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Silica, Crystalline Forms

CAS Registry Numbers:

14808-60-7 (quartz)

14464-46-1 (cristobalite)

1317-95-9 (tripoli)

15468-32-3 (tridymite)

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TABLE OF CONTENTS

LIST OF TABLES ..... **III**

LIST OF FIGURES ..... **III**

CHAPTER 1 SUMMARY TABLES **1**

CHAPTER 2 MAJOR SOURCES OR USES **4**

CHAPTER 3 ACUTE EVALUATION **4**

3.1 HEALTH-BASED ACUTE REV AND ESL 4
3.1.1 Physical/Chemical Properties and Key Studies *4*
3.1.1.1 Physical/Chemical Properties 4
3.1.1.2 Essential Data and Key Studies 5
3.1.1.2.1 Key Acute Study 5
3.1.1.2.2 Supporting Subacute Studies 6
3.1.2 Mode-of-Action (MOA) Analysis *7*
3.1.3 Dose Metric *8*
3.1.4 PODs for the Key and Supporting Studies *8*
3.1.5 Dosimetric Adjustments *8*
3.1.5.1 Default Exposure Duration Adjustments 8
3.1.5.2 Default Dosimetry Adjustments from Animal-to-Human Exposure 9
3.1.6 Critical Effect and Adjustments to the POD_{HEC} *10*
3.1.6.1 Critical Effect 10
3.1.6.2 Uncertainty Factors (UFs) 10
3.1.7 Comparison of Results *11*
3.1.8 Health-Based Acute ReV and $^{acute}ESL$ *11*
3.2. WELFARE-BASED ACUTE ESLS 12
3.2.1 Odor Perception *12*
3.2.2 Vegetation Effects *12*
3.3. SHORT-TERM ESL 13

CHAPTER 4 CHRONIC EVALUATION **13**

4.1 NONCARCINOGENIC POTENTIAL 13
4.1.1 Physical/Chemical Properties and Key Study *13*
4.1.1.1 Key Epidemiological Study - Hnizdo and Sluis-Cremer (1993) 14
4.1.1.2 Supporting Epidemiological Study - Hughes et al. (1998) 15
4.1.2 MOA Analysis *15*
4.1.3 Dose Metric *16*
4.1.4 PODs for Key and Supporting Studies *16*
4.1.4.1 Key Study 16
4.1.4.2 Supporting Study 17
4.1.5 Dosimetric Adjustments *18*

4.1.6 Critical Effect and Adjustments to the POD_{HEC} *19*
4.1.6.1 Critical Effect 19
4.1.6.2 UFs 19
4.1.7 Health-Based Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$ *20*
4.1.8 Comparison of Results *21*
4.2 CARCINOGENIC POTENTIAL 22
4.2.1 Carcinogenic Weight-of-Evidence *22*
4.2.1.1 Human Studies 22
4.2.1.1.1 International Agency for Research on Cancer (IARC) 22
4.2.1.1.2 National Institute of Occupational Health and Safety 23
4.2.1.1.3 Findings from Recent Meta-Analysis and Pooled Analysis 24
4.2.1.1.3.1 Relative Risks in Silicotics (Steenland and Stayner 1997) 24
4.2.1.1.3.2 Relative Risks in Silicotics (Smith et al. 1995) 24
4.2.1.1.3.3 Relative Risks in Silicotics (Tsuda et al. 1997) 25
4.2.1.1.3.4 Pooled Exposure-Response Analyses (Steenland et al. 2001; 2005) 25
4.2.1.1.3.5 Comparison of Relative Risks in Silicotics versus Non Silicotics (Pelucchi et al. 2006) 26
4.2.1.1.3.6 Comparison of Relative Risks in Silicotics versus Non Silicotics (Erren et al. 2008) 27
4.2.1.2 Animal Studies 28
4.2.1.3 WOE Classifications 29
4.2.2 Carcinogenic Mode of Action *29*
4.2.2.1 Interactions with DNA (Potential Linear MOA) 30
4.2.2.2 Recent Evidence for Indirect Mechanisms (Potential Nonlinear MOA) 31
4.2.2.3 Klein and Christopher (1995) (Potential Nonlinear MOA) 31
4.2.2.4 Conclusions 32
4.2.3 Epidemiological Studies and Exposure Estimates *32*
4.2.4 Dose-Response Assessment and Dose Metric *33*
4.2.4.1 Derivation of Potency Estimates Based on Observed Data 33
4.2.4.2 Dosimetric Adjustments 34
4.2.4.3 Extrapolation to Lower Exposures 34
4.2.4.3.1 Calculation of Air Concentrations at 1 in 100,000 Excess Cancer Risk and the $^{chronic}ESL_{linear(c)}$ 34
4.2.4.3.2 Model Selected to Represent Excess Lung Mortality Risk 36
4.2.5 Evaluating Susceptibility from Early-Life Exposures *37*
4.2.6 Sensitivity Analysis Assuming a Nonlinear MOA for Lung Cancer *38*
4.3. WELFARE-BASED CHRONIC ESL 38
4.4 LONG-TERM ESL 38

CHAPTER 5 REFERENCES 39

5.1 REFERENCES CITED IN THE DEVELOPMENT SUPPORT DOCUMENT 39
5.2 OTHER STUDIES AND DOCUMENTS REVIEWED BY THE TD 47

APPENDIX 1. TOXICITY FACTOR DEVELOPMENT FOR SUBACUTE STUDIES 54

DURATION ADJUSTMENTS 54
DOSIMETRY ADJUSTMENTS 54
APPLICATION OF UNCERTAINTY FACTORS 58
CALCULATION OF ACUTE REVS 59

APPENDIX 3. BENCHMARK DOSE MODELING RESULTS 61

APPENDIX 3A. HNIZDO ET AL. (1993) 61

APPENDIX 4. SILICA EPIDEMIOLOGICAL REVIEW AND DOSE-RESPONSE MODELING - INCLUSION OF INDIVIDUAL STUDIES 69

1. BACKGROUND 69
2. VERMONT GRANITE WORKERS (UNIVERSITY OF VERMONT AND NIOSH) 70
3. U.S. DIATOMACEOUS EARTH INDUSTRY (NIOSH) 71
4. CONCLUSIONS 72

APPENDIX 5. US AND TEXAS SURVIVAL AND LUNG CANCER MORTALITY RATES 73

LIST OF TABLES

Table 1 Health- and Welfare-Based Values 1

Table 2 Chemical and Physical Data 2

Figure 1 Crystalline Silica Health Effects and Regulatory Levels 3

Table 3 Derivation of the Acute ReV and ^{acute}ESL 12

Table 4 BMC Modeling Parameters from Hnizdo and Sluis-Cremer (1993) 17

Table 5 BMC Modeling Parameters from Hughes et al. (1998) 18

Table 6 Derivation of the Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$ 21

Table 7 Beta (β), Standard Error (SE), and 95% UCL β Values (mg/m^3-years) 34

Table 8 Air Concentrations (µg/m^3) Corresponding to 1 in 100,000 Excess Lung Cancer Risk Using Various Background Rates and Models 35

LIST OF FIGURES

Figure 1 Crystalline Silica Health Effects and Regulatory Levels 3

Chapter 1 Summary Tables

A summary of health- and welfare-based values from an evaluation of the acute and chronic toxicity of crystalline silica can be found in Table 1. Summary information on the physical/chemical parameters of crystalline silica can be found in Table 2.

Table 1 Health- and Welfare-Based Values

Short-Term Values	**Concentrations**	**Notes**
$^{acute}ESL$[1 h] (HQ = 0.3)	14 μg/m^3 [a] **Short-Term ESL for Air Permit Reviews**	**Critical Effects:** respiratory inflammation–increased neutrophils and lactate dehydrogenase in bronchoalveolar lavage fluid in Crl:CD BR rats (male)
Acute ReV (HQ = 1.0)	47 μg/m^3	**Critical Effects:** Same as above
$^{acute}ESL_{odor}$	---	There are no odors associated with silica.
$^{acute}ESL_{veg}$	---	No negative impacts of silica were identified in plants.
Long-Term Values	**Concentrations**	**Notes**
$^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3)	0.60 μg/m^3 [b]	**Critical Effect:** silicosis in miners
Chronic ReV (HQ = 1.0)	2.0 μg/m^3 [b]	**Critical Effects:** Same as above
$^{chronic}ESL_{linear(c)}$	0.27 μg/m^3 [b, c] **Long-Term ESL for Air Permit Reviews**	**Cancer Endpoint:** lung cancer mortality in silica-exposed workers
$^{chronic}ESL_{veg}$	---	No negative impacts of silica were identified in plants.

[a] Values apply to respirable silica ≤ 10 μm in diameter

[b] Values apply to respirable silica ≤ 4 μm in diameter

[c] Based on unit risk factor (URF) = 3.6 E-05 per μg/m^3 and a risk level of 1 in 100,000 excess cancer risk

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

Table 2 Chemical and Physical Data

Parameter	**Value**	**Reference**
Molecular Formula	SiO_2	ChemFinder 2004
Molecular Weight	60.0848	ChemFinder 2004
Physical State	Solid granules	ChemFinder 2004
Color	Off-white	Mallinckrodt Chemicals 2006
Odor	Odorless	Mallinckrodt Chemicals 2006
CAS Registry Numbers	14808-60-7 (quartz) 14464-46-1 (cristobalite) 1317-95-9 (Tripoli) 15468-32-3 (tridymite)	ChemFinder 2004 CalEPA 2005; ACGIH 2006
Synonyms/Trade Names	Agate; Onyx; Quartz; Silica; Crystallized Silicon dioxide; Sand; Flint; Silica Flour, Cristobalite; Tripoli; Tridymite.	Mallinckrodt Chemicals 2006 ChemFinder 2004; ACGIH 2006
Solubility in water	Insoluble	ChemFinder 2004
Log K_{ow}	Not available	---
Vapor Pressure	10 mmHg @ 1732°C	Mallinckrodt Chemicals 2006
Vapor Density (air = 1)	Not available	---
Density (water = 1)	2.2	ChemFinder 2004
Melting Point	1703-1713°C	ChemFinder 2004/NIOSH 1994a, b, and c/ Fisher Scientific Material Safety Data Sheet
Boiling Point	2230°C	ChemFinder 2004/ Fisher Scientific Material Safety Data Sheet

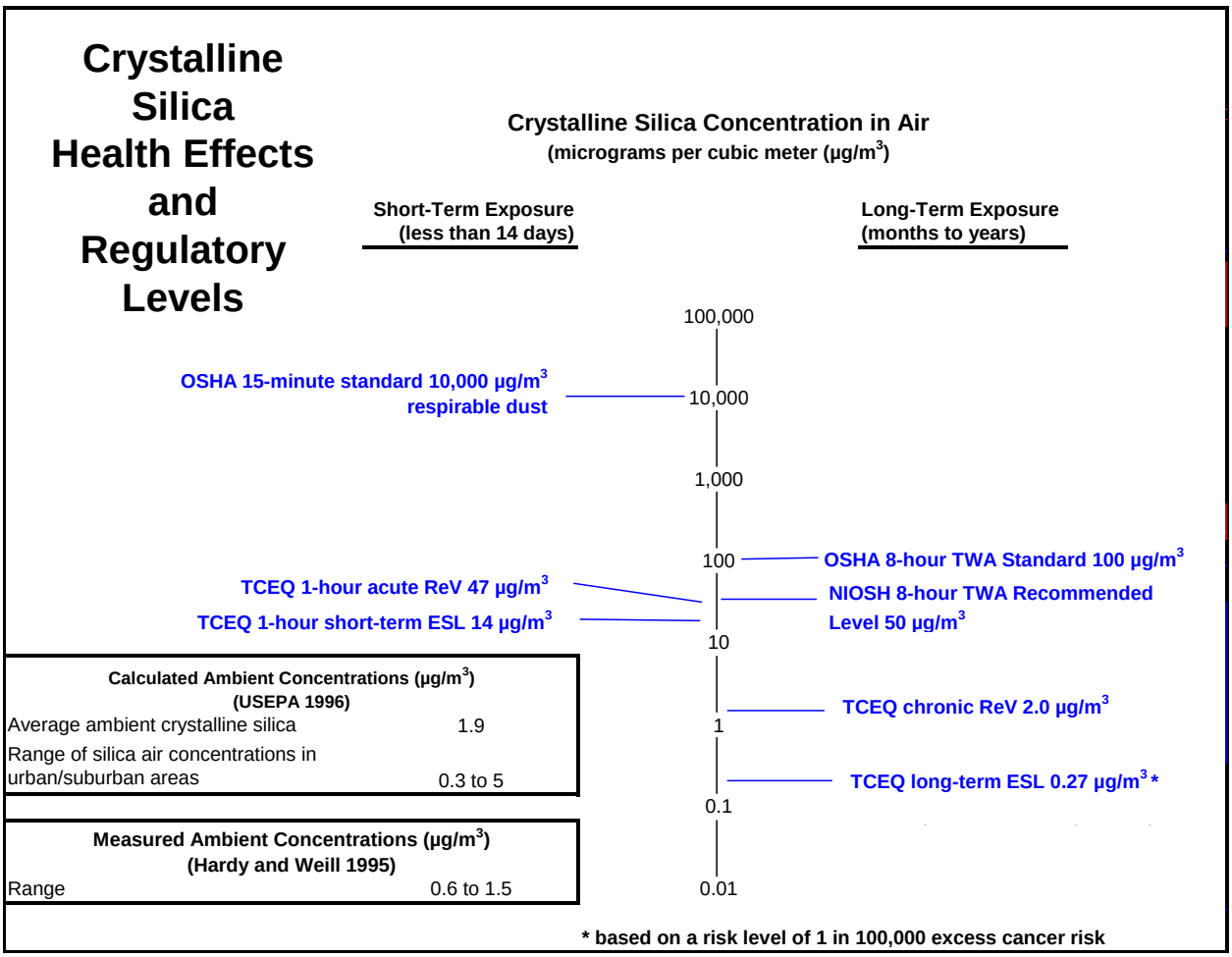

Figure 1 Crystalline Silica Health Effects and Regulatory Levels

This figure compares silica's acute toxicity values (acute ReV and health-based, short term ESL) and chronic toxicity values (chronic ReV and long-term ESL) found in Table 1 to OSHA's and NIOSH's occupational values. Calculated ambient concentrations were obtained from USEPA (1996) and measured ambient concentrations were obtained from Hardy and Weill (1995).

Abbreviations used: **TCEQ**, Texas Commission on Environmental Quality; **TWA**, Time-Weighted Average; **ESL**, Effects Screening Level; **ReV**, Reference Value; **OSHA**, Occupational Safety and Health Administration; **NIOSH**, National Institute of Occupational Safety and Health

Chapter 2 Major Sources or Uses

Crystalline silica occurs in three primary forms, quartz, cristobalite, and tridymite, and exposure occurs primarily in the workplace. Respirable quartz is present in 255 industries, including mining, foundries, metallurgical operations, ceramics, cement, and glass industries, construction, sandblasting, agriculture, and denture manufacture (HSDB 2005). There are several additional rare forms of crystalline silica, including tripoli, which are generally used as abrasives. Emissions of ambient crystalline silica generally occur as a fractional component of particulate emissions (Figure 1) (USEPA 1996).

Chapter 3 Acute Evaluation

3.1 Health-Based Acute ReV and ESL

Because most silica exposure occurs in the workplace, occupational safety agencies have established limits for occupational exposure to silica. Most agencies consider crystalline forms and amorphous or other non-crystalline forms of silica separately. The National Institute for Occupational Safety and Health (NIOSH) recommends an exposure limit of 0.05 mg/m^3 for crystalline silica and 6 mg/m^3 for amorphous silica. The current permissible exposure limit (PEL) set by the Occupational Safety and Health Administration (OSHA) for crystalline silica is 0.1 mg/m^3 (Figure 1), whereas the PEL for amorphous silica is 0.8 mg/m^3. In contrast, the American Conference of Governmental Industrial Hygienists (ACGIH) has set a threshold limit value (TLV) of 0.025 mg/m^3 for crystalline silica only and has indicated that there is insufficient information to set a limit for amorphous silica.

The critical effect of acute exposure to silica is increased inflammation and cytotoxicity in the respiratory tract. The key study exposed animals to crystalline silica as quartz. However, supporting studies indicate similar inflammation and cytotoxicity following exposure to other forms, including cristobalite, and amorphous silica. These results showed that the crystalline forms of silica dust are more potent in producing pulmonary inflammation compared with amorphous or other non-crystalline forms of silica (Warheit et al. 1995). The toxicity factors for amorphous and non-crystalline silica will be developed in a separate Development Support Document (DSD).

3.1.1 Physical/Chemical Properties and Key Studies

3.1.1.1 Physical/Chemical Properties

The main chemical and physical properties of silica are summarized in Table 2. Silica is an off-white granule that occurs naturally in various crystalline and amorphous or other non-crystalline forms (USEPA 1996). Crystalline silica is characterized by silicon dioxide (SiO_2) molecules oriented in fixed, periodic patterns to form stable crystals (NIOSH 1974). The primary

crystalline form of silica is quartz. Other crystalline forms of silica include cristobalite, tripoli and tridymite.

Particle size is a key determinate of silica toxicity, since toxicity is restricted to particles that are small enough to be deposited into the target regions of the respiratory tract. The acute studies discussed below evaluated the effects of silica particles that ranged in size from 1-4 μm in mass median aerodynamic diameter (MMAD). Because this is the mass median particle size range (ie: animals were exposed to larger and smaller particles) and bronchoalveolar lavage (BAL) fluids represent both the tracheobronchial and pulmonary regions of the lung, the acute toxicity factors developed will apply to all silica particles less than or equal to the median cut point for the thoracic region of 10 μm.

3.1.1.2 Essential Data and Key Studies

Acute silicosis, or silicoproteinosis, is a very rare and highly fatal lung disease. It results from massive over-exposure to inhaled silica over a short time, without effective respiratory protection. Acute silicosis is caused by filling of the lung's airspaces with fluid-containing debris from dismembered cells of the respiratory tract and lung. This condition is similar to pulmonary edema, and its symptoms include severe shortness of breath, with fluid accumulation in all lobes of the lung. Silico-tuberculosis is a serious side effect, with death occurring months after exposure and diagnosis. America's worst disaster with acute silica overexposure occurred during the drilling of the Gauley Bridge hydroelectric tunnel during 1930-31 in West Virgina, leading to acute silicosis in nearly 2000 workers (Cherniak 1986). In the early 1990s, there was a second outbreak of acute silicosis among hundreds of sandblasters in the oil industry in Midland-Odessa, Texas (Abraham and Weisenfeld 1997). Although there were some silica dust measurements in the early 1990s indicating between four and seven times the OSHA PEL of 0.1 mg/m^3, there were no reproducible levels of quartz for risk analysis. Hence, there are no human sources for development of risk assessment, and animal studies were used to develop the acute ReV and ESL. Animal studies investigated the following crystalline forms of silica:

- quartz (Warheit et al. 1991, Porter et al. 2001, Castranova et al. 2001, Porter et al. 2002a, and Porter et al. 2002b); and
- cristobalite (Warheit et al. 1995).

