers adjusting for year of hire, which supports the
13 accuracy of the fit to the Järup et al. (1989) data. This URF is slightly higher (i.e., more
14 conservative) than the URF calculated for the total cohort, without adjustment for year of hire.
15 The preferred URF estimates range from 8.76E-04 per $\mu\text{g}/\text{m}^3$ (95% LCL) to 2.13E-04 per $\mu\text{g}/\text{m}^3$
16 (95% UCL). The MLE estimate is preferred because it is the best estimate to be used when
17 combining URFs from the other cohorts (Enterline et al. 1995; Lubin et al. 2000; Jones et al.
18 2007) as discussed in Section 4.2.5.

19 Viren and Silvers (1994) also derived potency estimates and URFs based on the Järup et al.
20 (1989) study, but not SE estimates, and the best fitting model was based on the total cohort, with
21 no adjustment for year of hire. Viren and Silvers (1994) derived a URF of 3.9E-04 per $\mu\text{g}/\text{m}^3$
22 although they recommended using a URF of 8.9E-04 per $\mu\text{g}/\text{m}^3$ based on pooling the two
23 subcohort estimates. Viren and Silvers (1994) used an additive risk model, a life table with 1976
24 age-specific all-cause and lung cancer mortality, and evaluated the URF assuming a default
25 average life expectancy of 76.5 years. The TCEQ used a multiplicative model adjusting for year
26 of hire and an average life expectancy of 70 years. Viren and Silvers URF estimate of 8.9E-04
27 per $\mu\text{g}/\text{m}^3$ is 8-fold more conservative for the total cohort analyses than that derived by the
28 TCEQ of 1.11E-04 per $\mu\text{g}/\text{m}^3$ for all workers adjusting for year of hire.

29 **4.2.4.4 Jones et al. 2007**

30 Jones et al. (2007) investigated the relationships between excess lung cancer mortality at a UK
31 tin smelter in Humberside, UK and inhalation exposure to lead, antimony, arsenic, cadmium and
32 radioactivity, with the aim of identifying the cause or causes of the excess lung cancer and
33 quantitative measures of exposures. The cohort was composed of male former employees at the
34 tin smelter initially investigated by Binks et al. (2005). Refer to Section 4.2.1.2 *United Kingdom*
35 *(UK) Tin Smelter* for additional information on the cohort and findings from the Binks et al.
36 (2005) study.

37 Jones et al. (2007) results indicated there were no significant associations found between lung
38 cancer mortality and simple cumulative exposure to any of the substances studied. However,
39 when cumulative exposures were weighted according to time since exposure and attained age,

3 significant associations were found between lung cancer mortality and exposures to arsenic, lead
4 and antimony. Jones et al. (2007) concluded:

5 “the excess of lung cancer mortality in the cohort can most plausibly be explained
6 if arsenic is the principal occupational carcinogen (for which the ERR diminishes
7 with time since exposure and attained age) and if there is a contribution to excess
8 mortality from an enhanced prevalence of smoking within the cohort. The
9 implications of the dose-response for arsenic exposure for risk estimation merit
10 further consideration.”

11 **4.2.4.4.1 Exposure Estimates**

12 Jones et al. (2007) established exposure matrices for arsenic, cadmium, lead, antimony, and
13 polonium-210 (^{210}Po). Jones et al. (2007) used numerous air sample measurements to estimate
14 the concentrations of the different agents at the smelter. These measurements were recorded for
15 the period 1972 to 1991. Jones et al. (2007) commented that the use of ‘area’ or ‘static’ air
16 samples may not be representative of the air breathed by workers and are likely to underestimate
17 true personal exposures. In addition, Jones et al. used work history for each cohort member to
18 calculate the exposure profile of each worker. The air concentration measurements for jobs that
19 started before calendar years 1972 were not available (there were work histories starting in
20 1937). Jones et al. extrapolated exposures concentrations to years prior to 1972 using three
21 alternative extrapolation assumptions:

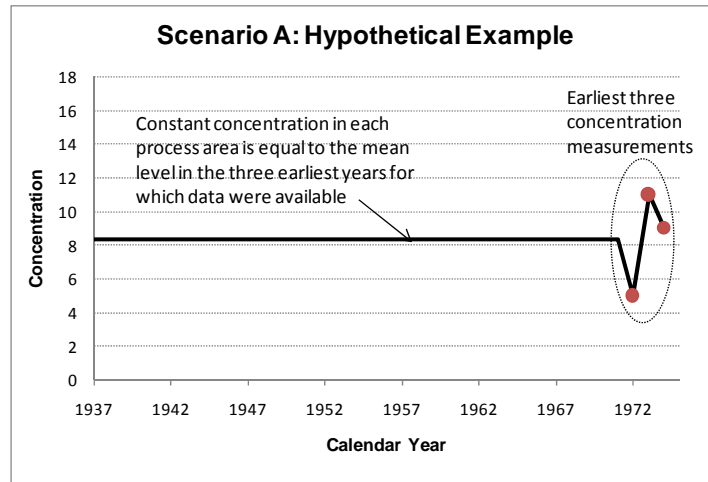
- 22 • Scenario A – constant back-extrapolation in each process area, as the mean of the levels
23 in the three earliest years for which data were available (Figure 2);
- 24 • Scenario B – back-extrapolation in each process area on a linear increasing trend from the
25 baseline value above, to values 2-fold higher in the early 1940s, based on a weak trend
26 seen in per-caput average exposure levels over the period 1972-1991 (Figure 4); and
- 27 • Scenario C – back-extrapolation in each process area from the baseline value above to
28 values 2-fold higher in 1960, subsequently, declining linearly to values one-half of the
29 baseline in 1937. In this scenario, air contamination levels initially increase as a
30 consequence of increasing production and ageing process plant, before declining as a
31 consequence of regulatory pressure and capital investment during the 1960s and 1970s
32 (Figure 5).

