# Silica, Amorphous

# and Other Non-Crystalline Forms

**CAS Registry Numbers:**

**7631-86-9 (synthetic amorphous silica)**

**60676-86-0 (fused)**

**69012-64-2 (silica fume)**

**61790-53-2 (uncalcined diatomaceous earth)**

**112945-52-5 (pyrogenic colloidal silica)**

**112926-00-8 (precipitated silica and silica gel)**

Prepared by

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# Acronyms and Abbreviations

| Acronyms and Abbreviations | Definition |
| --- | --- |
| ACGIH | American Conference of Governmental Industrial Hygienists |
| AMCV | Air monitoring comparison values |
| BAL | bronchoalveolar lavage |
| BMC | benchmark concentration |
| BMCL | benchmark concentration lower confidence limit |
| BMD | benchmark dose |
| BMDL | benchmark dose lower confidence limit |
| BMDS | benchmark dose software |
| BMR | benchmark response |
| C | concentration |
| Cal EPA | California Environmental Protection Agency |
| CIIT | Chemical Industry Institute of Toxicology |
| CNS | central nervous system |
| D | exposure duration, hour per day |
| d | day |
| DF | deposition fraction in the target region of the respiratory tract |
| DAF | dosimetric adjustment factor |
| DSD | development support document |
| E | exposure level or concentration |
| EC | effective concentration |
| ET | extrathoracic |
| ESL | Effects Screening Level |
| $^{acute}ESL$ | acute health-based Effects Screening Level for chemicals meeting minimum database requirements |
| $^{acute}ESL_{generic}$ | acute health-based Effects Screening Level for chemicals not meeting minimum database requirements |

| Acronyms and Abbreviations | Definition |
|---|---|
| $^{acute}ESL_{odor}$ | acute odor-based Effects Screening Level |
| $^{acute}ESL_{veg}$ | acute vegetation-based Effects Screening Level |
| $^{chronic}ESL_{linear(c)}$ | chronic health-based Effects Screening Level for linear dose response cancer effect |
| $^{chronic}ESL_{linear(nc)}$ | chronic health-based Effects Screening Level for linear dose response noncancer effects |
| $^{chronic}ESL_{nonlinear(c)}$ | chronic health-based Effects Screening Level for nonlinear dose response cancer effects |
| $^{chronic}ESL_{nonlinear(nc)}$ | chronic health-based Effects Screening Level for nonlinear dose response noncancer effects |
| $^{chronic}ESL_{veg}$ | chronic vegetation-based Effects Screening Level |
| F | exposure frequency, days per week |
| h | hour |
| $H_{b/g}$ | blood:gas partition coefficient |
| $(H_{b/g})_A$ | blood:gas partition coefficient, animal |
| $(H_{b/g})_H$ | blood:gas partition coefficient, human |
| HEC | human equivalent concentration |
| HQ | hazard quotient |
| IARC | International Agency for Research on Cancer |
| IRIS | Integrated Risk Information System |
| LDH | lactate dehydrogenase |
| LEC | lowest effective concentration |
| LOAEL | lowest-observed-adverse-effect-level |
| MF | modifying factor |
| MW | molecular weight |
| µg | microgram |
| min | minute |
| MMAD | mass median aerodynamic diameter |

| Acronyms and Abbreviations | Definition |
| --- | --- |
| MPPD | multiple pass particle dosimetry |
| MOA | mode of action |
| MRL | Minimal Risk Level |
| NAAQS | National Ambient Air Quality Standards |
| NAC | National Advisory Committee |
| NAG | N-acetyl glucosaminidase |
| N-L Ratio | NOAEL-to $LC_{50}$ Ratio |
| NOAEL | no-observed-adverse-effect-level |
| NOEL | no-observed-effect-level |
| NTP | National Toxicology Program |
| PBPK | physiologically-based pharmacokinetic model |
| PM | particulate matter |
| POD | point of departure |
| $POD_{ADJ}$ | point of departure adjusted for exposure duration |
| $POD_{HEC}$ | point of departure adjusted for human equivalent concentration |
| POE | portal of entry |
| PU | pulmonary |
| ppbv | parts per billion by volume |
| ppm | parts per million |
| RDDR | regional deposited dose ratio |
| ReV | Reference Value |
| RfC | Reference Concentration |
| RfD | Reference Dose |
| $RGD_A$ | regional gas dose in animal |
| $RGD_H$ | regional gas dose in human |
| RGDR | regional gas dose ratio |
| RIVM | Rijksinstituut voor Volksgezondheid en Milieu (Dutch National |