Warheit et al. (1991) was chosen as the key study because it included a well-conducted evaluation of the effects of acute exposure (6 hours (h)) (see Section 3.1.1.2.1), whereas the supporting studies examined subacute exposures (6 hours/day (h/d) for either 3 days or 5 days) (see Section 3.1.1.2.2).

3.1.1.2.1 Key Acute Study

Animal data indicate that acute and subacute crystalline silica exposures can elicit pulmonary inflammatory responses. Warheit et al. (1991) exposed male Crl:CD BR rats to 10, 50, or 100

mg/m^3 quartz (MMAD = 3.7 μm) or carbonyl iron particles (MMAD = 3.6 μm) for 6 h or for 6 h/d for 3 days (d). Quartz was purchased as Min-U-Sil, a high quality, commercially available crystalline silica that is generally greater than 99% pure silicon dioxide. Three animals exposed to 10 mg/m^3 silica, 3 animals exposed to 50 mg/m^3 silica, 6 animals exposed to 100 mg/m^3 silica, and 14 sham animals were evaluated at 0, 24, and 48 h post-exposure as well as 1, 2, and 3 months post-exposure. The study assessed various endpoints, including inflammation, cytotoxicity, and histopathology. Because the 6-h exposure duration is considered an acute exposure, this study was selected as the key study.

Rats exposed to 50 mg/m^3 silica for 6-h exhibited a sustained pulmonary inflammatory response. Rats exposed to 10 mg/m^3 silica for 6-h did not exhibit an initial inflammatory response, although the authors noted increased neutrophils in these animals at 1 and 3 months post-exposure. Similarly, alkaline phosphatase (ALP) activity, a marker of tissue damage and type II pneumocyte differentiation, did not initially differ significantly from controls in animals exposed to 10 mg/m^3; however, ALP activity was increased by 1 month post-exposure. Lactate dehydrogenase (LDH), a marker of cytotoxicity, increased in a concentration-dependent manner within 24-h after exposure and remained elevated up to 3 months post-exposure. Protein concentrations in BAL fluids did not differ from controls in animals exposed to 10 mg/m^3 silica. Interestingly, in vitro phagocytosis by macrophages was increased in animals exposed to 10 mg/m^3 silica but decreased in animals exposed to the two higher concentrations compared to controls. Animals exposed to the varying concentrations of silica for 6-h developed pulmonary lesions, but there is no discussion of concentration-specific effects. The delayed increases in inflammation and cytotoxicity and the potential for the development of pulmonary lesions led the TD to consider 10 mg/m^3 to be the lowest-observed-adverse-effect-level (LOAEL) and the relevant point of departure (POD).

3.1.1.2.2 Supporting Subacute Studies

Several repeat exposure, subacute studies support the key study and are discussed for comparison purposes. Warheit et al. (1995) examined the effects of short-term inhalation exposure of two different forms of crystalline silica and amorphous silica free of crystalline contamination. Groups of 24 CD rats were exposed to either 10 or 100 mg/m^3 of cristobalite (MMAD = 3.4-3.6. μm), Min-U-Sil 5 (MMAD = 3.3-3.5 μm), or amorphous silica (MMAD = 2.4-3.4 μm) for 6 h/d for 3 d. The study by Warheit et al. (1995) assessed the presence of granulocytes in BAL fluids as a marker of inflammation. Inflammation was observed at 24-h post-exposure to both concentrations of cristobalite and amorphous silica. However, the inflammation resolved by 8-d post-exposure in animals exposed to amorphous silica but remained in animals exposed to cristobalite. Therefore, 10 mg/m^3 is the POD and is considered a LOAEL.

A series of subacute studies (Porter et al. 2001; 2002a; 2002b and Castranova et al. 2001) evaluated the time course of pulmonary responses in rats following exposure to Min-U-Sil 5. The researchers exposed male Fisher 344 rats to either 15 mg/m^3 Min-U-Sil 5, determined to be

greater than 98.5% quartz by proton-induced x-ray spectrometry, or filtered air (controls) for 6 h/d, 5 days/week (d/wk) for up to a total of 116 d. The MMAD of the quartz particles was consistently less than 2 μm. Subgroups of rats were euthanized and examined after 5, 10, 16, 20, 30, 41, 79, and 116 d of exposure. The series of studies assessed a wide variety of endpoints, including cellular damage, inflammation, activation of transcription factors, cytokine production, fibrosis, and production of oxidants. Early effects, including cellular damage, inflammation, and cytokine production, occurred after 5 d of exposure in rats exposed to 15 mg/m^3. Therefore, 15 mg/m^3 is considered a LOAEL and the relevant POD.

3.1.2 Mode-of-Action (MOA) Analysis

Acute silica exposure causes respiratory tract inflammation. Numerous inflammatory mediators have been associated with silica toxicity, including interleukins, tumor necrosis factor-α, transforming growth factor β, chemokines, adhesion molecules, and nitric oxide (Rao et al. 2004). A recent study by Cassel et al. (2008) indicates that the Nalp3 inflammasome may be essential for silica-induced secretion of the pro-inflammatory cytokine, interleukin 1β. This and other inflammatory mediators recruit polymorphonuclear lymphocytes (PMNs) into the lung. This response has been documented via BAL in coal miners exposed to an average of 0.046 ± 0.029 mg/m^3 crystalline silica (Kuempel et al. 2003).

Crystalline silica also stimulates a respiratory burst in alveolar macrophages, leading to elevated production of reactive oxygen species (ROS) (Ding et al. 2002). The importance of ROS in silica-induced inflammation is supported by experiments that have shown that suppressive oligonucleotides that block ROS production by macrophages reduce the pulmonary damage associated with acute silicosis in mice (Sato 2008). Oxidative stress, resulting from ROS, leads to the production of antioxidant compounds, such as inducible nitric oxide synthase (iNOS), glutathione peroxidase and superoxide dismutase (SOD) (Fubini and Hubbard 2003). This response has also been documented in coal miners whose quartz lung burdens were shown to be a significant predictor of SOD levels in BAL fluids (Kuempel et al. 2003). Silica may also evoke oxidative stress through the pentose phosphate pathway, a primary antioxidant pathway in the cell. Polimeni et al. (2008) have recently shown that quartz inhibits the activity of glucose 6-phosphate dehydrogenase, an enzyme that catalyzes the first step in the pentose phosphate pathway. Interestingly, inhibition of this enzyme did not occur under short-term exposure (1 h) to silica.

Another potential mechanism of silica toxicity, which may be secondary to oxidative stress, is activation of transcription factors. Silica has been shown to activate nuclear factor-κB (NF-κB) in a time- and dose-dependent manner. NF-κB is a transcription factor associated with the transcription of several inflammatory mediators, including cyclooxygenase (COX) II. The COX II enzyme is considered the rate-limiting step for prostaglandin E_2 (PGE_2) formation, a mediator of inflammation following infection or tissue injury (Ding et al. 2002). It is assumed that a certain amount of silica (threshold) is required to initiate transcription factors and the

inflammatory cascade. Therefore, a nonlinear, threshold dose-response was applied for the development of an acute toxicity factor.

Studies in rats, mice, and hamsters after exposure to crystalline silica were discussed by Rabovsky (1997) and Saffiotti et al. (1993). Rabovsky noted that markers of silica-induced toxicity in experimental animals, particularly rats, were similar to those exhibited by humans. In fact, animal models may provide a model for resistant human populations (Rabovsky 1997; Saffiotti et al. 1993). Therefore, the findings in rats are relevant to humans.

3.1.3 Dose Metric

In the key and supporting studies, data on exposure concentration of the parent chemical are available. Estimates for the tissue concentration of silica were provided by Warheit et al. (1991). However, those estimates were only provided for the highest silica concentration. Since data on more specific dose metrics, such as tissue concentration or particle surface area, are not available for all concentrations in the key study or for any concentrations in the supporting studies, exposure concentration of the parent chemical will be used as the default dose metric.

3.1.4 PODs for the Key and Supporting Studies

The acute key study by Warheit et al. (1991) exposed rats to 10, 50, and 100 mg/m^3 silica as quartz for 6 h. The delayed increases in inflammation and cytotoxicity and the potential for the development of pulmonary lesions led the TD to consider 10 mg/m^3 to be the LOAEL and the relevant POD.

In the study by Warheit et al. (1995), inflammation was observed in rats 24-h post-exposure to both 10 and 100 mg/m^3 of cristobalite and amorphous silica for 6 h/d for 3 d. However, the inflammation resolved by 8-d post-exposure in animals exposed to amorphous silica but remained in animals exposed to cristobalite. Therefore, 10 mg/m^3 is considered a LOAEL and the relevant POD.

In the series of subacute studies by Porter et al. (2001; 2002a; 2002b) and Castranova et al. (2001) rats were exposed for 6 h/d for various durations, but adverse effects after exposure for 5-d were assessed for this evaluation. Rats exposed to 15 mg/m^3 showed evidence of inflammation and cell damage within 5 days of exposure. Therefore, 15 mg/m^3 is considered a LOAEL and the relevant POD.

3.1.5 Dosimetric Adjustments

3.1.5.1 Default Exposure Duration Adjustments

The 6-h exposure duration (C_1) in the key study by Warheit et al. (1991) was adjusted to a POD_{ADJ} of 1-h exposure duration (C_2) using Haber's Rule as modified by ten Berge et al. (1986) ($C_1^n \times T_1 = C_2^n \times T_2$) with n = 3, where both concentration and duration play a role in toxicity:

$$C_2 = [(C_1)^3 \text{ x } (T_1 / T_2)]^{1/3} = [(10 \text{ mg/m}^3)^3 \text{ x } (6 \text{ h}/1 \text{ h})]^{1/3} = 18.2 \text{ mg/m}^3 = POD_{ADJ}$$

Similar calculations were conducted for each supporting subacute study for comparison and are presented in Appendix 1 for comparison. The POD_{ADJ} for each subacute study is as follows:

- 18.2 mg/m^3 (Warheit et al. 1995)
- 27.2 mg/m^3 (Porter et al. 2001; 2002a; 2002b and Castranova et al. 2001)

3.1.5.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

As noted in Table 2, silica is a solid granule. Therefore, the Chemical Industry Institute of Toxicology (CIIT) Centers for Health Research and National Institute for Public Health and the Environment (RIVM) 2002 multiple path particle dosimetry model (MPPD) v 2.0 program (CIIT and RIVM 2002) was used to calculate the deposition fraction of silica in the target respiratory region. Parameters necessary for this program are particle diameter, particle density, chemical concentration, and pulmonary regions considered. According to Warheit et al. (1991), the MMAD of the silica used in their study was 3.7 μm with a geometric standard deviation of 1.5. The particle density is 2.2 g/cm^3 (Table 2). The chemical concentration is the POD_{ADJ} of 18.2 mg/m^3. Because the silica particles are small enough and the critical effects were identified from BAL fluids, the target region for silica was considered to be the total particle distribution for the tracheobronchial and pulmonary regions. All remaining values used were default. Once the total particle distribution was determined (Appendix 2), the Regional Deposition Dose Ratio (RDDR) was calculated as follows:

$$RDDR = [(V_E)_A / (V_E)_H] \text{ x } [DF_A / DF_H] \text{ x } [NF_H / NF_A]$$

where: V_E = minute volume
DF = deposition fraction in the target region of the respiratory tract
NF = normalizing factor
A =animal
H = human

RDDR = [137.3 mL/min / 13,800 mL/min] x [0.111 / 0.226] x [543,200 cm^2 / 3422.5 cm^2]
= 0.775

The RDDR was then used to dosimetrically adjust from an animal POD to a human equivalent concentration POD (POD_{HEC}).

$$POD_{HEC} = POD_{ADJ} \text{ x } RDDR = 18.2 \text{ mg/m}^3 \text{ x } 0.775 = 14.1 \text{ mg/m}^3 = 14{,}100 \text{ μg/m}^3$$

Similar calculations were conducted for each supporting subacute study and are presented in Appendix 1 for comparison. The POD_{HEC} for the subacute study series is as follows:

- 15,800 μg/m^3 (Warheit et al. 1995)
- 26,700 μg/m^3 (Porter et al. 2001; 2002a; 2002b and Castranova et al. 2001)

3.1.6 Critical Effect and Adjustments to the POD_{HEC}

3.1.6.1 Critical Effect

As indicated in Section 3.1.1.2.1, data suggest that pulmonary inflammation is the most sensitive endpoint for short-term exposure to silica. The specific critical effects of silica exposure in the key study (Warheit et al. 1991) are a delayed increase in neutrophils (marker of inflammation) and increased LDH levels (marker of cytotoxicity) in BAL fluid from male Crl:CD BR rats exposed to ≥ 10 mg/m^3 silica for 6 h. These effects are likely to be the same in humans, based on the clinical evidence from the Gaully Bridge (Cherniak 1986) and Midland-Odessa (Abraham and Weisenfeld 1997) episodes.

3.1.6.2 Uncertainty Factors (UFs)

The MOA by which silica may produce toxicity is discussed in Section 3.1.2. The default for noncarcinogenic effects is to determine a POD and apply appropriate UFs to derive a ReV (i.e., assume a threshold/nonlinear MOA).

The following UFs were applied to the POD_{HEC} derived from the key study by Warheit et al. (1991): 3 for extrapolation from a LOAEL to a NOAEL (UF_L), 3 for interspecies extrapolation (UF_A), 10 for intraspecies variability (UF_H), and 3 for database uncertainty (UF_D).

- The link between the inflammation and cytotoxicity noted in the key study and clinical outcomes is unknown. However, the study noted that the phagocytic activity of macrophages, presumably a protective mechanism promoting the clearance of silica, was increased by exposure to 10 mg/m^3 silica. In addition, the default exposure duration adjustment using Haber's Rule with an exponent of 3 tends to be conservative. Therefore, a moderate UF_L factor of 3 was used for extrapolation from a LOAEL to a NOAEL.
- A UF_A of 3 was used for extrapolation from animals to humans, because default dosimetric adjustments using the RDDR were conducted to account for toxicokinetic differences but not toxicodynamic differences.
- Because human data were insufficient to develop a toxicity factor, animal data were used and the variability of the acute response in humans is unknown. As a result, a full factor of 10 was used for the UF_H to account for potential sensitive human subpopulations, such as those with existing pulmonary inflammation due to other causes.
- Finally, a moderate UF_D of 3 was used to account for the lack of acute studies in other species and very few animals i.e., 3, 3 and 6 animals were exposed, respectively, to 10, 50 and 100 mg/m^3 exposure groups.
- The total UFs applied to the POD_{HEC} were 300.

$$\text{acute ReV} = POD_{HEC} / (UF_L \times UF_A \times UF_H \times UF_D)$$
$$= 14{,}100\ \mu g/m^3 / (3 \times 3 \times 10 \times 3)$$
$$= 47.0\ \mu g/m^3$$

Similar calculations were conducted for each supporting subacute study and are presented in Appendix 1 for comparison. The ReV for each subacute study is as follows:

- 52.7 $\mu g/m^3$ (Warheit et al. 1995)
- 26.7 $\mu g/m^3$ (Porter et al. 2001; 2002a; 2002b and Castranova et al. 2001)

3.1.7 Comparison of Results

The key and supporting studies investigated the risk of respiratory tract inflammation associated with exposure to crystalline forms of silica. The acute ReV calculated for the key study is 47.0 $\mu g/m^3$ compared to the supporting study values of 52.7 $\mu g/m^3$ (Warheit et al. 1995) and 26.7 $\mu g/m^3$ (Porter et al. 2001; 2002a; 2002b and Castranova et al. 2001) (see Appendix 1). The value based on the Warheit et al. (1995) study is similar to the ReV derived for the key study. The value based on the study series by Porter et al. (2001, 2002a, 2002b) and Castranova et al. (2001) is lower than the key study, but is not preferred because rats were exposed for 5 d to only one concentration. Even with the uncertainties surrounding the subacute studies, the values differ by less than a factor of two from the value obtained for the key study. Therefore, the acute ReV of 47.0 $\mu g/m^3$ based on the key study by Warheit et al. (1991) is selected.

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

The acute ReV was rounded to two significant figures at the end of all calculations. The rounded acute ReV was then multiplied by 0.3 to calculate the ^{acute}ESL. Rounding to two significant figures at the end of all calculations yields an acute ReV of 47 $\mu g/m^3$. At the target hazard quotient (HQ) of 0.3, the ^{acute}ESL is 14 $\mu g/m^3$ (Table 3).

Table 3 Derivation of the Acute ReV and ^{acute}ESL

Parameter	Summary
Study	Warheit et al. (1991)
Study population	Crl:CD BR rats (male)
Study quality	High
Exposure Methods	Inhalation
LOAEL	10 mg/m^3
NOAEL	None
Critical Effects	Increased neutrophils and lactate dehydrogenase in bronchoalveolar lavage fluid
POD_{animal}	10 mg/m^3 (LOAEL)
Exposure Duration	6 h/d
Extrapolation to 1 h	Haber's Rule n = 3
POD_{ADJ} (extrapolated 1-h concentration)	18.2 mg/m^3
POD_{HEC}	14.1 mg/m^3 (RDDR = 0.775)
Total Uncertainty Factors (UFs)	300
Interspecies UF	*3*
Intraspecies UF	*10*
LOAEL UF	*3*
Incomplete Database UF	*3*
Database Quality	*Moderate*
acute ReV [1 h] (HQ = 1)	**47 μg/m^3**
^{acute}ESL [1 h] (HQ = 0.3)	**14 μg/m^3**

3.2. Welfare-Based Acute ESLs

3.2.1 Odor Perception

There are no odors associated with silica (Mallinckrodt Chemicals 2006).

3.2.2 Vegetation Effects

No negative impacts of airborne silica were identified in plants. Therefore, no $^{acute}ESL_{veg}$ was developed.

3.3. Short-Term ESL

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

- acute ReV = 47 μg/m^3
- ^{acute}ESL = 14 μg/m^3

The short-term ESL for air permit reviews is the health-based ^{acute}ESL of 14 μg/m^3 (Table 1).

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

4.1.1 Physical/Chemical Properties and Key Study

Physical/chemical properties of silica are discussed in Chapter 3. As with acute exposure, the chronic toxicity of silica particles is related to particle size. The key study evaluated silicosis in miners exposed to silica in the size range of 0.5-5 μm. In addition, CalEPA noted that the chronic reference exposure level (REL) for silica is applicable to particles considered respirable as defined by the occupational hygiene methods described by ACGIH (≤ 4 μm), noting that this definition differs from the typical environmental definition of respirable as particles ≤ 10 μm (CalEPA 2005). Sufficiently fine (nanosized) particles are more readily diffused and translocated and probably pose less risk of fibrosis than larger particles. However, during the air permit review process, information on nanosized particles is not available. The TD would assume that nanosized particles have been included in the modeled respirable silica emissions for air permits. Therefore, the TD has chosen to apply the chronic toxicity values developed based on occupational epidemiology studies to particles ≤ 4 μm.