33

3 •

4 **Figure 3. Exposure Concentration Extrapolation for a Hypothetical Example using**
5 **Scenario A**

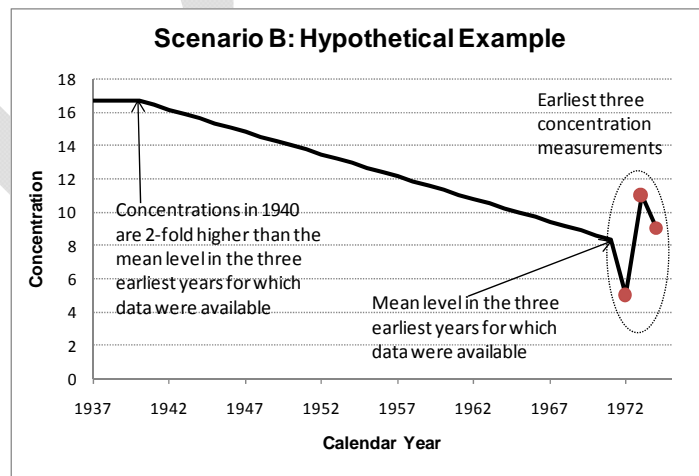
6 Constant back-extrapolation in each process area, as the mean of the levels in the three earliest
7 years for which data were available.



8
9

10 **Figure 4. Exposure Concentration Extrapolation for a Hypothetical Example using**
11 **Scenario B**

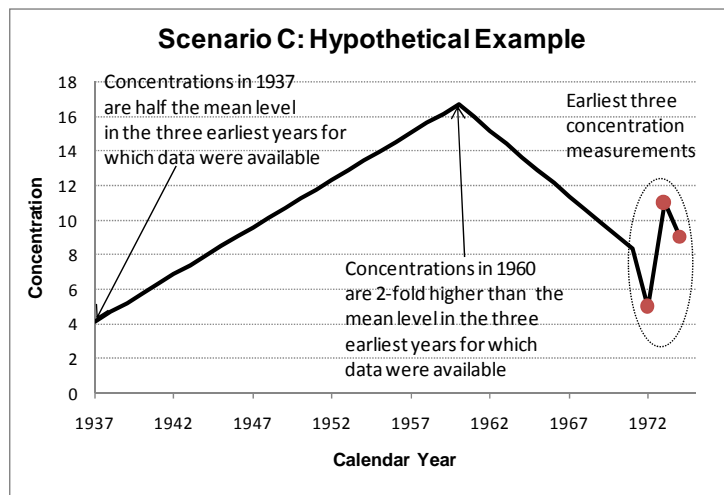
12 Back-extrapolation in each process area on a linear increasing trend from a baseline value to
13 values 2-fold higher in the early 1940s, based on a weak trend seen in per-caput average
14 exposure levels over the period 1972-1991.



15

3 **Figure 5. Exposure Concentration Extrapolation for a Hypothetical Example using**
4 **Scenario C**

5 Back-extrapolation in each process area from a baseline value to values 2-fold higher in 1960,
6 subsequently, declining linearly to values one-half of the baseline in 1937.



7

8 Sielken and Associates calculated the area under the curve (AUC) for each scenario (Appendix
9 G.2) and showed the $AUC_{\text{Scenario B}} > AUC_{\text{Scenario C}} > AUC_{\text{Scenario A}}$. That is, extrapolating
10 concentrations using Scenario B results in the largest cumulative exposures, followed by the
11 cumulative exposures estimated using Scenario C, and the smallest cumulative exposures of the
12 three scenarios are predicted using Scenario A.

13 Scenario A (which assumes a constant concentration equal to the average concentration of the
14 earliest three years of data) is probably an underestimate of the actual concentrations of arsenic
15 (see below). Scenario B (which assumes a concentration in the early 1940s that is twice the
16 average concentration of the earliest three years of data) is probably a more realistic estimate of
17 the concentrations of arsenic in the early years. Scenario C (which compromises between
18 Scenario A and Scenario B) is an estimate of the concentrations of arsenic in the early years that
19 incorporates production volume in the early years as a possible explanation of arsenic
20 concentration levels.

21 In most epidemiological studies, exposure concentrations tend to be higher in the early years and
22 decrease to lower exposure concentrations in later years (similar to the Scenario B assumption,
23 unlike Scenario A). Exposure concentrations like those described in Scenario C are not very
24 common in epidemiological studies. Production increases usually come with larger facilities or
25 newer technologies that tend to dilute exposure concentrations and, therefore, tend to not
26 necessarily increase the exposure concentration as assumed in Scenario C. *Based on the analyses*
27 *by Sielken and Associates (Appendix G), the TD prefers Scenario B exposure assessments over*
28 *Scenario A and C exposure estimates. In addition, Dr. Jones, in a personal communication, also*
29 *recommended Scenario B as being more realistic.* Results for Scenarios A and C are presented

3 for comparison.

4 **4.2.4.4.2 Modeling**

5 Jones et al. (2007) fit Poisson regression models to the number of lung cancer deaths split into
6 quintiles of the distribution of the dose metric among the lung cancer decedents. The weighted
7 average of the dose metric in each dose interval was used in fitting the relative risk linear dose
8 response model with additive intercept.

9 Jones et al. (2007) fit the dose response model using the following two dose metrics for each of
10 the five agents (arsenic, cadmium, antimony, lead, and polonium-210) they analyzed:

11 Cumulative exposure

12 Weighted cumulative exposure

13 The cumulative exposure dose metric is in units of concentration-year (e.g., mg/m³-yr). The
14 weighted dose metric is an exposure that is modified by other factors that weight the effect that
15 the concentration might have on lung cancer. Arsenic is rapidly cleared from the body after
16 intake, so weighting factors were used to investigate how arsenic concentration and the time
17 since exposure exert a modifying effect on the carcinogenic process during the period of
18 exposure, similar to radon daughters. Jones et al. suggest using a weighted dose metric that
19 diminishes the risk of lung cancer with the time since exposure and the age of the worker. They
20 indicate that Binks et al. (2005) “found evidence of diminution of lung cancer risk with time
21 since exposure.” The weights used by Jones et al. to calculate the weighted cumulative exposure
22 were taken from the “exposure-age-concentration model” in BEIR VI (Tables 3-3 and A-4 in
23 NRC 1999). These weights were initially derived from dose-response models for exposures to
24 radon progeny. The weighted cumulative exposure used by Jones et al. is as follows:

25 Weighted Cumulative Exposure at age n = $\varphi_n \times \sum_{i=1 \text{ to } n} C_i \times \theta_{n-i}$

26 where C_i is the exposure concentration at age i ,

27 $\varphi_{\text{age}} = 1$ if age < 50 years
28 $= 4.8 - 0.105 \times \text{age} + 0.000575 \times \text{age}^2$ if 50 years \leq age < 80 years
29 $= 0.09$ if age \geq 80 years

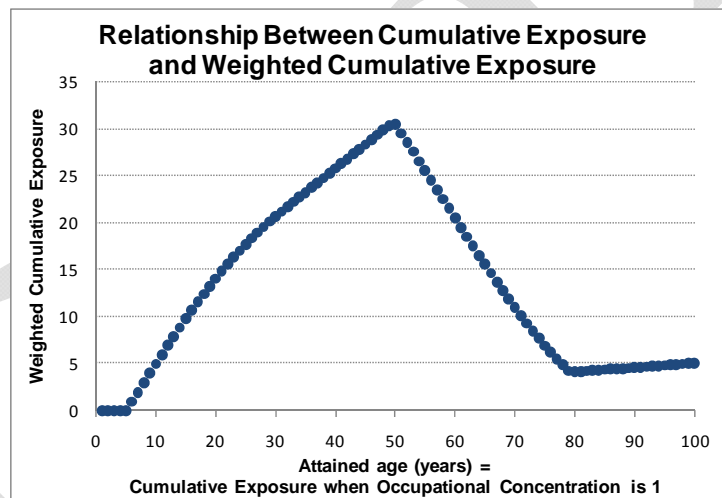
30 and, defining time since exposure (tse) as age n minus i in the above equation,

31 $\theta_{\text{tse}} = 0$ if tse < 5 years
32 $= 1$ if 5 years \leq tse < 10 years

$$\begin{aligned}
 &= 1.17 - 0.0145 \times tse - 0.00025 \times tse^2 && \text{if } 10 \text{ years} \leq tse < 30 \text{ years} \\
 &= 0.51 && \text{if } tse \geq 30 \text{ years}
 \end{aligned}$$

Jones et al. smoothed the step function for ϕ_{age} and θ_{tse} specified in Tables 3-3 and A-4 in BEIR VI (NRC 1999). Figures G-4 and G-5 in Appendix G show the step functions for the weights and the smoothed functions used by Jones et al. Jones et al. indicate that fitting the models using the smoothed function and the step-function version of the weights result in approximately the same estimates. For a fixed concentration or exposure rate, the weighted cumulative exposure used by Jones et al. (and also proposed in the “exposure-age-concentration model” in BEIR VI) is zero for the first 5 years of exposure, then increases for the next 45 years followed by a decrease for the next 30 years, to slowly increase following 80 years after the first exposure. Figure 6 shows the weighted cumulative exposure as a function of age using the smoothed weights derived by Jones et al (2007).

Figure 6. Weighted Cumulative Exposure using the Smoothed Weights for a Concentration of 1 (Jones et al. 2007)



Although BEIR VI used the following multiplicative relative risk model with a multiplicative intercept and the weighted cumulative exposure to radon progeny,

$$E(O_j) = \alpha \times E_{oj} \times (1 + \beta \times d_j)$$

Jones et al. used a multiplicative relative risk model with additive intercept given by

$$E(O_j) = E_{oj} \times (\alpha + \beta_a \times d_j)$$

where the α term adjusts for any possible differences between the population’s background cancer rates and the cohort’s observed cancer rates in unexposed workers.

3 In the equations above the variables are:

4 $E(O_j)$ = expected number of lung cancer deaths for exposure group j predicted by the
5 model;

6 E_{oj} = expected number of background lung cancer deaths for exposure group j based on
7 the reference population background cancer rates;

8 β = multiplicative factor by which the cohort's background risk increases with
9 cumulative exposure;

10 β_a = multiplicative factor by which the reference population's background risk increases
11 with cumulative exposure;

12 d_j = cumulative exposure (weighted or unweighted) for exposure group j ;

13 α = multiplicative factor that accounts for differences in cancer mortality background
14 rates between the study cohort and the reference population.

15 The interpretations of slope parameters β (in the multiplicative relative risk model with
16 multiplicative intercept) and β_a (in the multiplicative relative risk model with additive intercept)
17 are different. The interpretation of the intercept (α), however, is the same in both models.

18 **4.2.4.4.3 Results**

19 Table 3 in Jones et al. (2007) (reproduced in Appendix G) lists the maximum likelihood
20 estimates of the additive intercept (α) and slope (β_a) for the relative risk model along with a p-
21 value for trend and the logarithm of the maximum likelihood. The table shows the results for
22 both unweighted cumulative exposure and the weighted cumulative exposure for each of the five
23 agents analyzed and for each of the three exposure scenarios considered.

24 Arsenic has the largest logarithm of the maximum likelihood (i.e., the model with arsenic as the
25 explanatory variable describes the observed lung mortality data better than the model with any of
26 the other five agents as the explanatory variable) when the unweighted cumulative exposure is
27 used as the dose metric, regardless of which exposure scenario is used. However, when the
28 weighted cumulative exposure is used as the dose metric, antimony (Sb) has the largest
29 logarithm of the maximum likelihood for all three exposure scenarios.

30 Weighted cumulative exposures to antimony, arsenic, and lead were statistically significantly
31 associated with lung cancer mortality for the three exposure scenarios, whereas unweighted
32 cumulative exposures were not statistically significantly associated with lung cancer mortality.
33 *Therefore, only results from weighted exposure regressions were used for subsequent analysis.*
34 Results for both weighted and unweighted analyses are shown in Appendix G.

3 Exposure to antimony, arsenic and lead are highly correlated and Jones et al. (2007)
4 acknowledged that “the data alone do not permit unambiguous attribution of causality to arsenic
5 exposure, antimony exposure, lead exposure or a combination of the three.” Although the
6 likelihood of the data is largest when weighted cumulative exposure to antimony is used, the
7 difference in likelihood between using antimony versus arsenic or lead is not statistically
8 significant. Jones et al. concluded that arsenic exposure is the cause for the increased lung cancer
9 mortality because there is evidence from other studies that exposures to arsenic increase lung
10 cancer mortality, and because there is no strong historical evidence of a relationship between
11 antimony or lead exposure and lung cancer.