| Acronyms and Abbreviations | Definition |
|---|---|
| | Institute for Public Health and the Environment) |
| $R_{GM}$ | geometric mean ratio |
| RPF | relative potency factor |
| RTECS | Registry of Toxic Effects of Chemical Substances |
| SAS | synthetic amorphous silica |
| T | time or exposure duration |
| TB | trachiobronchial |
| TCEQ | Texas Commission on Environmental Quality |
| TH | thoracic |
| TLV | Threshold Limit Value |
| TD | Toxicology Division |
| TWA | Time-Weighted Average |
| TWA-TLV | Time-Weighted Average Threshold Limit Value |
| UF | uncertainty factor |
| $UF_H$ | interindividual or intraspecies human uncertainty factor |
| $UF_A$ | animal to human uncertainty factor |
| $UF_{Sub}$ | subchronic to chronic exposure uncertainty factor |
| $UF_L$ | LOAEL to NOAEL uncertainty factor |
| $UF_D$ | incomplete database uncertainty factor |
| USEPA | United States Environmental Protection Agency |
| VE | minute ventilation |
| $VE_{ho}$ | default occupational ventilation rate for an eight-hour day |
| $VE_h$ | default non-occupational ventilation rate for a 24-h day |

# Chapter 1 Summary Tables

Table 1 for air permitting and Table 2 for air monitoring provide a summary of health- and welfare-based values based on an acute and chronic evaluation of amorphous and other non-crystalline forms of silica (hereafter referred to as "amorphous silica. Please refer to the document entitled: "Uses of Effects Screening Levels (ESLs) and Air Monitoring Comparison Values (AMCVs)" and the Fact Sheet available at AMCVs at TCEQ for an explanation of the values used for review of ambient air monitoring data and air permitting. Table 3 provides summary information on amorphous silica's physical/chemical data.

**Table 1. Air Monitoring Comparison Values (AMCVs) for Ambient Air**

| Short-Term Values | Concentration | Notes |
|---|---|---|
| Acute ReV | 91 µg/m$^3$ $^a$ **Short-Term Health** | **Critical Effect(s):** respiratory inflammation – increased neutrophils and lactate dehydrogenase in bronchoalveolar lavage fluid in Crl:CD BR rats (male) |
| $^{acute}ESL_{odor}$ | --- | No data found |
| $^{acute}ESL_{veg}$ | --- | No data found |
| **Long-Term Values** | **Concentration** | **Notes** |
| Chronic ReV | 6.6 µg/m$^3$ $^a$ **Long-Term Health** | **Critical Effect(s):** Chronic inflammation, microscopic changes in the lungs, decreases in pulmonary function |
| $^{chronic}ESL_{linear(c)}$ $^{chronic}ESL_{nonlinear(c)}$ | --- | Inadequate information to assess carcinogenic potential via inhalation |
| $^{chronic}ESL_{veg}$ | --- | No data found |

$^a$ Values apply to respirable silica $\leq 10$ µm in diameter (PM$_{10}$)

**Table 2. Air Permitting Effects Screening Levels (ESLs)**

| Short-Term Values | Concentration | Notes |
|---|---|---|
| acuteESL [1 h]<br>(HQ = 0.3) | 27 µg/m$^3$ [a, b]<br>**Short-Term ESL for Air Permit Reviews** | **Critical Effect:** respiratory inflammation–increased neutrophils and lactate dehydrogenase in bronchoalveolar lavage fluid in Crl:CD BR rats (male) |
| acuteESL$_{odor}$ | **---** | There are no odors associated with silica |
| acuteESL$_{veg}$ | --- | No negative impacts of silica were identified in plants |
| **Long-Term Values** | **Concentration** | **Notes** |
| chronicESL$_{nonlinear(nc)}$<br>(HQ = 0.3) | 2.0 µg/m$^3$ [a, c]<br>**Long-Term ESL for Air Permit Reviews** | **Critical Effect:** Chronic inflammation, microscopic changes in the lungs, decreases in pulmonary function |
| chronicESL$_{linear(c)}$<br>chronicESL$_{nonlinear(c)}$ | --- | Inadequate information to assess carcinogenic potential via inhalation |
| chronicESL$_{veg}$ | --- | No data found |

[a] Values apply to respirable silica $\leq 10$ µm in diameter (PM$_{10}$)

[b] Based on the acute ReV (Table 1) of 91 µg/m$^3$ multiplied by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during the air permit review. This value is not used for the evaluation of ambient air monitoring data.