Both human and animal noncarcinogenic studies suggest that silicosis is the most sensitive endpoint for which data are available to support a dose-response relationship with long-term exposure to silica. Some studies have indicated possible respiratory obstruction in the absence of radiologically identifiable silicosis (Humerfelt et al. 1998, Meijer et al. 2001, and Neukirch et al. 1994). However, these studies do not provide adequate dose-response relationships upon which to base toxicity factors. A more recent evaluation of respiratory obstruction supports an association with silica exposure in the absence of silicosis (Rego 2008). However, this cross-sectional study has greater potential for selection bias than other epidemiological study designs, and the association between respiratory obstruction and silica exposure was only statistically significant at the highest exposure level (mean = 17.69 mg/m^3-yr). Therefore, this study was also rejected as the basis for developing a toxicity factor for chronic exposure to silica. Occupational exposure to silica has also been associated with kidney disease, but the data linking silica exposure and kidney disease are relatively sparse and less substantiated than the data linking silica exposure to silicosis (Steenland 2005 and McDonald et al. 2005). Additional associations

have been made between occupational exposure to silica and autoimmune disease, including systemic lupus erythematosus (Finckh et al. 2006), sarcoidosis (Rafnsson et al. 1998), and rheumatoid arthritis (Stolt et al. 2005). However, data for these endpoints are sparse and insufficient to determine a dose-response relationship.

Because chronic silicosis is the primary disease risk resulting from unprotected workplace exposure to respirable silica dust, several occupational epidemiology studies have been published. These relevant human studies were therefore reviewed and used to develop the chronic ReV. Chen et al. (2005) evaluated 4,028 tin miners, 14,417 tungsten miners, and 4,547 pottery workers for their risk of silicosis. However, the study did not provide sufficient dose-response data upon which to base a toxicity value. In another study, Churchyard et al. (2004) measured the prevalence of silicosis among 520 South African gold miners. This study reported an 18.3-19.9% incidence of silicosis, which was associated with length of service and cumulative exposure. Exposure-response curves for mean intensity of exposure were relatively flat compared to length of service, suggesting a primary role for duration of exposure within these dust levels. However, no historical dust data were available to determine cumulative lifetime exposures associated with this incidence of silicosis.

In contrast, the key and supporting studies are well-conducted and provide dose-response relationships for silicosis incidence. The occupational epidemiology study by Hnizdo and Sluis-Cremer (1993) was selected as the key study for derivation of the ReV, because quartz is the most common form of crystalline silica (IARC 1997) and the most likely form to which the general public may be exposed. This study was also used as the basis for CalEPA's chronic reference exposure level (Collins et al. 2005).

4.1.1.1 Key Epidemiological Study - Hnizdo and Sluis-Cremer (1993)

Hnizdo and Sluis-Cremer (1993) investigated the risk of silicosis in a cohort of 2,235 white, South African gold miners exposed primarily to crystalline silica as quartz. The miners had 24 years of service on average from 1940 to the early 1970s and were followed up to 1991 for radiological signs of silicosis. Cumulative dust exposure was calculated up to the onset of silicosis or the end of exposure based on the following equation:

> Cumulative dust exposure = (Σ dusty shifts x mean respirable dust concentration per shift x average # of h underground) / (270 x 8)

Average cumulative dust exposure for this cohort was 6.6 ± 2.7 mg/m^3-yr. According to Hnizdo and Sluis-Cremer (1993), the average quartz content of the dust was approximately 30%. However, Gibbs and Du Toitt (2002) indicated that the quartz exposure estimates in the report by Hnizdo and Sluis-Cremer (1993) were probably underestimated by a factor of about 1.8. Gibbs and Du Toitt (2002) estimated the actual quartz content would have been approximately 54%, rather than 30%. Silicosis was defined as a rounded radiographic opacity that reaches the International Labor Organization (ILO) category 1/1. The ILO classifies the profusion of small

opacities on a scale from 0/- to 3/+. The 1/1 classification is 5th out of twelve rankings. Radiographs were read blindly in reverse chronological order by two independent readers. The onset of silicosis was defined as the year when opacities of category 1/1 were first read. In this cohort, 313 miners (14%) developed signs of silicosis at an average age of 55.9 ± 6.9 years. The average latency period of 35 years was independent of exposure concentration below 11 mg/m^3-yr cumulative dust exposure. The risk of silicosis increased exponentially with increasing cumulative dust exposure. The dose-response relationship between silica levels and silicosis is amenable to benchmark dose (BMD) modeling for purposes of developing a chronic noncarcinogenic ReV and ESL.

4.1.1.2 Supporting Epidemiological Study - Hughes et al. (1998)

The occupational epidemiology study by Hughes et al. (1998) was selected as a supporting study for comparison of another form of crystalline silica to quartz. Hughes et al. (1998) investigated the risk of silicosis in a cohort of 2,342 Caucasian males employed in the diatomaceous earth industry exposed primarily to the cristobalite form of crystalline silica. The workers had been employed at a single plant in California for at least one year during the period between 1942 and 1987. Workers selected for the study had no known previous asbestos exposure. Estimates of exposure to respirable dust were derived from quantitative air-monitoring data. The estimated mean respirable dust and crystalline silica concentrations were 0.93 and 0.80 mg/m^3, respectively. For workers hired before 1940, average crystalline silica exposure was estimated to be 0.76 mg/m^3, compared to 0.12 mg/m^3 for workers hired after 1960. Silicosis was defined as agreement between at least 2 of 3 experienced readers of radiographic opacities reaching ILO category 1/0. There was agreement among the readers, as 5.4%, 6.2%, and 4.1% of workers were judged to be positive for opacities by each of the three readers. The median reading indicated a 4.5% prevalence of silicosis (81 out of 1,809 workers with readable x-rays were judged to be positive for opacities). The percentage of workers developing opacities differed substantially depending upon decade of hire. For workers hired before 1940, 23% (35 of 151) developed opacities. For workers hired during the installation of dust controls between 1940 and 1949, 7% (35 of 482) developed opacities. After 1950, only 1% (11 of 1,176) of workers developed opacities. In addition, none of the workers hired after 1950 had large opacities. For workers with average crystalline silica exposure less than 0.50 mg/m^3, smoking was significantly related to opacities, with 2.6% of smokers (20 out of 756) developing opacities, compared to 0.4% of non-smokers (1 out of 269).

4.1.2 MOA Analysis

When poorly soluble silica particles are inhaled, they are deposited in the lung. Silicosis/fibrosis, an inflammatory disease of the lung, is associated with the long-term inhalation of crystalline silica. Prolonged deposition of silica particles in the alveoli or bronchioles causes lung inflammation, formation of fibrotic scar tissue, and degradation of the mucociliary escalator. Castranova (2000) proposed four possible mechanisms for the initiation and progression of chronic silicosis: 1) direct cytotocity, 2) stimulation of oxidant production by alveolar

macrophages, 3) activation of mediator release from alveolar macrophages and/or alveolar epithelial cells, and 4) secretion of growth factors for alveolar macrophages and/or alveolar epithelial cells. Thus, chronic inflammation may be necessary, but is not sufficient for fibrosis, rather, improper repair of damaged lung tissue is essential for fibrosis. As with acute inflammation, it is assumed that a certain amount of silica is required to initiate and sustain the chronic inflammation required to develop silicosis. Therefore, a nonlinear, threshold dose-response is assumed for the development of fibrosis.

4.1.3 Dose Metric

Risk of silicosis strongly correlates with cumulative silica exposure. Correlations have also been shown between length of employment in many dusty industries and risk of silicosis (NIOSH 2002). Churchyard et al. (2004) also noted an association between mean intensity of exposure and silicosis risk. However, this association was relatively weak; indicating that cumulative exposure over time provides a better indicator of risk. Therefore, cumulative exposure was used as the dose metric in this evaluation.

4.1.4 PODs for Key and Supporting Studies

4.1.4.1 Key Study

Appendix 3A provides a summary of information used to perform benchmark dose modeling of the Hnizdo and Sluis-Cremer (1993) silicosis data using EPA's benchmark dose modeling software (version 1.4.1b). Briefly, the Hnizdo and Sluis-Cremer (1993) data were entered according to the table in Appendix 3A, which is adapted from Table IV in the original publication. The benchmark concentration low_{01} ($BMCL_{01}$) is the 95% lower bound estimate of the concentration at which 1% of the population develops silicosis. Section 2.6 of the ESL Guidelines (TCEQ 2006) indicates that the level of benchmark response (BMR) selected should be the lowest dose level that can be supported by the data. The benchmark response of 1% or BMR_{01} was within the range of the data from the large-scale study by Hnizdo and Sluis-Cremer (1993). Therefore, the data were modeled at a 1% benchmark response. As noted in Appendix 3A and summarized in Table 4, there are three models (log-probit, log-logistic, and multistage) that fit the data with a p-value greater than 0.1. The scaled residuals for the three models are all less than the absolute value of two, and visual inspection of the model fits in the low-dose region indicates that these models fit well. However, the Akaike Information Criteria (AIC) values for the models are separated by more than a value of 2 (Table 4 and Appendix 3A). Therefore, the model with the lowest AIC value (log-probit) was selected as the best fitting model. The $BMCL_{01}$ value of 0.635 mg/m^3-yr from the log-probit model represents the cumulative silica concentration associated with a 1% response level and is the occupational POD (POD_{OC}) used for derivation of the chronic ReV.

There is little difference between $BMCL_{01}$ values from the different models in Table 4. The values range from 0.422 mg/m^3-yr (highest AIC) to 0.635 mg/m^3-yr (lowest AIC)] implying that

the difference between the largest or smallest estimate in Table 4 and the best parameter that can be estimated from those four points is less than a factor of 1.5. The ratio between the BMC_{01} and $BMCL_{01}$ for all models were less than 1.2 fold. This indicates model uncertainty is low. The scaled residuals at the estimated response closest to the BMR_{01} from the log-probit model were much lower than the other models, thus supporting the $BMCL_{01}$ results from the log-probit model.

Table 4 BMC Modeling Parameters from Hnizdo and Sluis-Cremer (1993)

BMDS Model	BMC_{01}	$BMCL_{01}$	p-value for fit	AIC	Scaled Residuals *
Log Probit	0.734	0.635	0.9957	1512	-0.167
Gamma	0.646	0.537	0.8546	1515	-0.710
Log Logistic	0.620	0.519	0.8446	1515	-0.825
Multistage	0.485	0.422	0.5017	1517	-0.886

*Scaled residuals at estimated response closest to the BMR_{01}

The $BMCL_{01}$ value of 0.635 mg/m^3-yr was based on the estimates of cumulative (respirable) dust exposure for the cohort of gold miners assuming the dust contained an average quartz content of approximate 30%. However, according to Gibbs and Du Toitt (2002), the actual quartz content would have been approximately 54%, rather than the 30% (see Section 4.1.1.1). Therefore, it would be more appropriate to multiply the $BMCL_{01}$ value of 0.635 mg/m^3-yr by a ratio of 54/30. Accordingly, the adjusted $BMCL_{01}$ value is 1.143 mg/m^3-yr and was used as a $POD_{OC\ ADJ}$.

4.1.4.2 Supporting Study

Appendix 3B provides a summary of information used to perform benchmark dose modeling on the silicosis data from the Hughes et al. (1998) study. Briefly, the Hughes et al. (1998) data were entered according to the table in Appendix 3B, which were obtained using the raw data provided by Dr. Harvey Checkoway (author) via Robert Park (Centers for Disease Control and Prevention). The large-scale study by Hughes et al. (1998) had sufficient power to calculate the $BMCL_{01}$. As noted in Appendix 3B and summarized in Table 5, there are six models (log probit, log logistic, gamma, Weibull, multistage, and quantal linear) that fit with a p-value greater than 0.1. The absolute value of the scaled residuals does not vary greatly from 1, and visual inspection of the model fits in the low-dose region indicates that all models fit well. The log probit model has the lowest AIC value. Therefore, the $BMCL_{01}$ value obtained for the log probit model (0.791 mg/m^3-yr) represents the cumulative silica concentration associated with a 1% response level.

Table 5 BMC Modeling Parameters from Hughes et al. (1998)

BMDS Model	BMC_{01}	$BMCL_{01}$	p-value for fit	AIC	Scaled Residual*
Log Probit	1.20	0.791	0.8116	529.9	0.100
Log Logistic	0.891	0.523	0.6554	531.5	0.149
Gamma	0.848	0.455	0.5508	532.5	0.142
Weibull	0.737	0.411	0.4844	533.2	0.169
Multistage	0.932	0.781	0.3099	535.2	0.206
Quantal Linear	0.357	0.291	0.2743	535.3	0.330

* Scaled residuals at estimated response closest to the BMR_{01}

4.1.5 Dosimetric Adjustments

Using the BMCLs from the key study (Hnizdo and Sluis-Cremer 1993) and the supporting study (Hughes et al. 1998), the $PODs_{OC\ ADJ}$ were adjusted to PODs applicable to the general population (POD_{HEC}) using the following dosimetric adjustments:

Hnizdo and Sluis-Cremer (1993) key study:

Cumulative POD_{HEC} = Cumulative $POD_{OC\ ADJ}$ x (VE_{ho}/VE_h) x (shifts per $year_{oc}$/days per $year_{res}$)

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

VE_h = non-occupational ventilation rate for a 24-h day (20 m^3/day)

shifts per $year_{oc}$ = yearly occupational exposure frequency (study specific)

days per $year_{res}$ = yearly residential exposure frequency (365 days per year)

Cumulative POD_{HEC} = 1.143 mg/m^3-yr x (10/20) x (270/365) = 0.423 mg/m^3-yr

Yearly occupational exposure frequency and yearly residential exposure frequency were used for the Hnizdo and Sluis-Cremer (1993) study, because this allowed for extrapolation from POD_{OC} to the POD_{HEC} based on the specific working patterns of the occupational cohort.

Hughes et al. (1998) supporting study:

Cumulative POD_{HEC} = Cumulative $POD_{OC\ ADJ}$ x (VE_{ho}/VE_h) x (days per $week_{oc}$/days per $week_{res}$)

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

VE_h = non-occupational ventilation rate for a 24-h day (20 m^3/day)

days per $week_{oc}$ = yearly occupational exposure frequency (5 days per week)

days per $week_{res}$ = yearly residential exposure frequency (7 days per week)

Cumulative POD_{HEC} = 0.791 mg/m^3-yr x (10/20) x (5/7) = 0.282 mg/m^3-yr

Crystalline silica is insoluble, the clearance rate from the lungs is slow, and the toxic effects are cumulative (See Section 4.1.2). In addition, fibrosis may be a necessary precursor to the development of cancer, as discussed in Section 4.2.2. Therefore, the TD chose to conservatively convert cumulative mg/m^3-yr to an average yearly lifetime exposure concentration over a 70 year lifetime applicable to the general public, rather than using the average exposure experienced by the workers in the key study. This adjustment is shown in the following calculations:

POD_{HEC} = Cumulative POD_{HEC}/Lifetime Exposure Duration

Hnizdo and Sluis-Cremer (1993) POD_{HEC} = 0.423 mg/m^3-yr/70 yr = 0.00604 mg/m^3 = 6.04 μg/m^3

Hughes et al. (1998) POD_{HEC} = 0.282 mg/m^3-yr/70 yr= 0.00403 mg/m^3 = 4.03 μg/m^3

4.1.6 Critical Effect and Adjustments to the POD_{HEC}

4.1.6.1 Critical Effect

Data from both human and animal noncarcinogenic studies suggest that silicosis is the most sensitive endpoint for exposure to crystalline silica. The specific critical effect for the key study (Hnizdo and Sluis-Cremer 1993) is silicosis in gold miners in relation primarily to quartz exposure, supported by Hughes et al. (1998), which reported silicosis risk among diatomaceous earth workers in relation primarily to cristobalite exposure. The POD_{HEC} values from both studies are similar, and the UFs applied to both studies are identical (Section 4.1.6.2).

4.1.6.2 UFs

Determining a POD and applying appropriate UFs (i.e., assuming a threshold/nonlinear MOA) is the default for noncarcinogenic effects. Therefore, the following UFs were applied to the POD_{HEC} of 6.04 μg/m^3 for the key study (Hnizdo and Sluis-Cremer 1993) and 4.03 μg/m^3 for the supporting study (Hughes et al. 1998) to derive the chronic ReV: 1 for UF_L, 3 for UF_H, and 1 for UF_D (total UF = 3). Choice of UFs is discussed below.

A UF_L of 1 was used because benchmark dose modeling at a 1% response rate was used, and the $BMCL_{01}$ was considered to be a NOAEL surrogate.

The TD applied a UF_H of 3 to account for variability within the human population. The Barnes et al. (1995) summary of a benchmark dose workshop indicates that the UF for a BMD obtained from human data could be set equal to one if the study included an assessment of sensitive subpopulations. The workers included in the Hnizdo and Sluis-Cremer (1993) and Hughes et al. (1998) studies did not include sensitive subpopulations. Therefore, a UF of 1 was not considered appropriate. However, variability in healthy adults was likely captured in the key and supporting

studies due to the large cohort sizes. Studies evaluating possible gender differences are contradictory, two indicating that women may be more susceptible to the effects of silica than men (Fillmore et al. 1999 and Zitting et al. 1996) and two indicating no difference in susceptibility (Gerhardsson and Ahlmark 1985 and Rastogi et al. 1991). Importantly, a 1% response rate was modeled using the available occupational data. The resulting toxicity factor based on occupational exposure is therefore considered to be conservative by the TD. In addition, the cumulative occupational exposure was adjusted to a lifetime exposure of 70 years. Finally, because silica particles are not metabolized, it is not necessary to consider possible kinetic variability in metabolism, although it is important to consider the possible effects of underlying respiratory disease on inflammation and respiratory damage. As a result, a moderate UF of 3 was applied to account for susceptibility in the general population.

No subchronic-to-chronic UF was needed for either study, since the mean exposure durations were 24 years for Hnizdo and Sluis-Cremer (1993) and 12 years for Hughes et al. (1998). These average exposure durations exceed 10% of an average lifespan and are therefore considered chronic. Moreover, the POD was adjusted to a 70-year lifetime.

The toxicological database for crystalline silica is extensive. Although there is evidence of systemic effects resulting from crystalline silica exposure, silicosis is the most sensitive endpoint. Therefore, a database UF of 1 was applied to the POD_{HEC}.

4.1.7 Health-Based Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

As discussed in the previous section, UFs were applied to the POD_{HEC} to derive the chronic ReV:

Hnizdo and Sluis-Cremer (1993)

$$\text{chronic ReV} = POD_{HEC} / (UF_L \times UF_H \times UF_D) = 6.04\ \mu g/m^3 / (1 \times 3 \times 1) = 2.01\ \mu g/m^3$$

Hughes et al. (1998)

$$\text{chronic ReV} = POD_{HEC} / (UF_L \times UF_H \times UF_D) = 4.03\ \mu g/m^3 / (1 \times 3 \times 1) = 1.34\ \mu g/m^3$$

The ReV from the key study is similar to the ReV from the supporting study. Rounding the results from the key study to two significant figures at the end of all calculations yields a chronic ReV of 2.0 $\mu g/m^3$. At the target HQ of 0.3, the $^{chronic}ESL_{nonlinear(nc)}$ is 0.60 $\mu g/m^3$ (Table 6).