12 **4.2.4.4.4 Data for Dose-Response Modeling**

13 Jones et al. (2007) present the estimates and 90% confidence intervals of the intercept (α) and
14 slope (β_a) for the relative risk model with additive intercept under the three extrapolation
15 exposure scenarios (A, B, and C), the two dose metrics (cumulative exposure and weighted
16 cumulative exposure), and the five agents analyzed (lead, antimony, arsenic, cadmium, and
17 polonium-210) (Jones’s Table 3 is reproduced in Appendix G). The SEs for the intercept and the
18 slope of the relative risk model with additive intercept could be obtained separately from their
19 respective 90% confidence intervals. The maximum likelihood estimate of the slope
20 corresponding to the multiplicative relative risk model can be obtained from the maximum
21 likelihood estimates of the intercept and the slope of the relative risk model with additive
22 intercept given in Table 3 of Jones et al. (2007). That is, if the maximum likelihood estimate of
23 the intercept (α) and the slope (β_a) for the following relative risk model with additive intercept
24 are known,

$$25 \quad E(O_j) = E_{oj} \times (\alpha + \beta_a \times d_j)$$

26 then, the maximum likelihood estimates of the intercept (α) and the slope (β) for the
27 multiplicative relative risk model

$$28 \quad E(O_j) = \alpha \times E_{oj} \times (1 + \beta \times d_j)$$

29 are,

$$30 \quad \alpha = \alpha$$

31 and

$$32 \quad \beta = \beta_a / \alpha.$$

33 Although the maximum likelihood estimates of the multiplicative relative risk model can be
34 obtained from the maximum likelihood estimates of the relative risk model with additive
35 intercept, the SE for the slope of the multiplicative relative risk model with multiplicative

3 intercept cannot be estimated from the SEs for the parameters of the relative risk model with
4 additive intercept (estimates and the SEs of the estimates are identical for the intercept of both
5 models). Dr. Steve Jones sent an email message showing the calculation of the maximum
6 likelihood estimates of the slope for the relative risk parameter from the maximum likelihood
7 estimates for the relative risk model with additive intercept for the weighted cumulative exposure
8 to arsenic using the three exposure extrapolation scenarios. The slope β parameter estimates for
9 the multiplicative relative risk model with multiplicative intercept from Dr. Jones' intercept (α)
10 and slope (β_a), are as follows:

11 Scenario A: $1.35/1.25 = 1.08$ per $\text{mg}/\text{m}^3\text{-yr} = 0.00108$ per $\mu\text{g}/\text{m}^3\text{-yr}$ (occupational)

12 Scenario B: $0.85/1.33 = 0.64$ per $\text{mg}/\text{m}^3\text{-yr} = 0.00064$ per $\mu\text{g}/\text{m}^3\text{-yr}$ (occupational)

13 Scenario C: $0.95/1.27 = 0.75$ per $\text{mg}/\text{m}^3\text{-yr} = 0.00075$ per $\mu\text{g}/\text{m}^3\text{-yr}$ (occupational)

14 Jones et al. (2007) *do not provide SEs for the slope estimates, and there is no sufficient*
15 *information in the Jones et al. (2007) paper to infer these SEs.* One way to estimate the SEs of
16 the slope for the multiplicative relative risk linear model using the weighted cumulative exposure
17 to arsenic and the three extrapolation exposure scenarios is using the data given in Table 4 of
18 Jones et al. (2007) which is shown in Table 16.

19

3

Table 16. Observed, Expected, and Observed/Expected from Jones et al. (2007)				
Arsenic Exposure Range ($\mu\text{g}/\text{m}^3\text{-yr}$)	Arsenic Mean Exposure ($\mu\text{g}/\text{m}^3\text{-yr}$)	Observed	Expected	Observed/Expected
Scenario A				
0.0 to ≤ 42	8.8	13	11.1	1.17
$>42 - \leq 110$	75	12	6.8	1.78
$>110 - \leq 290$	190	12	8.8	1.36
$>290 - \leq 620$	430	12	7.4	1.61
> 620	1200	13	4.2	3.11
Scenario B				
0.0 to ≤ 45	9.7	13	10.4	1.25
$>45 - \leq 120$	81	12	6.7	1.78
$>120 - \leq 320$	210	12	8.8	1.37
$>320 - \leq 710$	480	12	7.5	1.60
> 710	1400	13	4.9	2.67
Scenario C				
0.0 to ≤ 44	9.3	13	10.2	1.28
$>44 - \leq 120$	83	12	7.0	1.72
$>120 - \leq 350$	230	12	9.3	1.29
$>350 - \leq 840$	540	12	7.8	1.55
> 840	1700	13	4.1	3.17

4

5 Table 16 shows observed and expected number of lung cancer deaths in the cohort for each
6 interval of weighted cumulative exposure assuming exposure extrapolation scenarios A, B and C.
7 Jones et al. also show in Table 16 the mean weighted cumulative exposure for each of the
8 intervals defined therein. Using these data, the parameters and corresponding SEs of a
9 multiplicative relative risk model for each exposure scenario can be estimated using Poisson
10 regression.

11 4.2.4.4.5 Slope Parameter (β) Estimates

12 For the cumulative dose levels and summary data presented in Table 16, Poisson regression
13 modeling with maximum likelihood estimation procedures were used to calculate the β (MLE)
14 estimate for lung cancer mortality using procedures outlined in Appendix B (i.e., the
15 multiplicative relative risk model with multiplicative intercept). The relative risk model used to
16 calculate the β value included a term (α) to account for different background rates in the

3 epidemiological cohort and the reference population group, as described previously. The
4 maximum likelihood estimate β (MLE), SE, β (95% LCL), and β (95% UCL) based on the
5 summary data are presented in Table 17. Estimates based on unweighted cumulative exposure of
6 β (MLE), SE, β (95% LCL) and β (95% UCL) (Jones et al. 2007) are shown in Table G-1 of
7 Appendix G.