[b] Based on the chronic ReV (Table 1) of 6.6 µg/m$^3$ multiplied by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during the air permit review. This value is not used for the evaluation of ambient air monitoring data.

**Table 3. Chemical and Physical Data**

| Parameter | Value | Reference |
|---|---|---|
| Molecular Formula | $SiO_2$ | ACGIH 2001 |
| Molecular Weight | 60.09 | ACGIH 2001 |
| Physical State | Solid granules | ACGIH 2001 |
| Color | Off-white | ACGIH 2001 ECETOC 2006 |
| Odor | Odorless | ACGIH 2001 |
| CAS Registry Numbers | 7631-86-9 (synthetic amorphous silica)<br>60676-86-0 (fused)<br>69012-64-2 (fume)<br>61790-53-2 (diatomaceous earth, diatomite)<br>91053-39-3 (calcined)<br>68855-54-9 (flux-calcined)<br>112945-52-5 (pyrogenic colloidal silica)<br>112926-00-8 (precipitated silica, silica gel) | ACGIH 2001ECETOC 2006 |
| Synonyms/Trade Names | Agate; Onyx, Silicon dioxide, Sand, Silica Flour, Fused Silica, Silica Fume, Celatom, Diatomaceous Earth, Celite, Kieselguhr, Diatomite, Dicalite | ChemFinder 2004 |
| Solubility in water | Insoluble | ACGIH 2001 |
| Log $K_{ow}$ | Not available | --- |
| Vapor Pressure | Not applicable | --- |
| Vapor Density (air = 1) | Not applicable | --- |
| Density (water = 1) | 1.8-2.2 | ECETOC 2006 ACGIH 2001 ScienceLab.com 2010 |
| Melting Point | 1610°C (CAS No. 7361-86-9)<br>1700°C (CAS No. 112945-52-5) | ScienceLab.com 2010 CABOT 2007 |
| Boiling Point | 2230°C (CAS No. 112945-52-5) | CABOT 2007 |

# Chapter 2 Major Sources or Uses

Amorphous silica is divided into naturally occurring amorphous silica and synthetic forms. Naturally occurring amorphous silica such as uncalcined diatomaceous earth usually contains certain amounts of crystalline silica, sometimes up to 8 %. Certain industrial processes such as manufacture of elemental silicon and silicon alloys produce silica fume and fused silica as by-products that may contain impurities, particularly crystalline silica. Amorphous silica includes synthetic amorphous silica (SAS), and non-SAS forms of amorphous silica such as diatomaceous earth, precipitated amorphous silica and amorphous silica gel, pyrogenic silica, fumed amorphous silica, fused amorphous silica, colloidal amorphous silica (Warheit 2001). Diatomaceous earth is used in clarifying liquids; in the manufacture of fire brick and heat insulators; and in metal polishes and dentifrices. Precipitated amorphous silica and amorphous silica gel are used as a grease thickener, diluents for insecticide, and fillers for paint, rubber, and paper. Industrial by-products of amorphous silica include fused silica and silica fume. Fumed amorphous silica, a fine white powder, is a by-product of ferrosilicon, an electrometallurgical process. Fused amorphous silica is used in making camera lenses, and to reinforce plastics (ACGIH 2001). SAS is intentionally manufactured amorphous silica that does not contain measurable levels of crystalline silica (< 0.01% by weight relative to quartz). SAS is produced by the wet route (precipitated silica, silica gel) or the thermal route (pyrogenic silica). SAS, including pyrogenic silicas, precipitated silicas and silica gels, is white, fluffy powders or milky-white dispersions of these powders (usually in water). SAS is hydrophilic, but can be made hydrophobic by surface treatment. (ECETOC 2006, Arts et al. 2007). According to Arts et al. (2007), SAS is used in synthetic resins, plastics, lacquers, vinyl coatings, adhesives, paints, printing inks, and silicone rubber. SAS is also used as fillers in the rubber industry, insulation material, and toothpaste additives as free-flow and anti-caking agents in powder materials. SAS may be used in pharmaceuticals, cosmetics, and liquid carriers in the manufacture of agrochemicals and animal feed.