Table 6 Derivation of the Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

Parameter	Summary
Study	Hnizdo and Sluis-Cremer 1993
Study Population	2,235 gold miners
Study Quality	High
Exposure Method	Occupational
Critical Effects	Silicosis
POD_{OC} ($BMCL_{01}$)	0.635 mg/m^3-yr
$POD_{OC\ ADJ}$ ($BMCL_{01\ ADJ}$)	1.143 mg/m^3-yr
Exposure Duration	270 d/yr
Extrapolation to continuous lifetime exposure (POD_{HEC})	6.04 μg/m^3
Total UFs	3
Interspecies UF	*1*
Intraspecies UF	*3*
LOAEL UF	*1*
Subchronic to chronic UF	*1*
Incomplete Database UF	*1*
Database Quality	*High*
chronic ReV (HQ = 1)	**2.0 μg/m^3**
$^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3)	**0.60 μg/m^3**

4.1.8 Comparison of Results

The key and supporting studies investigated the risk of silicosis associated with exposure to two different forms of crystalline silica, quartz (Hnizdo and Sluis-Cremer 1993) and cristobalite (Hughes et al. 1998). The chronic ReVs calculated based on the POD_{HEC} values from these studies are very similar (2.0 versus 1.3 μg/m^3). The chronic ReV of 2.0 μg/m^3 based on Hnizdo and Sluis-Cremer (1993) is expected to be health-protective and conservative since the modeling was conducted using a 1% benchmark response. Additionally, this value is slightly lower than the chronic REL of 3 μg/m^3 derived for this study by CalEPA (Collins et al. 2005), primarily due to the TCEQ's decision to extrapolate the occupational dust exposures to a 70-year lifetime exposure.

4.2 Carcinogenic Potential

4.2.1 Carcinogenic Weight-of-Evidence

4.2.1.1 Human Studies

There have been up to 70 epidemiological studies investigating the relationship between silica exposure and lung cancer in various occupations: 22 studies investigated by the International Agency for Research on Cancer (IARC) in 1997 and about 50 studies identified by Pelucchi et al. (2006) that were published after the IARC Monograph. The carcinogenic potential of silica is controversial. Some studies have found a statistically significant association between occupational exposure to silica and lung cancer, whereas others have not. The differences in the studies may be related to the following:

- IARC (1997) noted that the carcinogenicity of quartz or cristobalite "may be dependent on inherent characteristics of the crystalline silica or on external factors affecting its biological activity or distribution of its polymorphs." Quartz is a variable entity (Donaldson and Borm 1998) and its toxicity may depend upon surface characteristics, the age of the crystalline silica particle, and other factors. It is not surprising that epidemiological analyses of exposure to silica in some cohorts have found a statistically significant association, whereas others have not. Steenland et al. (2001) suggests that physical differences in silica, such as freshness of particle cleavage or degree of coating with dust, may contribute to the different relative risks (RRs) observed among different cohorts after exposure to silica.
- Steenland et al. (2001) concluded that silica appeared to be a weaker carcinogen than other lung carcinogens such as metals measured on the same ''per weight'' basis (i.e., cadmium, arsenic, nickel, and hexavalent chromium). The RRs observed in epidemiological studies generally range close to a value from 1 up to 2 to 3.
- Checkoway and Franzblau (2000) discuss other reasons for discrepancies between studies (e.g., confounding by cigarette smoking, use of silicosis compensation registers).

4.2.1.1.1 International Agency for Research on Cancer (IARC)

Silica has been classified as carcinogenic to humans by IARC (1997) and as a suspected human carcinogen by the ACGIH. IARC reviewed the existing occupational epidemiology data available at the time of the review. Twenty-two studies evaluating lung cancer mortality among silica-exposed workers in the ore mining industry were considered. However, only a few of these studies evaluated potential confounding by other known respiratory carcinogens.

The IARC working group noted that carcinogenicity was not detected in all industrial settings studied (Wilbourn et al. 1997). For example, two studies from refractory brick plants and one study from a diatomaceous earth plant provided evidence of an increased overall RR of lung cancer of 1.5. There were conflicting results from two large cohort studies performed in foundry

workers, and a third study in foundry workers found a slightly elevated risk of lung cancer in silicotics compared to non-silicotics. Consistent with the possibility that lung cancer is secondary to silicosis, studies reported excess lung cancer among registered silicotics across countries, industries, and time periods.

Although the studies evaluated provided conflicting results, the IARC working group determined that "overall the epidemiological findings support increased lung cancer risks from inhaled crystalline silica (quartz and cristobalite) resulting from occupational exposure." Importantly, the IARC working group noted that adequate evidence of carcinogenic potential exists only for occupational exposures to crystalline silica. No epidemiological studies were available on environmental exposures at the time of their evaluation. Epidemiological data were limited for amorphous silica, and separate analysis for cancer risk among the subset of diatomaceous earth workers exposed primarily to amorphous silica was not conducted by IARC (1997). The IARC working group concluded that there is inadequate evidence in humans and experimental animals for the carcinogenicity of amorphous silica and other non-crystalline silica.

4.2.1.1.2 National Institute of Occupational Health and Safety

In 2002, the National Institute of Occupational Health and Safety (NIOSH) reviewed the IARC classification. Ten studies were identified by IARC (1997) that provided the least confounded investigations of an association between occupational exposure to crystalline silica and lung cancer. Although a few of these ten studies did not find a statistically significant association between occupational exposure to crystalline silica and lung cancer, most of the studies did. In addition, some of the least confounded studies reported that lung cancer risk tended to increase for (refer to NIOSH 2002 for references):

- cumulative exposure to respirable silica (i.e., Checkoway et al. 1993, 1996)
- duration of exposure (i.e., Merlo et al. 1991; Partanen et al. 1994 ; Costello and Graham 1988 ; Costello et al. 1995 ; Dong et al. 1995)
- peak intensity of exposure (Burgess et al. 1997; Cherry et al. 1997; McDonald et al. 1997)
- the presence of radiographically defined silicosis (Amandus et al. 1992; Dong et al. 1995), and
- length of follow up time from data of silicosis diagnosis (Partanen et al. 1994)

NIOSH concurred with the following conclusions of the IARC working group and ATS (1997) and recommended that crystalline silica be considered a potential occupational carcinogen (54 Fed. Reg. 2521 1989):

- "The available data support the conclusion that silicosis produces increased risk for bronchogenic carcinoma

- Less information is available for lung cancer risk among silicotics who never smoked and workers who were exposed to silica but did not have silicosis
- Whether silica exposure is associated with lung cancer in the absence of silicosis is less clear."

4.2.1.1.3 Findings from Recent Meta-Analysis and Pooled Analysis

4.2.1.1.3.1 Relative Risks in Silicotics (Steenland and Stayner 1997)

This summary was obtained from NIOSH (2002):

> "Steenland and Stayner (1997) and IARC (1997) found that the majority of studies of silicotics reported statistically significant excess lung cancer risks across different countries, industries, and time periods while controlling for the effects of cigarette smoking (Steenland and Stayner 1997; IARC 1997). Exposure-response gradients were also observed. The summary RR was 2.3 (95% CI=2.2–2.6) for 19 cohort and case control studies of silicotics - excluding studies of miners and foundry workers because of potential exposure to other carcinogens, and omitting autopsy studies and proportionate mortality studies because of possible selection biases (Steenland and Stayner 1997). Fifteen of the 19 studies directly or indirectly controlled for the effects of smoking. The summary RR of 16 cohorts (cohort size ranged from 969 to 6,266 workers) and case-control studies of silica-exposed workers was 1.3 (95% CI= 1.2–1.4)—a moderate and statistically significant RR estimate (Steenland and Stayner 1997). Eight of the 16 studies controlled for the effects of smoking, either directly or indirectly."

4.2.1.1.3.2 Relative Risks in Silicotics (Smith et al. 1995)

Smith et al. (1995) investigated lung cancer risks in epidemiologic studies of silicotics. After adjustment for competing risks (i.e. risks of different causes of death, including silicosis itself), all 29 studies demonstrated lung cancer RR estimates greater than one. The pooled RR estimate for the 23 studies that could be combined was 2.2, with a 95% CI of 2.1-2.4. The pooled estimates by study design were:

- 2.0 (95% CI = 1.8-2.3) for cohort studies;
- 2.5 (95% CI = 1.8-3.3) for case-control studies;
- 2.0 (95% CI = 1.7-2.4) for combined proportional mortality studies; and
- 2.7 (95% CI = 2.3-3.2) for studies of cancer incidence.

Smith et al. (1995) concluded that "Although statistical tests demonstrated heterogeneity between studies, and the CIs given above may therefore be a little too narrow, the overall findings could not be attributed to chance, confounding by smoking, or other sources of

bias. We conclude that the association between silicosis and lung cancer is causal, either due to silicosis itself, or due to a direct effect of the underlying exposure to silica."

4.2.1.1.3.3 Relative Risks in Silicotics (Tsuda et al. 1997)

Tsuda et al. (1997) conducted a meta-analysis using 32 eligible studies on the relationship between silicosis/pneumoconiosis and lung cancer mortality in Japan. Study estimates were then pooled by using both the fixed effect model and the random effect model. All studies showed an excess of lung cancer mortality among people with silicosis/ pneumoconiosis. The estimated rate ratio was 2.74 (95% CI 2.60-2.90) in all 32 studies, and 2.77 (2.61-2.94) in 25 cohort studies. Tsuda et al. (1997) concluded:

> "The estimates in the Japanese studies were a little higher than the overall estimates, which indicated that lung cancer mortality was about three times higher among silicotic patients than among people in the control. This indicated a causal-relationship between silicosis and lung cancer. This means that lung cancer should be regarded as one of the important complications of silicosis/pneumoconiosis. We recommend further research on the relationship."

4.2.1.1.3.4 Pooled Exposure-Response Analyses (Steenland et al. 2001; 2005)

Steenland et al. (2001), as part of an IARC multicentre study, conducted a pooled exposure-response analyses and risk assessment for lung cancer in 10 cohorts of silica-exposed workers, which included 65,980 workers and 1072 lung cancer deaths. Respirable crystalline collected for workers in these studies are collected by personal dust collector for particles smaller than 5 μm in diameter (NIOSH 1974). Follow-up was extended for five of these cohorts beyond the published data. 't Mannetje et al. (2001) adopted, modified, or developed quantitative exposure estimates by job and calendar time to permit common analyses by respirable silica (mg/m^3) across cohorts. There was a positive monotonic trend with odds ratios increasing from 1.0, 1.0, 1.3, 1.5, and 1.6 using categorical analyses by quintile of cumulative exposure. At the permissible level in many countries for silica of 0.1 mg/m^3 silica, the estimated excess lifetime risk (through age 75) of lung cancer for a worker exposed from age 20 to 65 was 1.1-1.7% above background risk of 3-6%. (In 2005, Steenland noted that for the South African cohort, exposures were underestimated, causing an overestimate of the exposure-response coefficient (Steenland et al. 2005)). The investigators concluded that silica appeared to be a weaker carcinogen than other lung carcinogens such as metals measured on the same ''per weight'' basis (i.e., cadmium, arsenic, soluble nickel, and hexavalent chromium). However, the Steenland et al. (2001) dose-response analyses supported the IARC classification of silica as a carcinogen and was the first quantitative exposure-response analysis and risk assessment for silica using data from multiple studies.

It was not believed that confounding by smoking was likely to account for the results, since in those studies where complete or partial smoking data were collected and considered, either little

confounding of exposure-response trends was observed or smoking was actually a negative confounder.

There were no data on silicosis morbidity in most cohorts so there was no attempt to analyze the effect of silicosis on lung cancer risk, independent of silica exposure levels (Steenland et al. 2001). However, in 2005, Steenland et al. reviewed the available exposure-response data for silica and silicosis, lung cancer, and renal disease. They compared the corresponding excess risks (or absolute risks in the case of silicosis) of death or disease incidence by age 75 for these three diseases, subsequent to a lifetime (45 years) of exposure to silica at the current US standard (0.1 mg/m^3 respirable crystalline silica). They concluded:

> "It has been speculated that the risk of lung cancer among the silica-exposed is restricted to those who develop silicosis, or that silicosis is a risk factor for lung cancer independent of exposure (Checkoway and Franzblau, 2000). Silicosis is a marker of high exposure, and it is therefore logical—under the assumption that silica per se increases lung cancer risk— that silicotics would have higher risk than nonsilicotics, even absent any independent role for silicosis. Existing epidemiologic data is not, and probably never will be, sufficient to disentangle this issue (Checkoway and Franzblau, 2000). One would need very good longitudinal data on exposure and silicosis throughout the follow-up period in a large cohort; existing data to date have not been sufficient."

4.2.1.1.3.5 Comparison of Relative Risks in Silicotics versus Non Silicotics (Pelucchi et al. 2006)

Pelucchi et al. (2006) conducted a systematic review of approximately 50 studies that had been published since 1996 (i.e., published after the IARC Monograph), on the relation between occupational silica exposure and lung cancer. There were 28 cohort studies, 15 case-control and two proportionate mortality ratio studies. Their results indicated:

- The pooled RR of lung cancer, calculated using random effects models from all cohort studies considering occupational exposure to silica was 1.34 [95% CI: 1.25, 1.45];
- The pooled RR for all case-control studies was 1.41 [95% CI: 1.18, 1.70]; and
- For all proportionate mortality ratio studies, the RR was 1.24 [95% CI: 1.05, 1.47].

Pelucchi et al. (2006) also investigated RRs in (1) workers with silicosis, (2) when silicosis status was undefined, and (3) in non silicotic subjects:

- For cohort studies, the RRs were:
  - 1.69 (95% CI: 1.32, 2.16) in 11 studies in silicotics only,
  - 1.25 (95% CI: 1.18, 1.33) in 24 studies where silicosis status was undefined and
  - 1.19 (95% CI: 0.87, 1.57) in one study among nonsilicotic subjects.

- In case-control studies, the RRs were:
    - 3.27 (95% CI: 1.32, 8.2) in one study in silicotics only;
    - 1.41 (95% CI: 1.18, 1.70) in 13 studies where silicosis status was undefined; and
    - 0.97 (95% CI: 0.68, 1.38) in one study among nonsilicotic subjects.

Based on a very limited number of studies for non silicotic workers (i.e., one cohort study and one case-control study), Pelucchi et al. (2006) concluded:

> "In this re-analysis, the association with lung cancer was consistent for silicotics, but the data were limited for non silicotic subjects and not easily explained for undefined silicosis status workers. This leaves open the issue of dose-risk relation and pathogenic mechanisms and *supports the conclusion that the carcinogenic role of silica per se in absence of silicosis is still unclear*." (italics added for emphasis)

4.2.1.1.3.6 Comparison of Relative Risks in Silicotics versus Non Silicotics (Erren et al. 2008)

Erren et al. (2008) conducted a meta-analytical approach to answer the question "Is silicosis a necessary condition for the elevation of silica-associated lung cancer risks?" The results are as follows:

- There was a significant link between silicosis and lung cancer based on 38 eligible studies of silicotics published until January 2007. RRs averaged 2.1 in analyses based on both fixed and random effect models ((95% CI = (2.0–2.3) and (1.9–2.3), respectively)).
- There were only three studies of lung cancer in silica-exposed workers without silicosis that had data that allowed for adjustment for smoking habits. The pooled RR estimate from the three studies was 1.0 (95% CI = (0.8–1.3)).
- There were eight studies of lung cancer in silica-exposed workers without silicosis, with no adjustment for smoking habits. Analyses from the eight studies suggested a marginally elevated risk of lung cancer (RR = 1.2; 95% CI (1.1–1.4)), but with significant heterogeneity between studies ($P \approx 0.05$).
- There was a 20% increased risk based on the summary RRs from the 11 relevant studies of non silicotics, but differences between study-specific results were not easily attributable simply to sampling variability. These results were heavily dependent on results from eight studies that had not been adjusted for possible confounding by smoking.

Erren et al. (2008) stated: "But as for the main issue, the hypothesised association between lung cancer and exposure to silica in the absence of silicosis, *our efforts have failed to resolve the matter unambiguously."* (italics added for emphasis)

4.2.1.2 Animal Studies

Based on animal studies, IARC (1997) concluded that evidence was sufficient to show that crystalline silica causes cancer in experimental animals. Studies in rats, mice, and hamsters after exposure to crystalline silica are discussed by Rabovsky (1997) and Saffiotti et al. (1993). Rabovsky noted that markers of silica induced toxicity in experimental animals were similar to those exhibited by humans. In fact, animals may provide a model for resistant human populations (Rabovsky 1997; Saffiotti et al. 1993).

Rats develop tumors whereas mice and hamsters do not. Saffiotti et al. (1993) noted that lung tumors in rats are seen only when there is also a fibrotic response:

> "The cells that give rise to lung tumors induced by crystalline silica in the rat lung model are the epithelial cells of the lining of the alveoli. Normal lung alveolar lining cells, which are flat and thin, permit gaseous exchanges with the adjacent blood capillaries and are called alveolar type I cells. A few cells in the normal alveolar lining are cuboidal and contain lamellar bodies (round cytoplasmic organelles, which produce the pulmonary surfactant). These cells are called alveolar type II cells and are the stem cells (or progenitor cells) that divide and differentiate into type I cells. When exposed to crystalline silica, alveolar type II cells become larger and proliferate (hyperplasia) (Miller et al. 1986). In silica-treated rats, hyperplasia of the alveolar type II cells develops adjacent to the silicotic granulomas. This hyperplasia gives rise to (1) adenomatoid (i.e., "glandular-like") lesions, showing many contiguous alveoli lined by cuboidal cells, and eventually to (2) tumors, including benign adenomas and malignant carcinomas."

Jin et al. (2008) established a silicosis model in rats using single intratrachael admininistration to investigate the critical molecular mechanisms in the development of pulmonary fibrosis by using identification of differentially expressed genes by suppression subtractive hybridization analysis. Typical microscopic fibrosing silicotic nodules formed in the lung. Alveolar epithelial cells and bronchial epithelial cells proliferated around partial fibrosing silicotic nodules and some cells showed atypical hyperplasia. The atypical hyperplasia suggested a correlation between silicosis and lung cancer. Diffused pulmonary interstitial fibrosis was also observed. Jin et al. (2008) concluded "These results revealed that fibrotic reaction of recurrent inflammation and repair may cause repeat cellular injury, genetic damage to local epithelial cells, and a predisposition to the development of cancer through sequential cellular morphologic alterations of atypia (Daniels and Jett 2005; Bouros et al. 2002)."

After single intratracheal administration, hamsters store the silica in macrophages, but do not develop a fibrotic response nor do they develop lung tumors. Mice do not develop persistent epithelial hyperplasia or lung tumors after single intratracheal administration of quartz or tridymite. Mice do develop fibrosis although less fibrosis when compared to rats.

Saffiotti et al. (1993) hypothesized that in humans, host susceptibility differences may explain different susceptibilities, similar to the responses in rodent species:

- Some humans may respond to exposure to silica by developing fibrosis and lung cancer;
- others may respond as mice (i.e., develop moderate fibrosis but no lung cancer); and
- others may respond as hamsters, (i.e., be resistant to both silica-induced fibrosis and lung cancer).

Although animal data indicate that tumor formation may be secondary to silicosis, in most cases, only one dose was used in animal studies. Rabovsky (1997) indicates the temporal and dose-response relationships linking the two endpoints are unknown.

4.2.1.3 WOE Classifications

As mentioned previously, IARC (1997) has classified silica in Group 1, as chemicals and groups of chemicals which are casually associated with cancer in humans. Based on a review of epidemiological data and animal data, and according to guidance in the new cancer guidelines (USEPA 2005a), the TD considers crystalline silica to be "Carcinogenic to Humans" via inhalation. Consistent with IARC (1997), the TD acknowledges that the carcinogenicity of silica "may be dependent on inherent characteristics of the crystalline silica or on external factors affecting its biological activity or distribution of its polymorphs." (IARC 1997).