Table 17. Estimates based on Weighted Cumulative Exposure of β (MLE), SE, β (95% LCL) and β (95% UCL) (Jones et al. 2007) ^a				
Extrapolation assumption for exposures prior to 1972	Intercept (α) \pm SE	β (MLE) \pm SE per $\mu\text{g}/\text{m}^3\text{-yr}$	B (95% LCL)^b per $\mu\text{g}/\text{m}^3\text{-yr}$	β (95% UCL)^b per $\mu\text{g}/\text{m}^3\text{-yr}$
Scenario A	1.24E+00 \pm 2.43E-01	1.10E-03 \pm 7.03E-04	-5.86E-05	2.26E-03
Scenario B	1.33E+00 \pm 2.47E-01	6.49E-04 \pm 4.90E-04	-1.56E-04	1.45E-03
Scenario C	1.27E+00 \pm 2.40E-01	7.48E-04 \pm 4.89E-04	-5.67E-05	1.55E-03

8 ^a Units are in ERR per $\mu\text{g}/\text{m}^3\text{-yr}$

9 ^b 95% LCL = $\beta - (1.645 \times \text{SE})$ for a standard normal distribution; 95% UCL = $\beta + (1.645 \times \text{SE})$
10 for a standard normal distribution

11 *The maximum likelihood estimates of the intercept α and slope β parameters of the multiplicative*
12 *relative risk model using Poisson regression on the observed and expected number of lung*
13 *cancer deaths given in Table 4 of Jones et al. (2007) are essentially equal to the intercept α and*
14 *slope β parameters estimates back-calculated from the data in Table 3 of Jones et al. (2007) for*
15 *the relative risk model with additive intercept and weighted cumulative exposure to arsenic.*

16 4.2.4.4.6 Dosimetric Adjustments

17 Occupational concentrations were converted to environmental concentrations for the general
18 population using the equation in Section 4.2.4.1.2.

19 4.2.4.4.7 URFs and 10^{-5} -Risk Air Concentration

20 URFs and 10^{-5} -risk air concentrations were calculated using procedures discussed in Section
21 4.2.4.1.3, although the values for the estimates based on the weighted cumulative exposures to
22 arsenic were obtained using a modified spreadsheet of the BEIR IV life-table calculations
23 whereby the weighted (instead of the unweighted) cumulative exposures are used in calculating
24 the extra risk at age 70 years. Table 18 shows estimates of URFs and 10^{-5} -risk air concentration
25 for excess lung cancer mortality calculated based on different exposure estimate scenarios with
26 weighted cumulative exposures (Jones et al. 2007) and based on β (MLE), β (95% LCLs) and β
27 (95% UCLs) from Table 17 using Texas lung cancer mortality and survival rates. Since the β

3 (95% LCL) values were negative (Table 17), suggesting zero risk, calculation of a URF and 10^{-5} -
4 risk air concentration was not possible.

5 Table G-2 in Appendix G shows results based on unweighted cumulative exposure for
6 comparison. URFs based on unweighted cumulative exposure were less conservative than URFs
7 based on weighted cumulative exposure (Table G-2). Results using US lung cancer mortality and
8 survival rates are in Table D-4 of Appendix D for weighted cumulative exposure and Table G-3
9 for unweighted cumulative exposure.

Table 18. URFs and 10^{-5}-Risk Air Concentration (Jones et al. 2007)^a				
Extrapolation assumption for exposures prior to 1972	Back-ground Rates	β (MLE) URF 10^{-5}-Risk Air Concentration	β (95% UCL) URF 10^{-5}-Risk Air Concentration	Ratio: URF (95% UCL) to URF (MLE)
Scenario A	Texas	1.19E-03 / $\mu\text{g}/\text{m}^3$ 0.00839 $\mu\text{g}/\text{m}^3$	2.45E-03 / $\mu\text{g}/\text{m}^3$ 0.00408 $\mu\text{g}/\text{m}^3$	2.1
Scenario B	Texas	7.04E-04 / $\mu\text{g}/\text{m}^3$ 0.0142 $\mu\text{g}/\text{m}^3$	1.57E-03 / $\mu\text{g}/\text{m}^3$ 0.00636 $\mu\text{g}/\text{m}^3$	2.2
Scenario C	Texas	8.13E-04 / $\mu\text{g}/\text{m}^3$ 0.0123 $\mu\text{g}/\text{m}^3$	1.68E-03 / $\mu\text{g}/\text{m}^3$ 0.00595 $\mu\text{g}/\text{m}^3$	2.1
Ratio: high to low URFs (MLE)		1.7		

10 ^a Since the β (95% LCL) values were all negative, suggesting zero risk, calculation of a 10^{-5} -risk
11 air concentration was not possible.

12 4.2.4.4.8 Preferred β and URF Potency Estimate (Jones et al. 2007)

13 The URF of 7.04E-04 per $\mu\text{g}/\text{m}^3$ with a corresponding 10^{-5} -risk air concentration of 0.0142
14 $\mu\text{g}/\text{m}^3$ is preferred because it is based on the preferred Scenario B exposure estimates (as
15 discussed in Section 4.2.4.4.1). The URF (MLE) for the different exposure scenarios ranged
16 from 7.04E-04 per $\mu\text{g}/\text{m}^3$ (Scenario B) to 1.19E-03 per $\mu\text{g}/\text{m}^3$ (Scenario A), approximately a
17 factor of 1.7. There was a 2.2 ratio between URF estimates using the MLE compared to the 95%
18 UCL. The MLE estimate is preferred because it is the best estimate to be used when combining
19 URFs from the other cohorts (Enterline et al. 1995; Lubin et al. 2000; Järup et al. 1989) as
20 discussed in Section 4.2.5. URF estimates range from zero risk (95% LCL) (i.e., the 95% LCL
21 on the slope parameter estimate was negative) to 1.57E-03 per $\mu\text{g}/\text{m}^3$ (95% UCL).

3 **4.2.5 Final URF and *chronic* $ESL_{linear(c)}$**

4 The URFs based on Enterline et al. (1995), Lubin et al. (2000; 2008), Järup et al. (1989), and
5 Jones et al. (2007) are considered appropriate estimates of the carcinogenic potency of arsenic
6 based on their respective studies, and ranged from 1.11E-04 per $\mu\text{g}/\text{m}^3$ to 7.04E-04 per $\mu\text{g}/\text{m}^3$, a
7 6.4-fold difference (Table 19). The Lubin et al. (2000; 2008) study with 256,850 PY and the
8 Järup et al. (1989) studies with 127,189 PY had significantly more workers and PY included in
9 the study than the Enterline et al. (1995) study with 84,916 PY and Jones et al. (2007) study with
10 35,942 PY. Therefore, a weighted URF using PY was calculated and will be used as the final
11 URF.