# Chapter 3 Acute Evaluation

## 3.1 Health-Based Acute ReV and ESL

The critical effect of acute exposure to crystalline and non-crystalline forms of silica is increased inflammation and cytotoxicity in the respiratory tract. Various forms of amorphous silica produce less potent and more transient pulmonary inflammatory effects relative to crystalline forms of silica dust (Warheit et al. 1991, 1995; Warheit 2001; Lee and Kelly 1992; Arts et al. 2007). The inhalation toxicity factors for crystalline forms of silica are described in a separate Development Support Document (DSD) (TCEQ 2009). Since no acute or subacute studies of non-synthetic amorphous silica (non-SAS) forms were available, the acute ReV and ESL developed for SAS are used for all forms of amorphous and non-crystalline silica, including fused, silica fume, uncalcined diatomaceous earth, pyrogenic colloidal silica, precipitated silica, and silica gel. The Toxicology Division (TD), however, may develop separate acute toxicity factors for non-SAS forms of amorphous silica if available studies for non-SAS forms become available.

## 3.1.1 Physical/Chemical Properties

The main chemical and physical properties of amorphous silica are summarized in Table 3. Amorphous silica occurs naturally as raw diatomite and calcined and flux-calcined forms. Certain industrial processes produce silica fume and fused silica as by-products. 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 (i.e., animals were exposed to larger and smaller particles) and bronchoalveolar lavage (BAL) fluids represent both the tracheobronchial (TB) and pulmonary (PU) regions of the lung, the acute toxicity factors developed will apply to all non-crystalline silica particles less than or equal to the median cut point for the thoracic region of 10 μm ($PM_{10}$), i.e., 50% thoracic particulate matter (TPM) fraction collected. The TPM fraction consists of those particles that are hazardous when deposited anywhere within the lung airways and the gas-exchange region (ACGIH 2010).

## 3.1.2 Animal Studies

Information from human studies regarding the acute toxicity of amorphous silica is limited and insufficient for the development of the Rev and ESL. Therefore, animal studies that investigated SAS were used to develop the acute ReV and ESL. There are no relevant toxicity data available for silica fume, fused silica, or diatomaceous earth. Therefore, the toxicity values derived for SAS will be used for these forms of silica as a policy decision. Animal data indicate that acute and subacute amorphous silica exposures can elicit pulmonary inflammatory responses. However, few studies have provided exposure dose-response data to identify a no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL). Animal studies investigated amorphous silica by Warheit et al. (1995), Arts et al. (2007), Reuzel et al. (1991), and Lee and Kelly (1992) have provided NOAEL and/or LOAEL values used to develop the acute ReV and ESL.

### *3.1.2.1 Key Animal Study (Warheit et al. 1995)*

The Warheit et al. (1995) study was chosen as the key study. Warheit et al. (1995) examined the effects of short-term inhalation exposure of two different forms of crystalline silica (cristobalite and Min-U-Sil) and amorphous silica free of crystalline contamination (Zeofree 80 and Ludox) in groups of 24 CD rats exposed to:

- 10 or 100 mg/m3 of cristobalite (MMAD = 3.4-3.6. μm) for 6 hour/day (h/d) for 3 d
- 10 or 100 mg/m3 of Zeofree 80 (precipitated silica) (MMAD = 2.4-3.4 μm) for 6 h/d for 3 d
- 100 mg/m3 of Min-U-Sil (α-quartz, MMAD = 3.3-3.5 μm) for 6 h/d for 3 d
- 10, 50, or 150 mg/m3 of Ludox colloidal silica (MMAD = 2.9-3.7 μm) for 6 h/d, 5 d/week for 2 or 4 weeks.

The study assessed the presence of granulocytes, extracellular lactate dehydrogenase (LDH), protein, and N-acetyl glucosaminidase (NAG) levels in BAL fluids as biomarkers of pulmonary toxicity. Pulmonary inflammatory response, characterized by the presence of granulocytes in BAL fluids, was observed at 24-h post exposure to both concentrations (10 and 100 mg/m$^3$) of cristobalite and Zeofree 80. However, the inflammation resolved by 8-d post exposure in animals exposed to Zeofree 80 but remained in animals exposed to cristobalite throughout a 3-month post exposure period. Similarily, exposures to Ludox at 50 or 150 mg/m$^3$, but not at 10 mg/m$^3$, produced increased numbers of granulocytes ($p < 0.05$) but were significantly reduced following a 3-month recovery period.