4.2.2 Carcinogenic Mode of Action

As early as 1984, Saffiotti et al. proposed a working hypothesis for carcinogenesis for crystalline silica. This working hypothesis was proposed at the 1984 meeting on "Silica, Silicosis and Cancer (Saffiotti, 1986), and modified by recent updates in Saffiotti et al. (1993):

> "a) cell mediators, released by silicotic granulomas (from macrophages and other cells), include cytokines, such as interleukin-1 (IL-1), tumor necrosis factor-α (TNF- α) and transforming growth factor-β (TGF- β), mast cell products and oxygen radicals; some of these mediators act upon the adjacent epithelial cells of the distal airways and induce cell injury and/or cell proliferation, on a continuous basis.
>
> b) Crystalline silica-induced hyperplastic epithelial cells also produce mediators (e.g., TGF-β), that stimulate fibrogenesis (feedback effect).
>
> c) Crystalline silica penetrates into alveolar cells and causes DNA damage and/or chromosomal alterations, directly and/or through oxygen radicals.
>
> d) The combined effects of direct genetic damage to target epithelia and their chronic stimulation by cell mediators produced during fibrogenesis can account

> for crystalline-silica-induced carcinogenesis in pulmonary epithelia of susceptible hosts."

Although the exact MOA for the carcinogenic effects of silica are not known, and the scientific community have not agreed on the key steps leading from silica exposure to lung tumors in humans, the most likely steps are those proposed by Saffiotti et al. (1993). The MOA for silica may be similar to other agents that cause interstitial lung disease. In humans, Bouros et al. (2002) found that various causes of interstitial lung disease, including fibrosis, are correlated with a higher incidence of lung malignancy, although the exact role of fibrosis as a predisposing factor for the development of malignancy is unclear. Daniels and Jett (2005) state that the evidence supports an increased risk of lung cancer due to specific fibrotic and inflammatory lung diseases. The potential pathogenetic mechanisms indicate that recurrent injury and inflammation result in genetic alterations that predispose to lung cancer.

In the case of silica, there is limited evidence that silica interacts directly with DNA (Saffiotti et al. 1993; Rabovsky 1997; Daniel et al. 1995) although Jacobsen et al. (2007) did not find evidence of an interaction of silica with DNA, as discussed below.

4.2.2.1 Interactions with DNA (Potential Linear MOA)

Quartz exposures have generally yielded negative results in gene mutation assays, especially at low doses (Lewinson et al. 1994, Jacobsen et al. 2007, Nagalakshmi et al. 1995, and Pairon et al. 1990). However, increased gene mutation and DNA damage have also been documented following exposure to quartz or tridymite, particularly at high doses (Driscoll et al. 1997, Fanizza et al. 2007, Pairon et al. 1990, and Nagalakshmi et al. 1995). Changes at the chromosome level have been observed by Sobti and Bhardwaj (1991) (as reported in Rabovsky 1997). Sobti and Bhardwaj (1991) observed an increased level of chromosome aberrations in a study of workers exposed to stone dust (in which silica represented 50-60% of the total contents) when compared to controls. These increases could not be accounted for by cigarette smoking or alcohol consumption. These investigators also noted that sister chromatid exchange occurred, but the correlation between exposure and sister chromatid exchanges was weaker than that for chromosome aberrations.

Saffiotti et al. (1993) and Daniel et al. (1995) observed silica-induced double strand breaks in isolated DNA. Daniel et al. (1995) noted small particles in the nuclei and mitotic spindles of alveolar epithelial cells exposed to quartz in cell culture, indicating the possibility that these particles interact directly with DNA. These researchers provided further evidence of a direct interaction between silica and the phosphate backbone of DNA using infrared spectroscopy. The authors noted that the direct interaction of silica with DNA may promote carcinogenesis by anchoring DNA close to sites of free radical production or interfering with DNA replication or repair. However, Jacobsen et al. (2007) recently found that incubation of Muta^{TM} mouse lung epithelial cells with quartz did not increase the number of DNA strand breaks or significantly

increase the mutation frequency of the *cII* or *lacZ* transgenes. Instead, indirect mechanisms may be responsible for the carcinogenic effects of silica.

4.2.2.2 Recent Evidence for Indirect Mechanisms (Potential Nonlinear MOA)

Evidence appears to support an indirect mechanism associated with increased cell proliferation. Ding et al. (2002) proposed that silica activates mitogen activated protein kinases (MAPKs), leading to activation of the activating protein-1 (AP-1) transcription factor. These events are associated with cell proliferation and may contribute to cellular proliferation of cells with altered DNA if activated chronically. The role of this pathway is supported by data from Shen et al. (2006) which indicate that the expression of cell cycle regulating proteins, cyclin D1 and cyclin D kinase 4 (CDK4), is induced by the MAPK/AP-1 signaling pathway in human embryonic lung fibroblasts. This indirect mechanism is supported by the detection of increased p53 protein, a tumor suppressor gene that plays an important role in the negative regulation of cell growth, in the sputum of workers exposed to high levels of silica for an average of 13 years compared to unexposed workers (Shaham et al. 2007).

4.2.2.3 Klein and Christopher (1995) (Potential Nonlinear MOA)

Klein and Christopher (1995) concluded that lung cancer is secondary to the development of fibrotic lesions and that silica should therefore be considered a threshold carcinogen. The authors noted three postulated mechanisms to explain the co-dependence of fibrogenesis and carcinogenicity:

- fibrosis causes disorganization of the lung that leads to cytokine release which can cause chronic dysplasia, increased cell proliferation, and an increased chance of survival for mutated cells;
- increased fibrosis may reduce the lung's ability to clear other bioactive agents and increase the chances that these agents will interact with susceptible cells; and
- pulmonary macrophages, which scavenge particles in the lungs, release cytokines when damaged that may set off autoimmune reactions which may accelerate fibrotic changes and/or proliferation of mutated cells (Klein and Christopher 1995).

Klein and Christopher (1995) did consider the direct action of silica on cellular DNA, and concluded "there is some evidence that crystalline silica has the ability to enter the cell nucleus and interact directly with DNA under *in vitro* conditions but, as yet, there is no evidence that these events occur *in vivo* and little evidence that silica is mutagenic." Klein and Christopher (1995) did not discuss the results of Sobti and Bhardwaj (1991) who observed an increased level of chromosome aberrations in a study of workers exposed to stone dust. The review of experimental evidence conducted by Rabovsky (1997) was not available to Klein and Christopher in 1995.

4.2.2.4 Conclusions

As mentioned previously, Rabovsky (1997) indicates that although there is substantial experimental data in animals where lung cancer is secondary to the development of silicosis, the temporal and dose-response relationships linking the two endpoints are unknown. In addition, nongenetic mechanisms have not been unequivocally proven.

There is epidemiological evidence that RRs in silicotics are higher than in nonsilicotics (Section 4.2.1.1.3) although results were inconclusive on whether silicosis was necessary for the development of lung cancer (Pelucchi et al. 2006 in Section 4.2.1.1.3.5 and Erren et al. 2008 in Section 4.2.1.1.3.6). Checkoway and Franzblau (2000) state:

> "The association between silica and lung cancer is generally, but not uniformly, stronger among silicotics than nonsilicotics. However, the existing literature is ambiguous due to incomplete or biased ascertainment of silicosis, inadequate exposure assessment, and the inherently strong correlation between silica exposure and silicosis which hinders efforts to disentangle unique contributions to lung cancer risk. . . Until more conclusive epidemiologic findings become available, population-based or individually-based risk assessments should treat silicosis and lung cancer as distinct entities whose cause/effect relations are not necessarily linked."

Checkoway and Franzblau (2000) then discuss the potential uncertainties in epidemiologic studies of silica. Thus, a definitive MOA is not available for silica. In the absence of definitive MOA information, the ESL guidelines indicate the default for the TD is to use a linear approach (TCEQ 2006). This approach utilizes a straight line extrapolation from the POD to zero incremental response. The resulting slope of the straight line extrapolation is the unit risk factor (URF) from which the 10^{-5} excess cancer risk can be calculated.

4.2.3 Epidemiological Studies and Exposure Estimates

Several epidemiological studies have been conducted to assess the dose-response relationship between occupational silica exposure and lung cancer:

- Vermont granite workers (Costello and Graham 1988; Graham, Costello and Vacek 2004; Attfield and Costello 2004);
- Diatomaceous earth industry (Checkoway et al. 1997; Rice et al. 2001); and
- Pooled cohorts (Steenland et al. 2001; 't Mannetje et al. 2002).

Steenland et al. (2001) pooled exposure-response analysis of ten studies. The pooled data account for exposure to different forms of crystalline silica at different concentrations and were deemed by the TD as the most appropriate data set for developing the $^{chronic}ESL_{linear(c)}$. The

individual studies each have limitations, such as confounding by smoking, which is associated with approximately 90% of lung cancer cases (DeMarini 2004). The pooled cohort evaluated by Steenland et al. (2001) is comprised of 65,980 workers from several different industries, including mining (gold, tin, and tungsten), pottery, industrial sand, granite, and diatomaceous earth (cristobalite). Quantitative exposure estimates of respirable silica in mg/m^3 were used from the original studies or developed to provide a common metric for evaluation.

The development of quantitative exposure estimates is described by 't Mannetje et al. (2002). The cohort-specific median range of exposure varied widely (0.13-11.37 mg/m^3-years), allowing evaluation of the risk of lung cancer across a wide range of cumulative exposure. The authors indirectly validated the quantitative exposure estimates by determining whether or not increasing exposure led to increasing silicosis. Based on the relationship between cumulative exposure and silicosis mortality (Odds Ratios: 1.0, 3.1, 4.6, 4.5, and 4.8) based on quintiles of cumulative exposure, 't Mannetje et al. (2002) concluded "…the exposure estimates were reasonably successful in estimating exposure, in so much as a positive and reasonably monotonic exposure-response trend was observed." The relationship between increasing cumulative exposure and a known disease outcome (silicosis) provides confidence that exposure misclassification of exposure did not obscure any exposure-response relationship.

The most recent literature for two studies in the Steenland et al. (2001) meta-analysis of lung cancer and silica exposure was reviewed by Sielken and Associates (Appendix 4). The U.S. diatomaceous earth updates (Checkoway et al. 1997; Rice et al. 2001) and the U.S. granite study updates (Costello and Graham 1988; Graham, Costello and Vacek 2004; Attfield and Costello 2004) were independently evaluated. These scientists found results very similar to those reported by Steenland et al. (2001). The fact that the recent findings of these two studies are supportive of Steenland et al. results raises confidence in their pooled analysis based on ten cohorts.

4.2.4 Dose-Response Assessment and Dose Metric

4.2.4.1 Derivation of Potency Estimates Based on Observed Data

Steenland et al. (2001) used continuous data and a nested case-control analyses using conditional logistic regression in which the likelihood is equivalent to Cox regression analysis to derive potency estimates. The exposure metrics evaluated were cumulative exposure lagged 15 years, the log of cumulative exposure lagged 15 years, and average exposure (cumulative exposure/duration). The Steenland et al. (2001) assessment evaluated a log-linear model, power model, and linear model, although results were not shown for the linear model. The authors indicate that lung cancer was consistently related to silica exposure across all studies. All ten individual studies resulted in positive slopes, indicating that lung cancer mortality increases with increasing cumulative exposure to silica (refer to Table 3 in Steenland et al. 2001). In addition, four of the associations (i.e., slope) using the log-linear model with cumulative exposure lagged 15 years are statistically significant at the 5% significance level.

The cumulative exposure metric was used in this assessment because it fits the data better than the model with the average exposure metric. Corresponding cancer potency estimates (β) and standard error (SE) values were obtained from Table 3 of Steenland et al. (2001), and 95% upper confidence limits (95% UCLs) on the β values were calculated using reported SEs as summarized in Table 7.

Table 7 Beta (β), Standard Error (SE), and 95% UCL β Values (mg/m^3-years)

Model	Exposure Metric	β	SE	95% UCL β [a]
Log Linear	Cumulative Exposure	0.0105	0.0022	0.0141
Power	Log Cumulative Exposure	0.062	0.015	0.0867

[a] 95% UCL = β + (1.645 x SE)

4.2.4.2 Dosimetric Adjustments

Occupational concentrations ($Concentration_{OC}$) were converted to environmental concentrations for the general population ($Concentration_{HEC}$) using the following equation recommended by TCEQ (2006):

$$Concentration_{HEC} = Concentration_{OC} \times (VE_{ho}/VE_h) \times (days\ per\ week_{oc}/days\ per\ week_{res})$$

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

4.2.4.3 Extrapolation to Lower Exposures

4.2.4.3.1 Calculation of Air Concentrations at 1 in 100,000 Excess Cancer Risk and the $^{chronic}ESL_{linear(c)}$

URFs and silica air concentrations at 1 in 100,000 excess cancer risk were calculated with life-table analyses using the BEIR IV approach (NRC 1988), extra risk, and the following mortality and survival rates, which are listed in Appendix 5:

- US mortality rates for 2000-2004 for all lung and bronchus cancer (Surveillance, Epidemiology, and End Results database (SEER 2007));
- US survival probabilities for 2003 (Arias 2006); and

- Texas-specific mortality rates for lung cancer provided by the Texas Department of State Health Services, Cancer Epidemiology and Surveillance Branch, Texas Cancer Registry (personal communication from Dr. David Risser).

Since Steenland et al. (2001) used a lag time of 15 years to conduct modeling using the cumulative exposure metric, an exposure lag time of 15 years must be used in the cumulative exposure assessment to calculate air concentrations. Utilizing the data and inputs described above, air concentrations corresponding to the target excess cancer risk of 1 in 100,000 using the maximum likelihood estimate (MLE) or 95% UCL were calculated based on lifetime exposure of 70 years, the default used by TCEQ for exposure analysis (TCEQ 2006) (Table 8).

Table 8 Air Concentrations (µg/m^3) Corresponding to 1 in 100,000 Excess Lung Cancer Risk Using Various Background Rates and Models

Model	Background Rates	Exposure Metric	EC001 Air Concentration 1 in 100,000 excess cancer risk using URF (MLE) a	LEC001 Air Concentration 1 in 100,000 excess cancer risk using URF (95% UCL) b	β (MLE) Air Concentration 1 in 100,000 excess cancer risk using model	β (95% UCL) Air Concentration 1 in 100,000 excess cancer risk using model
Log Linear	US	Cumulative	0.3029 (URF = 3.301 E-05)	0.2256 (URF = 4.433 E-05)	0.3093	0.2303
Power	US	Log Cumulative	0.0738 (URF = 1.355 E-04)	0.0474 (URF = 2.109 E-04)	0.0526	0.0375
Log Linear	TX	Cumulative	0.2749 (URF = 3.637 E-05)	0.2047 (URF = 4.884 E-05)	0.2800	0.2085
Power	TX	Log Cumulative	0.0642 (URF = 1.557 E-04)	0.0418 (URF = 2.393 E-04)	0.0476	0.0340

[a]URF = $0.001/EC_{001}$
[b]URF = $0.001/LEC_{001}$

For cancer data modeled by non-linear models, the TCEQ (2006) recommends deriving an effective concentration (EC) and the lower 95% confidence limit of the effective concentration (LEC) at a response level that can be supported by the data as the point of departure and extrapolating to low doses using a default linear approach. Typically, the response rate for tumor

data from animal data is at the 10% response level (EC_{10} or LEC_{10}) but since the pooled epidemiological data from a cohort of 65,980 were available, a 0.1% response rate was defensible and within the observed range of the data. The upper-bound lifetime excess cancer risk resulting from continuous exposure to silica at 1 $\mu g/m^3$ in air (i.e., the URF in Table 8) was then calculated using the following equation:

$$URF = 0.001 / (EC_{001} \text{ or } LEC_{001})$$

The 10^{-5} risk air concentration in columns four and five of Table 8 were calculated based on the URFs using the following equation:

$$10^{-5} \text{ risk air concentration} = 1 \times 10^{-5} / URF$$

Since the log linear and power models are not linear models, the models themselves can be used to calculate the air concentration at the 10^{-5} risk level as an alternative to the default linear extrapolation method used by the TD. The data are presented in the last two columns of Table 8 for comparison.

As can be seen from Table 8, use of Texas background lung cancer mortality rates and survival rates resulted in slightly more conservative values and are preferred since the purpose of the DSD is to develop health-protective air concentrations for citizens of Texas. Therefore, air concentrations calculated with Texas-specific rates are used in all subsequent discussions.

4.2.4.3.2 Model Selected to Represent Excess Lung Mortality Risk

The preferred model is the log linear model using cumulative dose, a 15-year lag, and a default linear extrapolation from the POD of the EC_{001} to zero. Steenland et al. (2001) noted that the log of cumulative exposure (power model) with a 15-year lag was a strong predictor of lung cancer across studies. However, Steenland and Deddens (2004) later noted that the best-fitting statistical model is not necessarily the best model for risk assessment. The TD selected the log linear model based on the historical use of this model for human epidemiological data (i.e., parsimonious models such as linear or log-linear multiplicative RR models are to be preferred over other less-plausible models) and the lack of a biological basis for selecting an alternative model (i.e., the carcinogenic MOA for silica is not known in sufficient detail).

The resulting URFs are listed in Table 8. There was only a 1.3 fold difference between the URF derived from the EC_{001} and LEC_{001}. In addition, the air concentration associated with 10^{-5} excess cancer risk differ little regardless of whether the concentration is derived from the model itself or from the default linear extrapolation approach applied by the TD. According to Section 4.5.3.1 of the ESL Guidelines (TCEQ 2006), use of the EC rather than the LEC may be appropriate when certain types of uncertainty are addressed by human epidemiology studies (TCEQ 2006). Although estimates of mortality were available rather than incidence, mortality rates for lung cancer are high and correlate well with incidence (i.e., five-year survival is only about 15%

according to the American Cancer Society 2005). The key study also indicated that exposure to other occupational carcinogens was not a likely confounder since the exposure-response trend was similar in miners potentially exposed to radon and non-miners. Most importantly, the key study was a well-conducted pooled study, which developed a common exposure measure and uniform approach to data analysis to compare the results of 10 separate studies. Similar to meta-analysis, the pooled approach decreases uncertainty. Finally, the TD believes that the application of the LEC_{001} would be overly conservative due to the lack of evidence of lung cancer in response to environmental concentrations of silica (Figure 1).

Texas-specific air concentrations corresponding to the target excess cancer risk of 1 in 100,000 using the calculated URFs ranged from 0.042 $\mu g/m^3$ (LEC_{001}) based on the power model to 0.275 $\mu g/m^3$ (EC_{001}) for the log-linear model, less than a seven-fold difference. Based on the log-linear model for lung cancer, the URF is 3.6 E-05 per $\mu g/m^3$, rounded to two significant figures, and the resulting $^{chronic}ESL_{linear(c)}$ at the target risk of 1 in 100,000 excess lung cancer mortality is 0.27 $\mu g/m^3$.