DRAFT

3

Table 19. Preferred URFs and 10⁻⁵-Risk Air Concentrations from all Studies					
Study And PY	Back- ground Rates	β (MLE) URF 10⁻⁵-Risk Air Concentration	β (95% LCL) URF 10⁻⁵-Risk Air Concentration	β (95% UCL) URF 10⁻⁵-Risk Air Concentration	Ratio: URF (95% UCL) to URF (MLE)
Enterline et al. (1995) All workers adjusting for year of hire 84,916 PY	Texas	1.19E-04/ μg/m ³ 0.0837 μg/m ³	2.72E-05/ μg/m ³ 0.367 μg/m ³	2.12E-04/ μg/m ³ 0.0471 μg/m ³	1.8
Lubin et al. (2008) Full cohort 256,850 PY	Texas	2.18E-04/ μg/m ³ 0.046 μg/m ³	1.18E-04/ μg/m ³ 0.0850 μg/m ³	3.19E-04/ μg/m ³ 0.0313 μg/m ³	1.5
Järup et al. (1989) All workers adjusting for year of hire 127,189 PY	Texas	1.11E-04/ μg/m ³ 0.0902 μg/m ³	8.76E-04/ μg/m ³ 1.14 μg/m ³	2.13E-04/ μg/m ³ 0.0470 μg/m ³	1.9
Jones et al. (2007) Scenario B 35,942 PY	Texas	7.04E-04/ μg/m ³ 0.0142 μg/m ³	---	1.57E-03/ μg/m ³ 0.00636 μg/m ³	2.2
Ratio: high to low URFs (MLE)		6.4			

4

5

3 Final URF (risk per $\mu\text{g}/\text{m}^3$)

$$4 \quad = \frac{[(\text{URF}_1 \times \text{weight}_1) + (\text{URF}_2 \times \text{weight}_2) + (\text{URF}_3 \times \text{weight}_3) + (\text{URF}_4 \times \text{weight}_4)]}{5 \quad [\text{weight}_1 + \text{weight}_2 + \text{weight}_3 + \text{weight}_4]}$$

$$6 \quad = \frac{[(1.19\text{E-}04 \times 84,916) + (2.18\text{E-}04 \times 256,850) + (1.11\text{E-}04 \times 127,189) + (7.04\text{E-}04 \times 35,942)]}{7 \quad [84,916 + 256,850 + 127,189 + 35,942]}$$

$$8 \quad = 2.09\text{E-}04 \text{ per } \mu\text{g}/\text{m}^3$$

9 The final PY-weighted URF based on Texas lung cancer mortality rates and survival
10 probabilities is $2.09\text{E-}04$ per $\mu\text{g}/\text{m}^3$ which is similar to the geometric mean of the URFs from the
11 four studies of $2.12\text{E-}04$ per $\mu\text{g}/\text{m}^3$. The final URF is $2.1\text{E-}04$ per $\mu\text{g}/\text{m}^3$ and the resulting air
12 concentration at a 1 in 100,000 excess lung cancer risk is $0.048 \mu\text{g}/\text{m}^3$ (rounded to two
13 significant figures). Therefore, the $\text{chronicESL}_{\text{linear}(c)}$ is $0.048 \mu\text{g}/\text{m}^3$.

14 Similar calculations using the US lung cancer mortality rates and survival probabilities are
15 shown in Table D-5 in Appendix D. There the weighted URF is $2.2\text{E-}04$ per $\mu\text{g}/\text{m}^3$ and the
16 resulting air concentration at a 1 in 100,000 excess lung cancer risk is $0.045 \mu\text{g}/\text{m}^3$ (rounded to
17 two significant figures) which is similar to the values calculated using Texas lung cancer
18 mortality rates and survival probabilities.

19 The final weighted URF of $2.1\text{E-}04$ per $\mu\text{g}/\text{m}^3$ is based on the four occupational epidemiological
20 studies with the best available data. This URF is less conservative than the range of URFs of
21 $6.81\text{E-}03$ per $\mu\text{g}/\text{m}^3$ to $7.60\text{E-}03$ per $\mu\text{g}/\text{m}^3$ and the geometric mean URF of $7.19\text{E-}03$ per $\mu\text{g}/\text{m}^3$
22 calculated by USEPA (1984). Consequently, the 10^{-5} -risk air concentration of $0.048 \mu\text{g}/\text{m}^3$ is
23 higher than the air concentration of $0.0014 \mu\text{g}/\text{m}^3$ based on the USEPA (1986). Reasons for the
24 difference have been discussed in Section 4.2.4.2.5 *Comparison of TCEQ's URF to USEPA's*
25 *URF (Lubin 2000, Lubin 2008)* and Section 4.2.4.1.5 *Comparison of TCEQ's URF from*
26 *Enterline et al. (1995) to USEPA's URF.*

27 **4.2.6 Evaluating Susceptibility from Early-Life Exposures**

28 USEPA (2005) provides default age-dependent adjustment factors (ADAFs) to account for
29 potential increased susceptibility in children due to early-life exposure when a chemical has been
30 identified as acting through a mutagenic MOA for carcinogenesis. The mechanisms of arsenic
31 carcinogenesis have not been established, although a variety of mechanisms are likely to be
32 involved as discussed in Section 4.2.3 *Carcinogenic MOA.*

33 Arsenic has not been identified by USEPA as having a mutagenic MOA (USEPA 2005b), and
34 data are not sufficient to determine the carcinogenic MOA. As the MOA for arsenic-induced
35 lung cancer has not been determined to be mutagenic by consensus of the scientific community,

3 ADAFs will not be applied to the URF. This issue will be reevaluated periodically as new
4 scientific information on arsenic's carcinogenic MOA becomes available.

5 There is some evidence indicating transplacental arsenic carcinogenesis in mice exposed to very
6 high concentrations via drinking water (Waalkes et al. 2007; Ahlborn et al. 2009). However,
7 these studies are limited for extrapolating cancer risk to humans via the inhalation route. Oral
8 toxicity data are the most common data available as alternatives to inhalation data. However,
9 USEPA (1994) recommends caution when using oral toxicity data for inhalation toxicity. Oral
10 data should not be used for route-to-route extrapolation when chemicals are expected to have
11 different toxicity by the two routes (e.g. metals, irritants, and sensitizers).