The URF of 3.6E-05 per $\mu g/m^3$ is slightly higher (more conservative) than the range of URFs based on epidemiologic studies, but is slightly smaller or falls at the low end of the range of URFs developed based on rat experimental data:

- 6.8E-07 to 1.85E-05 per $\mu g/m^3$ developed by Ruble and Goldsmith (1993) for workers (as referenced by Goldsmith and Hertz-Picciotto 1997) based on epidemiologic findings among gold workers and diatomaceous earth workers. Both epidemiological studies demonstrated dose-response lung cancer findings for silica exposure;
- 4.5E-05 per $\mu g/m^3$ to 2.9E-04 per $\mu g/m^3$ (without and with a surface area correction, respectively) developed by Collins and Marty (1997) based on four experimental studies conducted in rats; and
- 2.3E-05 to 6.0E-03 per $\mu g/m^3$ based on experimental rat studies (Goldsmith et al. 1995), (as referenced in Goldsmith and Hertz-Picciotto 1997).

Goldsmith and Hertz-Picciotto (1997) states there is a more shallow slope for human data, compared to that derived from experimental research in animals for silica URF extrapolations.

4.2.5 Evaluating Susceptibility from Early-Life Exposures

USEPA (2005) provides default age-dependent adjustment factors (ADAFs) to account for potential increased susceptibility in children due to early-life exposure when a chemical has been identified as acting through a mutagenic MOA for carcinogenesis. However, silica is not currently identified by USEPA as having a mutagenic MOA and data are not sufficient to determine what mechanisms or key steps are critical for lung cancer development. As mentioned previously in the MOA section, quartz exposures have generally yielded negative results in gene mutation assays, especially at low doses (Lewinson et al. 1994, Jacobsen et al. 2007,

Nagalakshmi et al. 1995, and Pairon et al. 1990). However, increased gene mutation and DNA damage have also been documented following exposure to quartz or tridymite, particularly at high doses (Driscoll et al. 1997, Fanizza et al. 2007, Pairon et al. 1990, and Nagalakshmi et al. 1995). Other evidence appears to support an indirect mechanism (Sections 4.2.2.2 and 4.2.2.3). Therefore, consistent with TCEQ guidance (TCEQ 2006), silica is not considered to have a mutagenic MOA, and ADAFs will not be applied to the URF. This issue will be reevaluated periodically as new scientific information on silica's carcinogenic MOA becomes available.

4.2.6 Sensitivity Analysis Assuming a Nonlinear MOA for Lung Cancer

Klein and Christopher (1995) concluded that lung cancer is secondary to the development of fibrotic lesions and that silica should therefore be considered a threshold carcinogen (Section 4.2.2.3). As a result of this hypothesis, the TD chose to compare the $^{chronic}ESL_{nonlinear(nc)}$ based on the development of silicosis/fibrosis to the $^{chronic}ESL_{linear(c)}$ developed using a default linear extrapolation to zero approach to excess cancer risk. The noncarcinogenic toxicity factor developed in Section 4.1 is based on fibrotic changes in the lung. The resulting $^{chronic}ESL_{nonlinear(nc)}$ of 0.60 µg/m^3 is only 2.2-fold higher than the $^{chronic}ESL_{linear(c)}$ 0.27 µg/m^3 at the target risk air concentration of 1 in 100,000 obtained from a linear extrapolation of the lung cancer data.

4.3. Welfare-Based Chronic ESL

Evidence primarily indicates that silica, in the form of silicic acid, is beneficial to plants (see Section 3.2.2). However, it has been hypothesized that silica accumulation in long-lived leaves may inhibit photosynthesis. Motomura et al. (2007) investigated the possibility of reduced photosynthesis in bamboo leaves. They determined that silica content less than 25% on a dry mass basis did not negatively impact photosynthesis in the bamboo leaves. In their discussion, Motomura et al. (2007) indicated that this result is consistent with previous Japanese studies that found no negative impact on photosynthesis in rice leaves with silica concentrations up to 18%. Although silica may cause damage at high concentrations, it is absorbed through the soil rather than the air. Since there are no data indicating that plants are harmed by chronic exposure to silica in the air, the TD has chosen not to develop a $^{chronic}ESL_{veg}$.

4.4 Long-Term ESL

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

- $^{chronic}ESL_{linear(c)}$ = 0.27 µg/m^3
- URF = 3.6E-05 per µg/m^3
- chronic ReV = 2.0 µg/m^3
- $^{chronic}ESL_{nonlinear(nc)}$ = 0.60 µg/m^3

The long-term ESL for air permit reviews is the health-based $^{chronic}ESL_{linear(c)}$ of 0.27 µg/m^3 (Table 1) since it is slightly lower than the $^{chronic}ESL_{nonlinear(nc)}$ of 0.60 µg/m^3. Because the particle sizes for respirable crystalline exposure data collected in the occupational studies analysed by Steenland et al. (2001, 2005) were smaller than 5 µm in diameter, the $^{chronic}ESL_{linear(c)}$ of 0.27 µg/m^3 will apply to respirable crystalline silica ≤ 4 µm in diameter.

Chapter 5 References

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Appendix 1. Toxicity Factor Development for Subacute Studies

Duration Adjustments

The modified Haber's Rule with n = 3 was used to adjust exposure duration from the supporting subacute studies where both concentration and duration play a role in toxicity. The TD chose to conservatively adjust the exposure from 6 h/d to 1 h/d rather than adjusting the total duration of exposure in each study to protect against intermittent exposure and the possibility of delayed inflammation.

Warheit et al. (1995):

$$C_2 = [(C_1)^3 \times (T_1 / T_2)]^{1/3} = [(10\ mg/m^3)^3 \times (6\ h/1\ h)]^{1/3} = 18.17\ mg/m^3 = POD_{ADJ}$$

Subacute series by Porter et al. (2001; 2002a; 2002b) and Castranova et al. (2001):

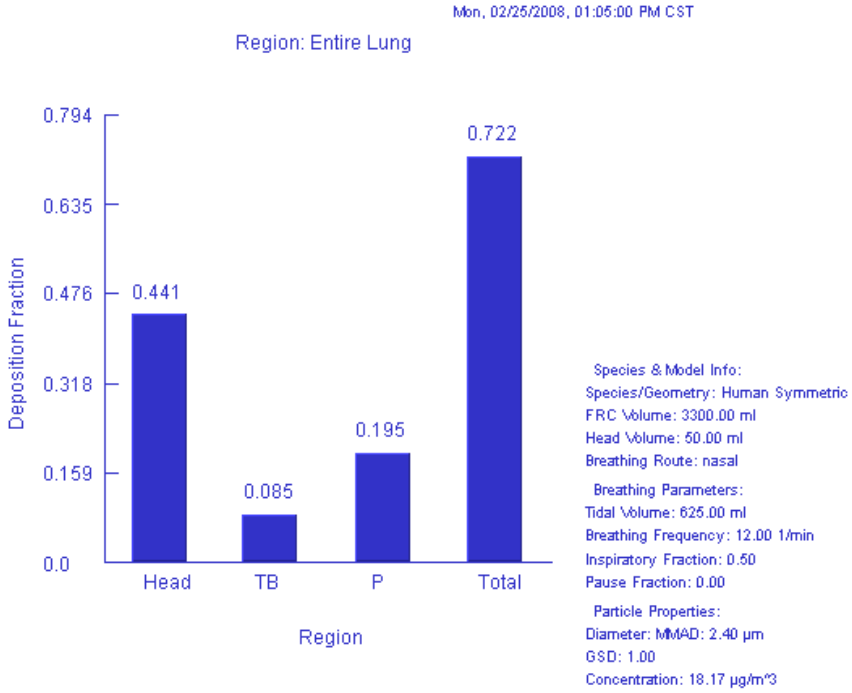
$$C_2 = [(C_1)^3 \times (T_1 / T_2)]^{1/3} = [(15\ mg/m^3)^3 \times (6\ h/1\ h)]^{1/3} = 27.2\ mg/m^3 = POD_{ADJ}$$

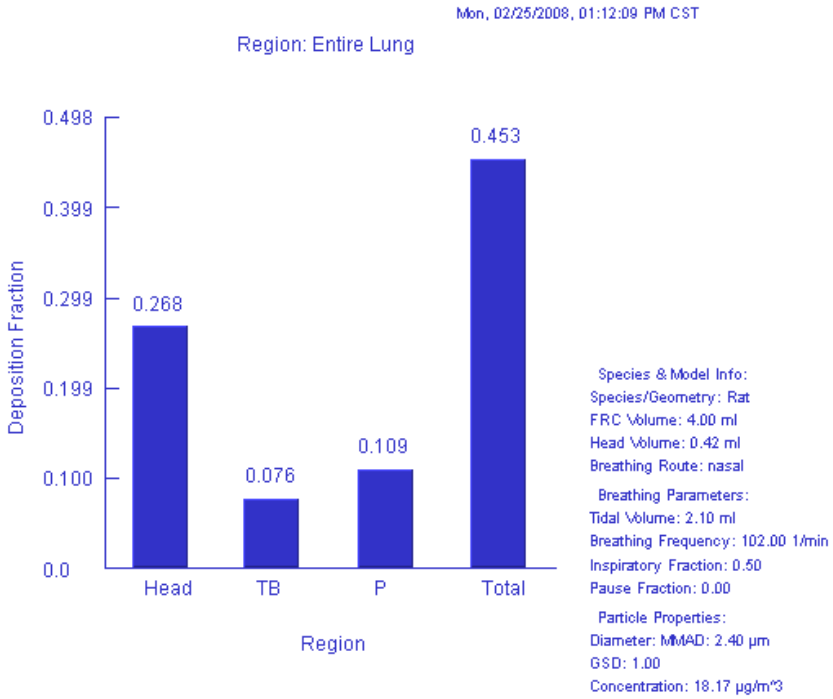
Dosimetry Adjustments

The deposition fraction of silica was calculated for each supporting study using the MPPD program. The MMAD of the SAS aerosol used in the study by Warheit et al. (1995) ranged from 2.4-3.4 μm. The low end (2.4 μm MMAD) and high end (3.4 μm MMAD) of these ranges were modeled in the MPPD program and are presented for comparison. The particle density is 2.3 g/cm^3 (Table 2). The chemical concentration is the POD_{ADJ} of 18.2 mg/m^3. The target region for SAS was considered to be the total particle distribution for the tracheobronchial and pulmonary regions. All remaining values used, including the geometric standard deviation, were default.

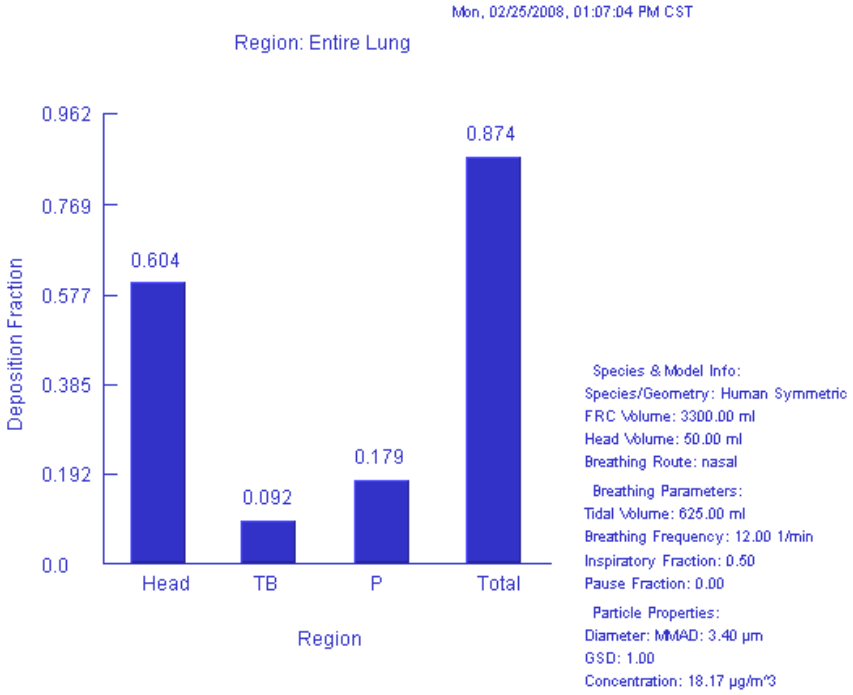
According to Porter et al. (2001), the mass median aerodynamic diameter of the silica aerosol used in their study was 1.70 μm with a geometric standard deviation of 1.78. The particle density is 2.3 g/cm^3 (Table 2). The chemical concentration is the POD_{ADJ} of 27.2 mg/m^3. The target region for silica was considered to be the total particle distribution for the tracheobronchial and pulmonary regions. All remaining values used were default.

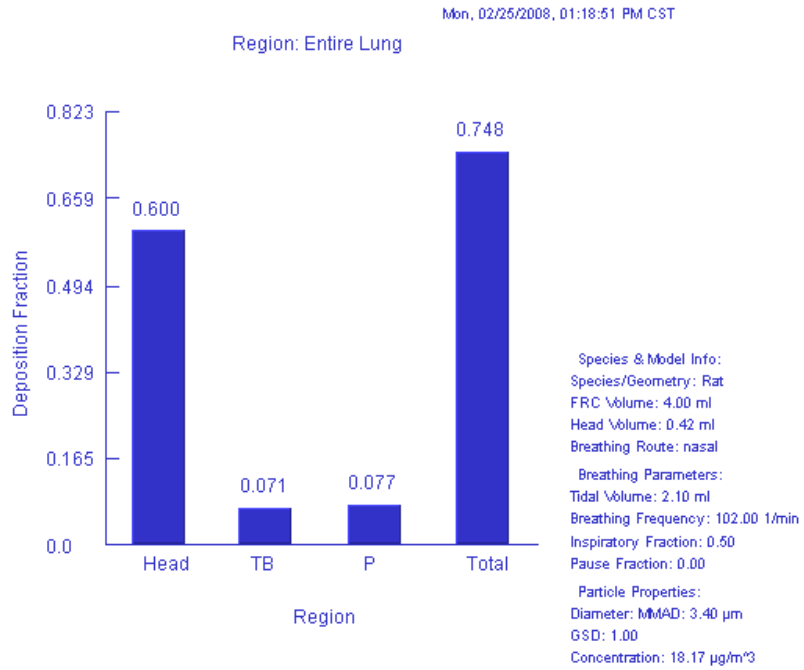
MPPD Program Output for Warheit et al. (1995) – lower end of range



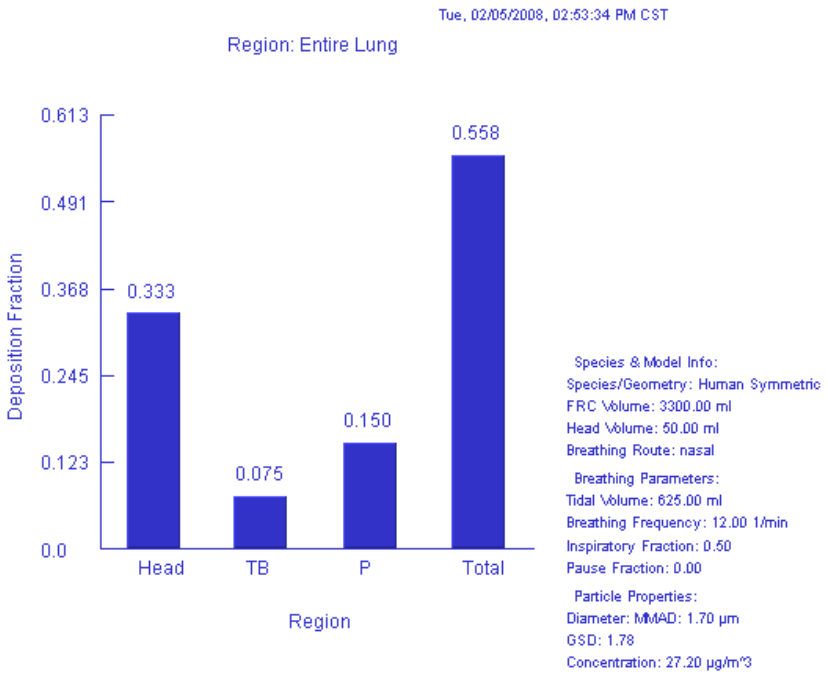


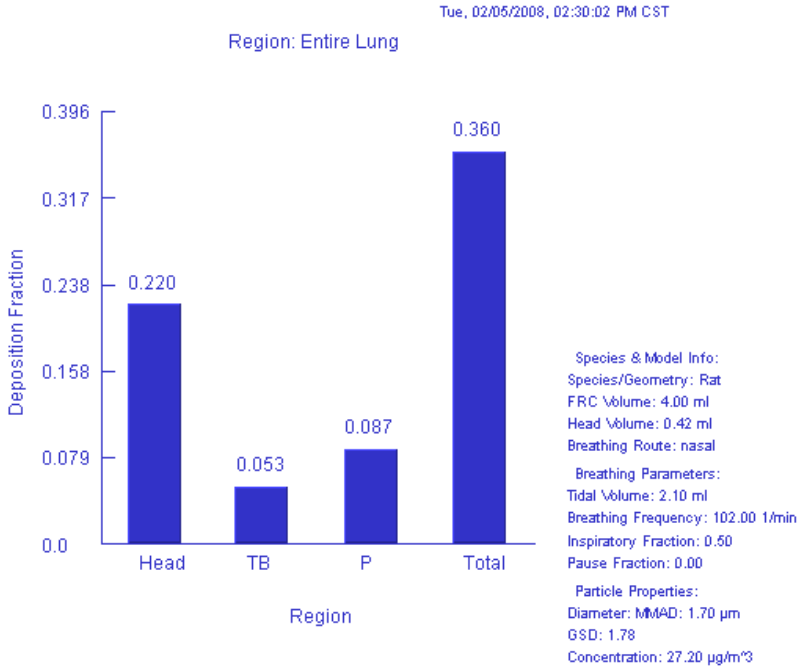
MPPD Program Output for Warheit et al. (1995) – upper end of range





MPPD Program Output for Subacute Study Series (Porter et al. 2001; 2002a; 2002b and Castranova et al. 2001)





The deposition fractions determined from the MPPD program above were then used to calculate the RDDR for each of the supporting studies.

Warheit et al. (1995):

$RDDR = [(V_E)_A / (V_E)_H] \times [DF_A / DF_H] \times [NF_H / NF_A]$

RDDR (low) = [(137.3 mL/min) / (13,800 mL/min)] x [0.185 / 0.280] x [543,200 cm^2 / 3422.5 cm^2] = 1.04

RDDR (high) = [(137.3 mL/min) / (13,800 mL/min)] x [0.149 / 0.271] x [543,200 cm^2 / 3422.5 cm^2] = 0.868

Subacute series by Porter et al. (2001; 2002a; 2002b) and Castranova et al. (2001):

RDDR = [(137.3 mL/min) / (13,800 mL/min)] x [0.140 / 0.225] x [543,200 cm^2 / 3422.5 cm^2] = 0.982

The RDDR was then used to dosimetrically adjust from an animal to human POD.

Warheit et al. (1995):

$POD_{HEC} = POD_{ADJ}$ x RDDR (low) = 18.2 mg/m^3 x 1.04 = 18.900 mg/m^3 = 18,900 $\mu g/m^3$

$POD_{HEC} = POD_{ADJ}$ x RDDR (high) = 18.2 mg/m^3 x 0.868 = 15.798 mg/m^3 = 15,798 $\mu g/m^3$

The more conservative POD_{HEC} of 15,800 $\mu g/m^3$ will be used in all future calculations.