12 **4.2.7. Uncertainty Analysis**

13 **4.2.7.1 Dose-Response Modeling**

14 For all studies, dose-response modeling was conducted with a multiplicative relative risk model
15 and linear Poisson regression modeling including a term to account for differences between
16 study and reference population background mortality rates. Linear Poisson regression is
17 commonly used to investigate dose-response relationships derived from occupational cohort
18 epidemiologic studies based on mortality and is generally considered to be biologically-plausible
19 for lung cancer. Modeling results for the linear-exponential model with concentration as an effect
20 modifier (Lubin et al. 2008) and the linear-exponential model with time since last exposure and
21 attained age as effect modifiers were also presented (Jones et al. 2007).

22 There is uncertainty due to the use of cumulative dose as the dose metric, the dose metric
23 available in all four cohorts. Smith et al. (2009) suggested that cumulative dose is not a good
24 metric for exposure when the outcome is relative risk, but rather dose rate in steady state as
25 reflected by urinary arsenic concentrations. Unfortunately, urinary arsenic concentrations were
26 not available in the four epidemiology studies used to derive the URF and therefore TD used the
27 available cumulative dose as the dose metric.

28 URFs calculated with slope β parameter estimates and both lower and upper confidence limit
29 estimates were reported for each cohort in order to provide information on uncertainty in the
30 relative risk estimates based on the different cohorts. For the preferred URFs from each study:

- 31 • For the Enterline et al. (1995) study, URF estimates range from 2.72E-05 per $\mu\text{g}/\text{m}^3$ (95%
32 LCL) to 2.12E-04 per $\mu\text{g}/\text{m}^3$ (95% UCL) (Section 4.2.4.1.4);
- 33 • For the Lubin et al. (2000; 2008) studies, URF estimates for the full cohort range from
34 1.18E-04 per $\mu\text{g}/\text{m}^3$ (95% LCL) to 3.19E-04 per $\mu\text{g}/\text{m}^3$ (95% UCL) (Section 4.2.4.2.4);
- 35 • For the Järup et al. (1989) study, URF estimates range from 8.76E-04 per $\mu\text{g}/\text{m}^3$ (95%
36 LCL) to 2.13E-04 per $\mu\text{g}/\text{m}^3$ (95% UCL) (Section 4.2.4.3.5); and

3 For the Jones et al. (2007) study, URF estimates range from zero risk (95% LCL) (i.e., 95% LCL
4 slope parameter estimate was negative) to 1.57E-03 per $\mu\text{g}/\text{m}^3$ (95% UCL) (Section 4.2.4.4.8).

5 The ratio of the URF (95% UCL) to the URF (MLE) for the preferred studies ranged from 1.5
6 for the Lubin et al. (2000; 2008) with the most PY to 2.2 for the Jones et al. (2007) study with
7 the least PY (Table 19), which indicates the precision of the estimates. The ratio of the highest
8 URF (MLE) to the lowest URF (MLE) of 6.4 indicates good agreement between dose-response
9 modeling from the different cohort studies.

10 **4.2.7.2 Epidemiological Occupational Studies**

11 Human studies are preferred over animal studies to develop toxicity factors for chemicals to
12 avoid uncertainty due to interspecies differences. However, human carcinogenic studies are
13 usually epidemiological occupational studies, which themselves are subject to inherent
14 uncertainty, as discussed in the following sections.

15 **4.2.7.2.1 Estimating Risks for other Potentially Sensitive Subpopulations**

16 The relationship between lung cancer mortality and exposure to arsenic was evaluated based on
17 healthy male workers employed in smelters. Although these workers were often healthier than
18 the general population, the approach used by TD estimates how the risk of lung cancer mortality
19 changes with exposure to arsenic after adjusting for the differences between the workers and the
20 general population background lung cancer mortality rates. The estimates of excess risks based
21 on the derived models apply to the target population (e.g., Texas all sexes and all races, Texas
22 white males, U.S. black females, etc.) whose background lung mortality cancer rates and survival
23 probabilities are used in the estimation of the extra risks. The assumption being made in the
24 calculation of the URFs is that the increase in the excess risk per a unit increase in the dose
25 metric (i.e., cumulative exposure or weighted cumulative exposure to arsenic) is the same for the
26 workers and for the target population. Subpopulations with higher background lung cancer
27 mortality rates will have higher estimated URFs.

28 The model may underestimate excess risks for subpopulations that are particularly more sensitive
29 than smelter workers to arsenic exposures. For example, Ihrig et al. (1998) reported that Hispanic
30 populations have a genetic impairment in folate metabolism, an essential component to protect
31 against arsenic toxicity. However, it is uncertain if this particular population were represented in
32 the four smelter cohort studies. Also, smelter workers in the cohorts are often white males and
33 therefore there is uncertainty about estimating the risk for subpopulations more sensitive to
34 arsenic exposures than these workers.

35 **4.2.7.2.2 Estimating Risks for the General Population from Occupational Workers**

36 While the database of human epidemiologic studies are vast, many of the studies are limited by
37 confounding factors such as smoking, exposure to other chemicals, and differences in population
38 characteristics (e.g., nutritional state, metabolism, toxicokinetics) (ATSDR 2007). These

3 confounders can limit the extrapolation of the study results to the general population. In addition,
4 the general population does not have the same exposure levels as occupational workers, who are
5 generally exposed to higher concentrations. Further, workers are often healthy and there is
6 uncertainty in extrapolating the results of epidemiology studies from occupational workers to the
7 general population (healthy worker survivor effect). Arrighi and Hertz-Picciotto (1996) reported
8 that for arsenic exposure, the healthy worker survivor effect was not strong enough to mask the
9 strong effect of arsenic exposure on respiratory cancer.

10 The available epidemiology data indicates lung cancer risk in workers exposed to high
11 concentrations of arsenic. Limited data are available on the risk of lung cancer among residents
12 in communities in the vicinity of a smelter exposed to lower concentrations. There appears to be
13 a disagreement amongst the scientific community in relating lung cancer to arsenic exposure for
14 residents of communities in close proximity to smelters who are exposed to lower
15 concentrations. The estimated exposure estimates indicated arsenic concentrations decrease as
16 one moves farther away from the smelter. While some investigators have reported no
17 associations (Rom et al. 1982, Pershagen et al. 1985, Greaves et al. 1981), others have reported
18 some associations (Blot and Fraumeni 1975, Matanoski et al. 1981) of lung cancer in residents of
19 communities close to smelters and pesticide facilities. However, these studies are limited by poor
20 exposure estimates.

21 **4.2.7.2.3 Occupational Exposure Estimation Error**

22 While the relationship of arsenic to increased risk of lung cancer in smelter workers is
23 unequivocal, there is sometimes insufficient characterization of the exposure data (e.g., range,
24 peak and mean exposure levels) in some of the exposure groups (high exposure).

25 Results from epidemiology studies have uncertainties because of potential exposure estimation
26 error. Lubin et al. (2000) discuss an example of the exposure estimation error in the analyses
27 conducted by Enterline and colleagues in 1987 and 1992 for the Tacoma smelter in Washington.
28 While Enterline et al. (1987, 1992) reported a concave relationship between lung cancer risk and
29 airborne arsenic exposure, they reported a linear relation with urinary levels of total arsenic. The
30 concave relationship can be perceived as an artifact of the exposure assessment procedures. The
31 exposure assessment error could have been introduced due to the differences in the
32 computational procedures of airborne arsenic and urinary arsenic as discussed previously in
33 Section 4.2.4.1. Several investigators including Lubin et al. (2000) have indicated that the
34 approach can induce bias in the risk estimates because urinary arsenic is a variable that is log-
35 normally distributed and the use of the geometric mean can underestimate the mean exposure for
36 a department. Lubin et al. (2000) further indicated that for a given urinary arsenic level, the
37 predicted value overestimated the airborne arsenic, and therefore introduced exposure estimation
38 error.

39 There was uncertainty in the exposure estimates from the Jones et al. (2007) study because air
40 sampling measurement results were available from 1972-1991, but not prior to 1972. Scenario B

3 was chosen to calculate the URF because it was the most realistic exposure scenario used to
4 estimate exposures prior to 1972 (Section 4.2.4.4.1).

5 **4.2.7.2.4 Uncertainty Due to Co-Exposures to other Compounds**

6 In addition to arsenic exposure, smelter workers can also be exposed to other potential
7 respiratory toxicants (e.g., sulfur dioxide) and many of the workers were smokers. The risk
8 estimates can therefore be confounded by co-exposure to other pollutants and/or smoking. Data
9 on the interaction of smoking and arsenic exposure are available for some of the cohorts and
10 indicate an intermediate effect that is between additive and multiplicative (Jarup and Pershagen
11 1991).

12 Although Lubin et al. (2000) did not investigate smoking, Welch et al. (1982) and Higgins et al.
13 (1981) found that smoking did not confound the association between inhaled arsenic exposure
14 and respiratory cancer based on a sample of 1,469 workers from the Montana cohort. The
15 relationship between respiratory cancer and exposure to airborne arsenic and sulphur dioxide
16 were investigated by Lubin et al. (2000). Relative risks did not increase with sulphur dioxide
17 exposure within arsenic-exposure categories whereas relative risk increased with increasing
18 duration of employment in work areas with heavy and medium arsenic exposure within each
19 sulphur dioxide category. This indicates that sulphur dioxide co-exposure did not confound the
20 arsenic dose-response. Järup et al. (1989) also found that there was no evident dose-response
21 relationship between estimated exposure to sulfur dioxide and lung cancer.

22 Lung cancer mortality at a UK tin smelter was studied by Jones et al. (2007). The investigators
23 reported that the workers at the smelter were potentially exposed to substances that included tin,
24 lead, antimony, arsenic, cadmium, sulfur dioxide, polonium-210, and combustion products. The
25 investigators further indicate that while there is strong evidence of a causative relationship with
26 excess risk of lung cancer with both arsenic and ionizing radiation, the evidence for cadmium is
27 conflicting. Evidence of a role for lead or antimony is weak and associations may have been
28 observed due to confounding from co-exposure to arsenic. For ionizing radiation, the 97.5
29 percentile of cumulative exposure to ^{210}Po in the Jones et al. (2007) study, at 3 Bq year m^{-3} ,
30 implies a radiation dose to lung of 0.2 Sv, which is a low dose. Radiation doses to lung in excess
31 of 100 Sv were experienced by cohorts of uranium miners and nuclear process workers showing
32 substantial excesses in lung cancer mortality. Jones et al. (2007) concluded that increases in lung
33 cancer mortality were primarily due to arsenic exposure.

34 **4.2.7.2.5 Uncertainty Due to Other Reasons**

35 According to ATSDR (2007), exposure to arsenic may include exposure to the more toxic
36 inorganic forms of arsenic, organic forms of arsenic, or both. According to Peters et al. (1986),
37 cancer risk is related to the intensity and duration of the cellular effects and additional biological
38 factors associated with the natural history of the disease.

39 As previously discussed in Section 4.2.4, Enterline et al. (1995) and Lubin et al. (2000; 2008)
40 examined respiratory cancer mortality whereas Järup et al. (1989) and Jones et al. (2007)

3 investigated lung cancer mortality. This may potentially overestimate lung cancer mortality since
4 there were additional deaths due to deaths in that category other than lung cancer. URFs may
5 underestimate lung cancer incidence because potency estimates were based on mortality as
6 discussed in Section 4.2.4.

7 **4.3 Welfare-Based Chronic ESL**

8 No data were found regarding vegetative effects.

9 **4.4 Long-Term ESL and Values for Air Monitoring Evaluation**

10 The chronic evaluation resulted in the derivation of the following chronic value:

11 $\text{chronicESL}_{\text{linear}(c)} = 0.048 \mu\text{g}/\text{m}^3$

12 The long-term ESL for air permit evaluations and for evaluation of long-term ambient air
13 monitoring data is the $\text{chronicESL}_{\text{linear}(c)}$ of $0.048 \mu\text{g}/\text{m}^3$.

14 **Chapter 5 References**

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