Subacute series by Porter et al. (2001; 2002a; 2002b) and Castranova et al. (2001):

$POD_{HEC} = POD_{ADJ}$ x RDDR = 27.2 mg/m^3 x 0.982 = 26.710 mg/m^3 = 26,710 $\mu g/m^3$

Application of Uncertainty Factors

The following UFs were applied to the POD_{HEC} of 15,798 $\mu g/m^3$ from the supporting subacute study by Warheit et al. (1995): 3 for UF_L, 3 for UF_A, 10 for UF_H and 3 for UF_D. A UF of 3 was used for extrapolation from a LOAEL to a NOAEL, because the effects noted were mild and reversible. A UF of 3 was used for interspecies extrapolation, because default dosimetric adjustments using the RDDR were conducted to account for toxicokinetic differences but not toxicodynamic differences. A UF of 10 was used to account for potential variation in human susceptibility. A UF of 3 was applied for database uncertainty, because data from only one species was available. The total UFs applied to the POD_{HEC} were 300.

The following UFs were applied to the POD_{HEC} of 26,710 $\mu g/m^3$ derived from the supporting subacute study series by Porter et al. (2001; 2002a; 2002b) and Castranova et al. (2001):3 for

UF_L, 3 for UF_A, 10 for UF_H, and 10 for UF_D. A UF_L of 3 was used for extrapolation from a LOAEL to a NOAEL, because the effects noted were mild and reversible. A UF_A of 3 was used for extrapolation from animals to humans, because default dosimetric adjustments using the RDDR were conducted to account for toxicokinetic differences but not toxicodynamic differences. A UF_H of 10 was used to account for potential sensitive human subpopulations, such as those with existing pulmonary inflammation due to other causes. Finally, a database UF_D of 10 was used to account for the lack of data from multiple species and a lack of dose response information, since only one dose was used in this study series. The total UFs applied to the POD_{HEC} were 1000.

Calculation of Acute ReVs

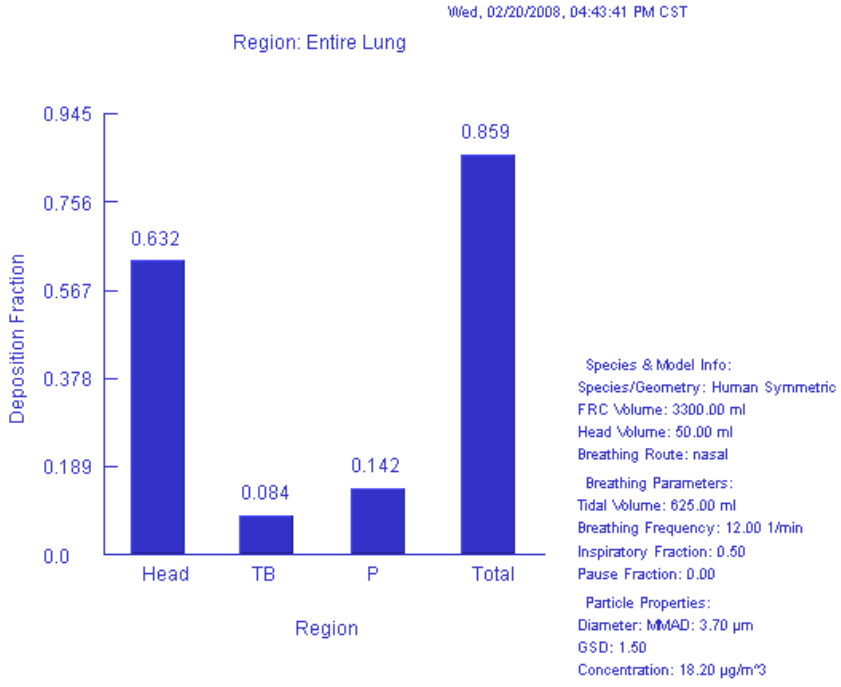
Warheit et al. (1995):

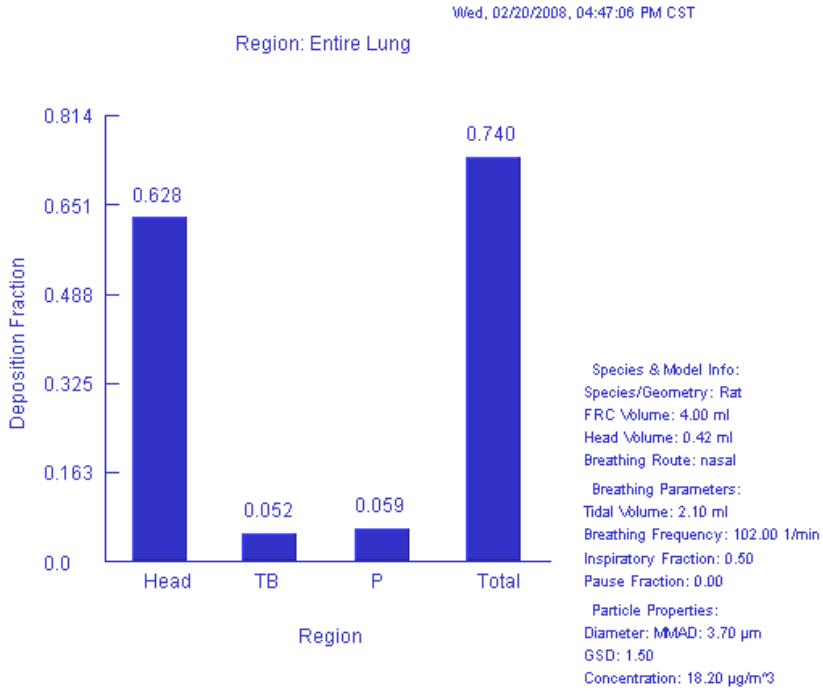
acute ReV = POD_{HEC} / (UF_L x UF_A x UF_H x UF_D) = 15,798 μg/m^3/ (3 x 3 x 10 x 3) = 52.6 μg/m^3

Subacute series by Porter et al. (2001; 2002a; 2002b) and Castranova et al. (2001):

acute ReV = POD_{HEC} / (UF_L x UF_A x UF_H x UF_D) = 26,710 μg/m^3/ (3 x 3 x 10 x 10) = 26.7 μg/m^3

Appendix 2. MPPD Program Output for Key Study-Warheit et al. (1991)





Appendix 3. Benchmark Dose Modeling Results

Appendix 3A. Hnizdo et al. (1993)

Benchmark dose modeling of silicosis incidence data was performed using data presented below. Midpoint cumulative dust exposure and number of cases were obtained from Figure IV in Hnizdo et al. (1993). The number of workers in each exposure category was calculated from the number at risk provided in Figure IV in Hnizdo et al. (1993). The authors indicated that the silica content of the dust in the mines was approximately 30%. Therefore, 30% of the midpoint of the cumulative dust exposure was used to model crystalline silica exposure.

Midpoint Cumulative Dust Exposure (mg/m^3-yr)	**Silica (30% of Cumulative Dust Exposure) (mg/m^3-yr)**	**Number of workers per exposure category**	**Number of cases per exposure category**
1	0.3	204	0
3	0.9	474	9
5	1.5	556	48
7	2.1	469	85
9	2.7	318	93
11	3.3	142	53
13	3.9	44	20
15	4.5	11	5

All available dichotomous models were run to determine which model best fit the data. The results for the four best fitting models (p-value greater than 0.1) are shown below. The results of the probit model using log-transformed data fit best and were used to develop the point of departure.

BMDS Model	**BMC_{01}**	**$BMCL_{01}$**	**p-value for fit**	**AIC**	**Scaled Residuals***
Log Probit	0.734223	0.634946	0.9957	1512.45	-0.167
Gamma	0.646433	0.537441	0.8546	1514.64	-0.710
Log Logistic	0.619776	0.519247	0.8446	1515.85	-0.825
Multistage	0.485232	0.422197	0.5017	1517.45	-0.886

* Scaled residuals at estimated response closest to the BMR_{01}

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Probit Model. (Version: 2.8; Date: 02/20/2007)
Input Data File: C:\BMDS\HNIZDO_SILICA_DATA.(d)
Gnuplot Plotting File: C:\BMDS\HNIZDO_SILICA_DATA.plt
Wed Jan 23 12:24:16 2008

==========

BMDS MODEL RUN

In order to obtain a complete copy of the above BMD modeling results, please send an email to the Toxicology Division providing the name of the DSD and the requested appendices to the following email address: tox@tceq.texas.gov.

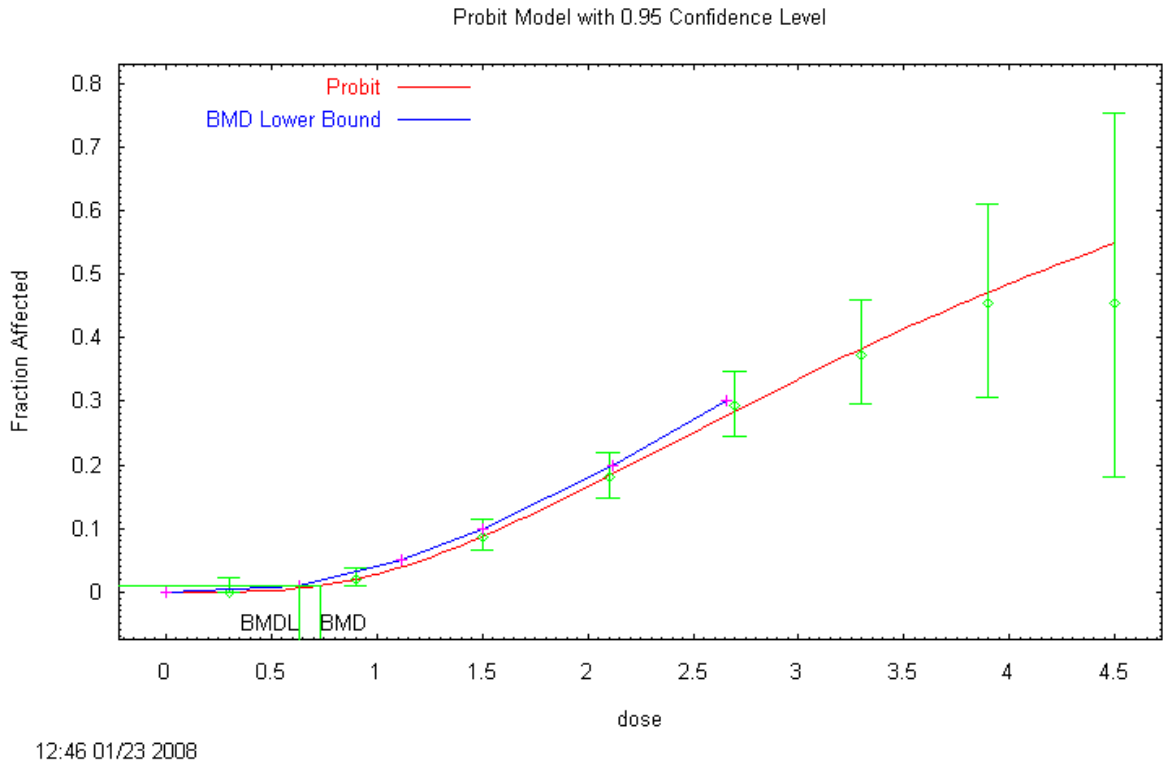
Benchmark Dose Computation

Specified effect= 0.01

Risk Type= Extra risk

Confidence level = 0.95

BMC =0.734223; BMCL = 0.634946



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Gamma Model. (Version: 2.11; Date: 10/31/2007)
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Gnuplot Plotting File: C:\BMDS\HNIZDO_SILICA_DATA.plt
Fri Sep 05 14:25:15 2008

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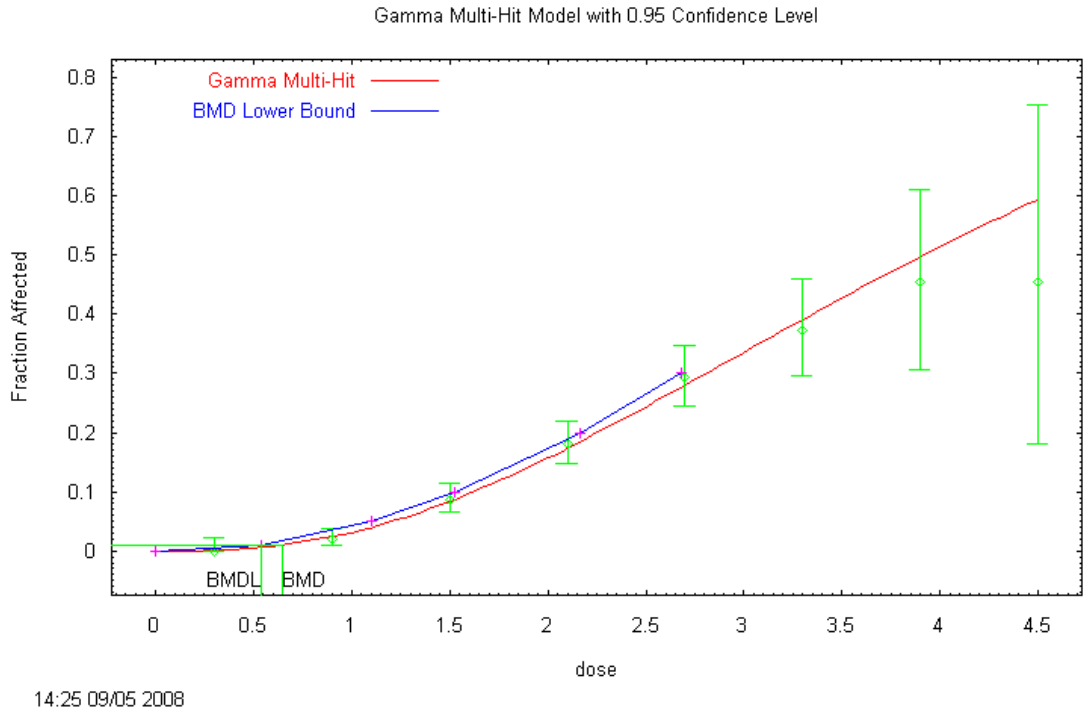
BMDS MODEL RUN

In order to obtain a complete copy of the above BMD modeling results, please send an email to the Toxicology Division providing the name of the DSD and the requested appendices to the following email address: tox@tceq.texas.gov.

Benchmark Dose Computation
Specified effect = 0.01
Risk Type = Extra risk
Confidence level = 0.95
BMC = 0.646433
BMCL = 0.537441



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Logistic Model. (Version: 2.9; Date: 02/20/2007)
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Gnuplot Plotting File: C:\BMDS\HNIZDO_SILICA_DATA.plt
Wed Jan 23 12:21:45 2008

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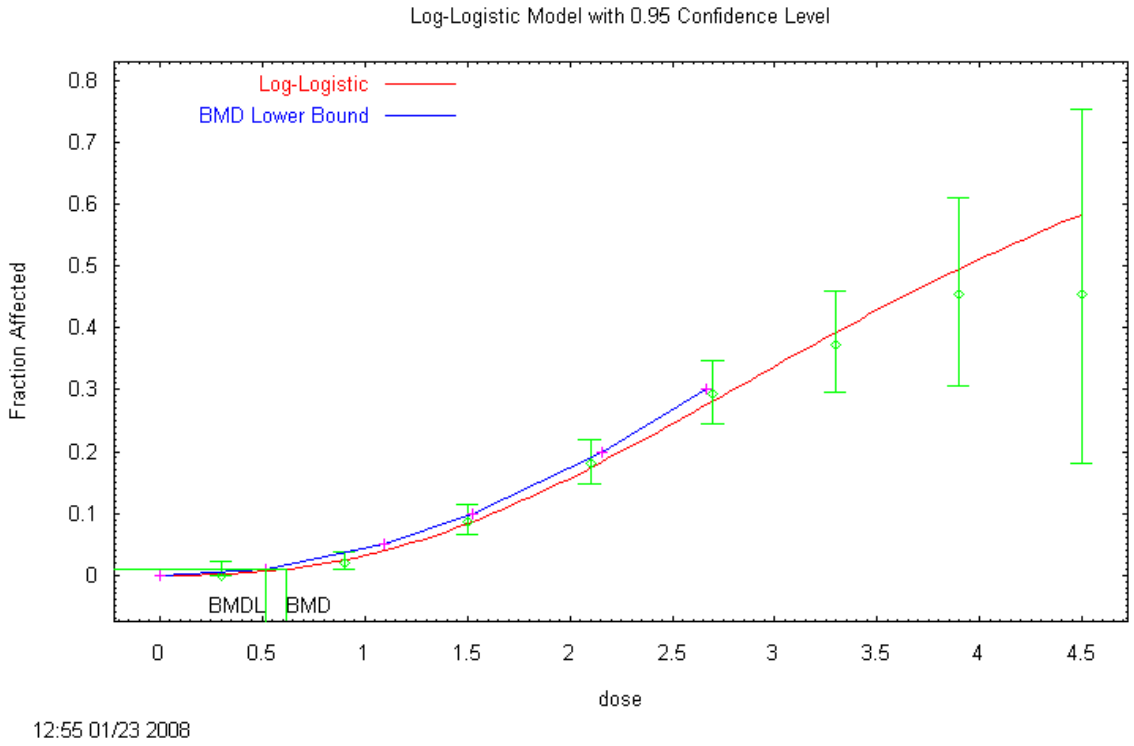
BMDS MODEL RUN

In order to obtain a complete copy of the above BMD modeling results, please send an email to the Toxicology Division providing the name of the DSD and the requested appendices to the following email address: tox@tceq.texas.gov.

Benchmark Dose Computation
Specified effect = 0.01
Risk Type = Extra risk
Confidence level = 0.95
BMC = 0.619776
BMCL = 0.519247



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Multistage Model. (Version: 2.8; Date: 02/20/2007)
Input Data File: C:\BMDS\HNIZDO_SILICA_DATA.(d)
Gnuplot Plotting File: C:\BMDS\HNIZDO_SILICA_DATA.plt
Fri Mar 07 14:56:37 2008

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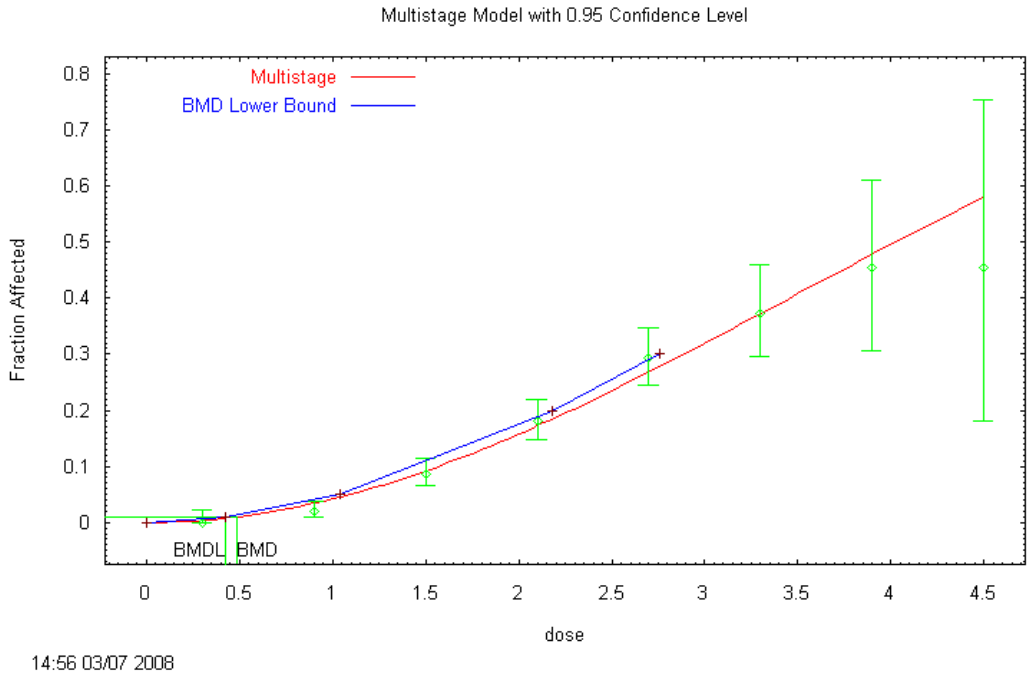
BMDS MODEL RUN

In order to obtain a complete copy of the above BMD modeling results, please send an email to the Toxicology Division providing the name of the DSD and the requested appendices to the following email address: tox@tceq.texas.gov.

Benchmark Dose Computation
Specified effect = 0.01
Risk Type = Extra risk
Confidence level = 0.95
BMC = 0.485232
BMCL = 0.422197
BMCU = 0.508803
Taken together, (0.422197, 0.508803) is a 90% two-sided confidence interval for the BMD



Appendix 3B. Hughes et al. (1998)

Benchmark dose modeling of silicosis incidence data was performed using data presented below. These data were generated from the raw data used in Hughes et al. (1998) kindly provided by Dr. Checkoway. The lower end of each exposure interval was conservatively used to model the data.

Cumulative Exposure (mg/m^3-yr)	**Number of workers restricted to exposure interval**	**Number of cases**
0	86	**1**
0.01-2	1111	**13**
2-4	325	**11**
4-6	152	**18**
6-8	49	**9**
8-10	32	**11**
10-12	12	**3**
12-14	17	**7**
14-16	7	**4**
16-18	4	**1**
18-20	6	**2**
>20	**10**	**4**

All available dichotomous models were run to determine which model best fit the data. Models with p-values less than 0.1 were rejected. The results for the six models with p-values greater than 0.1 are presented here. Based on the AIC, the probit model using log-transformed data is the best fitting model and was used to develop the point of departure.

BMDS Model	**BMC_{01}**	**$BMCL_{01}$**	**p-value for fit**	**AIC**	**Scaled Residual***
Log Probit	1.20237	0.790704	0.8116	529.934	0.100
Log Logistic	0.891493	0.522664	0.6554	531.512	0.149
Gamma	0.847794	0.45528	0.5508	532.465	0.142
Weibull	0.736723	0.410677	0.4844	533.15	0.169
Multistage	0.931604	0.781309	0.3099	535.217	0.206
Quantal Linear	0.357394	0.290944	0.2743	535.279	0.330

* Scaled residuals at estimated response closest to the BMR_{01}

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Probit Model (Version: 2.8; Date: 2/20/2007)
Input Data File: C:\BMDS\HUGHES_SILICA_DATA.(d)
Gnuplot Plotting File: C:\BMDS\HUGHES_SILICA_DATA.plt
Wed Jan 23 13:38:19 2008

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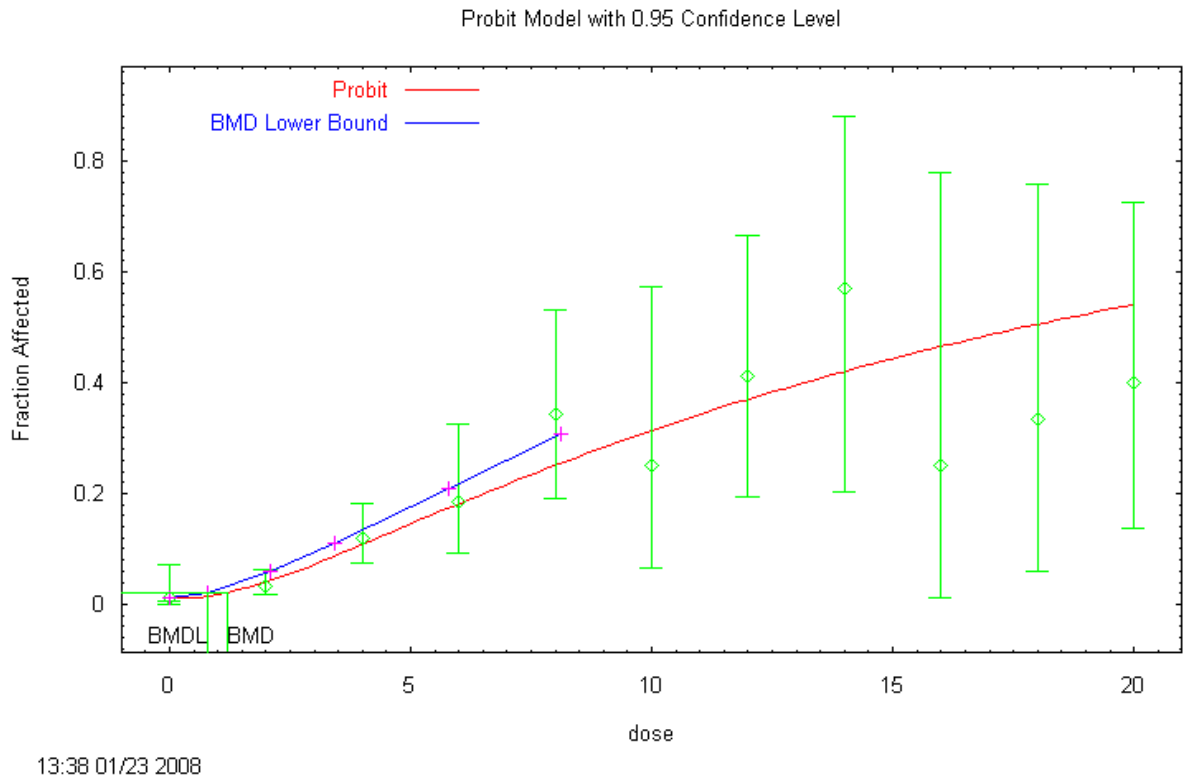
BMDS MODEL RUN

In order to obtain a complete copy of the above BMD modeling results, please send an email to the Toxicology Division providing the name of the DSD and the requested appendices to the following email address: tox@tceq.texas.gov.

Benchmark Dose Computation:

Specified effect = 0.01
Risk Type = Extra risk
Confidence level = 0.95
BMC = 1.20237; BMCL = 0.790704



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Logistic Model (Version: 2.9; Date: 2/20/2007)
Input Data File: C:\BMDS\HUGHES_SILICA_DATA.(d)
Gnuplot Plotting File: C:\BMDS\HUGHES_SILICA_DATA.plt
Wed Jan 23 13:36:06 2008

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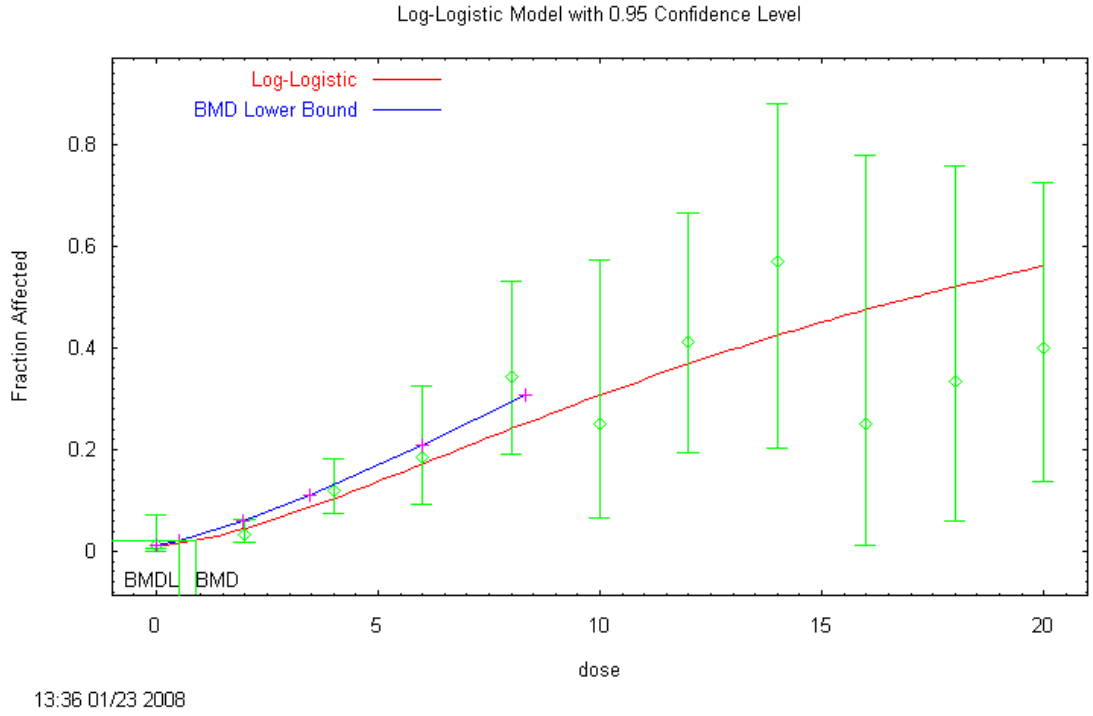
BMDS MODEL RUN

In order to obtain a complete copy of the above BMD modeling results, please send an email to the Toxicology Division providing the name of the DSD and the requested appendices to the following email address: tox@tceq.texas.gov.

Benchmark Dose Computation:
Specified effect = 0.01
Risk Type = Extra risk
Confidence level = 0.95
BMC = 0.891493
BMCL = 0.522664



Appendix 4. Silica Epidemiological Review and Dose-Response Modeling - Inclusion of Individual Studies

Robert L. Sielken Jr., Ph.D., and Ciriaco Valdez Flores, Ph.D., P.E.
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Tel: 979-846-5175; Fax: 979-846-2671;
Email: SielkenAssoc@aol.com

August 27, 2009

Sielken and Associates Consulting Inc. (Sielken & Associates) reviewed the literature related to the Vermont granite workers exposed to silica and its relation to lung cancer. Sielken & Associates also reviewed the published literature related to the study of workers exposed to silica in Diatomaceous earth industry and their lung cancer mortality. Sielken & Associates reviewed these two studies that have been published to determine if there are information in the literature that is not also reflected in the Steenland et al. (2001) meta-analysis of lung cancer mortality and exposure to silica. Recommendations as to whether to include separate analyses of the Vermont granite workers and the Diatomaceous earth industry cohorts in the silica DSD does not contradict or overlap the meta-analyses results obtained from Steenland et al. (2001).

1. Background

The principal study being considered by TCEQ is a pooled risk assessment published in Steenland, K., A. 't Mannetje, P. Boffetta, L. Stayner, M. Attfield, J. Chen, M. Dosemeci, N. DeKlerk, E. Hnizdo, R. Koskela, and H. Checkoway (2001). Pooled Exposure-Response Analyses and Risk Assessment for Lung Cancer in 10 Cohorts of Silica-Exposed Workers: An IARC Multicentre Study. Cancer Causes and Control, **22**:773-784.

Sielken & Associates has done preliminary analyses of the Steenland et al. (2001) meta-analysis risk assessment and the following two cohorts that are part of the Steenland et al. (2001) meta-analysis:

1) Vermont Granite Workers (University of Vermont and NIOSH) in

   a) Costello, J and GB Graham 1988. Vermont Granite Workers' Mortality Study. American Journal of Industrial Medicine 13:483-497,

   b) Attfield, MD and J Costello 2004. Quantitative Exposure-Response for Silica Dust and Lung Cancer in Vermont Granite Workers. American Journal of Industrial Medicine 45:129-138,

c) Graham, WGB, J Costello and PM Vacek 2004. Vermont Granite Mortality Study: An Update With an Emphasis on Lung Cancer. Journal of Occupational and Environmental Medicine, 46:459-466.

d) Graham, WGB 2004. RE: Attfield M, Costello J. Quantitative Exposure-Response for Silica Dust and Lung Cancer in Vermont Granite Workers. Am J Ind Med 45:129-138, 2004. Letter to the editor, American Journal of Industrial Medicine 46:89.

e) Vacek, PM 2007. Vermont Granite Worker Cohort. Electronic letters to Occupational and Environmental Medicine regarding the article by KM Applebaum, EJ Malloy, and E Eisen 2007. Reducing healthy worker survivor bias by restricting date of hire in a cohort study of Vermont granite workers. Occup Environ Med.

2) Diatomaceous Earth Industry (NIOSH) in

a) Checkoway H, NJ Heyer, NS Seixas, EAE Welp, PA Demers, JM Hughes, and H Weill 1997. Dose-Response Associations of Silica with Nonmalignant Respiratory Disease and Lung Cancer Mortality in the Diatomaceous Earth Industry. American Journal of Epidemiology, 145:680-688.

b) Rice, FL, R Park, L Stayner, R Smith, S Gilbert, H Checkoway 2001. Crystalline silisca exposure and lung cancer mortality in diatomaceous earth industry workers: a quantitative risk assessment, 58:38-45.

2. Vermont Granite Workers (University of Vermont and NIOSH)

The results reported by Steenland et al. (2001) for the Vermont U.S. granite workers study are based on the data first published by Costello and Graham (1988) with exposure estimates developed by Attfield in a personal communication to Steenland et al. This cohort was followed up to 1982 and, as described by Costello and Graham (1988), included men that had been employed between 1950 and 1982 and that had been x-rayed at least once in a special surveillance program. This original cohort included 5,414 workers with 1,643 deaths and 118 lung cancer deaths.

Attfield and Costello (2004) extended the period of follow up from 1982 to 1994. In addition, they presented dose response analyses of lung cancer with cumulative exposure to silica. The updated data set included 201 lung cancer deaths (83 more than in the original Costello and Graham (1988) study). Steenland et al. (2001), using Cox proportional hazards models, obtained a coefficient of 0.0146 and a standard error of the estimate of 0.0285 for the Vermont granite worker cohort with cumulative exposure lagged 15-years. Using a Wald's test for significance, the p-value of the coefficient estimated by Steenland et al. is 0.61. Attfield and Costello (2004), using Poisson regression models, obtained a coefficient of 0.012 (no standard error was reported)

with a significance level of 0.61. The ratio of the estimate obtained by Steenland et al. to that obtained by Attfield and Costello is only 1.2. The significance level of both estimates is 0.61.

It seems then, that using the Poisson model fit to the most recent data of the Vermont granite workers or the Cox proportional hazards model fit to the original data of the same cohort results in approximately the same estimates. Furthermore, it is expected that using the results of the most recent data would hardly change the estimate of the pooled analysis reported in Steenland et al. (2001).

3. U.S. Diatomaceous Earth Industry (NIOSH)

The results reported by Steenland et al. (2001) for the U.S. diatomaceous earth industry study are based on the data published by Checkoway et al. (1997) and Rice et al. (2001). This cohort was followed from 1942 to 1994 and included white men that were employed for at least 12 months and worked sometime between 1942 and 1987. The cohort was restricted to workers that were not exposed to asbestos. There were 749 deceased workers by the end of follow up and 77 of those had lung cancer.

Checkoway et al. (1997) used Poisson regression and cumulative exposure to respirable crystalline silica with 0 and 15-year lags to fit the lung cancer mortality in the diatomaceous earth industry cohort. Although Checkoway et al. did not specify the model used, most likely they used the standard log-linear model, namely;

$$RR = \exp\{\beta \times \text{CumulativeExposure}\}.$$

Checkoway et al. estimated the slope of rate ratio per mg/m^3-year to 1.05 for cumulative exposures lagged 5 years. Because the $RR=\exp\{\beta\}=1.05$, this implies an estimate of the parameter β of 0.0488 or approximately 0.05.

Rice et al. (2001) also used several Cox proportional hazards and Poisson regression models in addition to the Poisson regression models used by Checkoway et al. (1997). Rice et al. adjusted for the same covariate effects than Checkoway et al. Rice et al. found that the Cox and Poisson regression resulted in similar models and showed results for the Poisson regression models only. Rice et al. also found that cumulative exposures lagged 10 years provided the best fit to the data and only reported results for cumulative exposures lagged 10 year. For the log-linear model and cumulative exposures lagged 10 years Rice et al. estimated the parameter β to be 0.0508 with a significance value of 0.026.

The most comparable three estimates of the log-linear model fit to lung cancer mortality in the U.S. diatomaceous earth industry cohort are then given in the following table.

Source	Exposure Lag (years)	Parameter Estimate	p-value
Checkoway et al. (1997)	15	0.0488	Not Reported
Rice et al. (2001)	10	0.0508	0.026
Steenland et al. (2001)	15	0.0500	0.022

The parameter estimated by Rice et al. is for cumulative exposure lagged 10 years whereas the parameters estimated by Checkoway et al. and Steenland et al. are for cumulative exposure lagged 15 years. The parameters estimated by Checkoway et al. and Rice et al. are based on the same data while the estimate by Steenland et al. is based on the same cohort but with fewer years of follow-up. Although the parameter estimates are not based on exactly the same assumptions, they are within 5% of each other and with approximately the same level of statistical significance (i.e., similar p-value).

4. Conclusions

The most recent literature for two studies in the Steenland et al. (2001) meta-analysis of lung cancer and silica exposure was reviewed. The U.S. diatomaceous and the U.S. granite studies were independently evaluated and published by other scientists and found results very similar to those reported by Steenland et al. The fact that the findings of these two studies are supportive of Steenland et al. results raises confidence on their pooled analysis based on ten cohorts.

Appendix 5. US and Texas Survival and Lung Cancer Mortality Rates

Mortality Rates Age (years)	Mortality Rates US[3] (2003)	Mortality Rate Texas [2] (2003)	Survival Rates Age (years)	Survival Rates US[1] (2003)	Survival Rates Texas[2] (2003)
0	0	0	0	1	1
1	0	0	1	0.99313	0.993
5	0	0	5	0.99189	0.992
10	0	0	10	0.99116	0.991
15	0	0	15	0.9902	0.990
20	0.1	0.3	20	0.98693	0.987
25	0.2	0.4	25	0.98219	0.982
30	0.6	1.6	30	0.97752	0.977
35	2.6	6.9	35	0.9721	0.972
40	9.0	14.2	40	0.96442	0.964
45	20.7	26.9	45	0.95285	0.952
50	41.5	59.3	50	0.93584	0.935
55	85.2	109.2	55	0.91181	0.911
60	152.0	165.6	60	0.87774	0.876
65	234.9	228.9	65	0.82688	0.824
70	318.6	271.8	70	0.75555	0.751

[1] Arias (2006)

[2] personal communication from Dr. David Risser, Texas Department of State Health Services

[3] SEER (2007)