Similar results were observed for pulmonary cytotoxicity. Transient increases in LDH and protein levels were measured in rats within 24 h after exposure to Zeofree 80. Transient increase in protein levels was also observed in rats exposed to Ludox for 2 or 4 weeks at concentrations of 10, 50, or 150 mg/m$^3$. However, sustained increases in LDH and protein levels were observed in all of the groups of animals exposed to crystalline silica. Rats exposed to cristobolite or Min-U-Sil for 3 d demonstrated substantial increases in LDH and protein levels over those of the controls ($p < 0.05$) 3 months after exposure. In rats exposed to 150 mg/m$^3$ of Ludox, the LDH was significantly increased above the control level at 2 or 4 weeks, but was reduced after the recovery period. No significant differences were measured for LDH at any time post exposure between the rats exposed to 10 or 50 mg/m$^3$ concentrations of Ludox and the controls. NAG levels of rats exposed to cristobaslite or Min-U-Sil were significantly increased in BAL fluids ($p <0.05$) after 3-d exposure. However, the NAG levels of rats exposed to amorphous silica did not significantly differ from those of controls by 8-d post exposure.

The results of the Warheit et al. (1995) study demonstrated that transient pulmonary inflammatory responses were observed in a 3-d exposure to Zeofree 80 at 10 or 100 mg/m$^3$; and in a 2- or 4-week exposure to Ludox at 50 or 150 mg/m$^3$, but not at 10 mg/m$^3$. A subacute NOAEL of 10 mg/m$^3$ for Ludox colloidal silica and subacute LOAEL of 10 mg/m$^3$ for Zeofree 80 or crystalline silica were identified from this study. The NOAEL of 10 mg/m$^3$ for Ludox colloidal silica, however, is not preferred to develop acute ReV and ESL for amorphous silica since they are based on an exposure duration of two or four weeks. The results of this study showed that Ludox is less active in producing pulmonary effects relative to Zeofree 80.

While pulmonary toxicity was also observed in a 3-d exposure to 10 mg/m$^3$ Zeofree 80 within 24 h post-exposure (but resolved by 8-d post-exposure), the inflammatory and cytotoxic effects (characterized by the presence of granulocytes and extracellular LDH and protein levels in BAL fluids) are considered transient and mild. Additionally, an acute LOAEL (delayed increases in inflammation and cytotoxicity and the potential for the development of pulmonary lesions) of 10 mg/m$^3$ for the crystalline form of silica was also indentified from their previous study (Warheit et al. 1991 in TCEQ 2009). The results of the Warheit et al. (1995) study support their previous study (Warheit et al. 1991) that crystalline forms of silica are much more potent in producing pulmonary toxicity than amorphous or colloidal forms of silica are. Therefore, the level of 10 mg/m$^3$ (identified from the Warheit et al. (1995) study) was considered a minimal LOAEL for

pulmonary toxicity for amorphous silica. This minimal LOAEL was conservatively used as the relevant point of departure (POD) to develop the acute ReV and ESL for all forms of amorphous silica. The TD acknowledges that 10 mg/m$^3$ for Zeofree 80 amorphous silica, according to the USEPA Effects Severity Levels (USEPA 1994 in TCEQ 2006), can also be considered a practical NOAEL which is in agreement with the subacute NOAEL of 10 mg/m$^3$ for Ludox colloidal silica identified from the two- or four-week study. In consideration of the inherent conservativeness of using 10 mg/m$^3$ as a minimal LOAEL, a reduced LOAEL-to-NOAEL uncertainty factor will be used (Section 3.1.6.2 Uncertainty Factors (UFs)).

### 3.1.2.2 Supporting Animal Study (Arts et al. 2007)

Arts et al. (2007) evaluated the effects of inhalation exposure to three different types of SAS: Zeosil 45 (precipitated silica), Syloid 74 (silica gel), and Cab-O-Sil M5 (pyrogenic silica). These SAS types contain greater than 97.3%, 99.5%, and 99.7% silicon dioxide, respectively. The mean particle size was selected to obtain MMAD of 2-3 μm in the test atmospheres for each SAS type. Groups of 10 male Wistar rats were exposed to 1, 5, or 25 mg/m$^3$ (nominal concentrations, head/nose-only exposure) of each SAS type for 6 h/d for 5 d. Rats exposed to filtered air served as negative controls, and rats exposed to 25 mg/m$^3$ quartz served as positive controls. This study assessed cytotoxicity, organ weight, and histopathological lung changes. Exposure to the individual three SASs at 25 mg/m$^3$ induced slight but significant elevations in biomarkers of cytotoxicity in BAL fluids, slight increases in lung and tracheobronchial lymph node weight and histopathological lung changes 1-d post-exposure. Exposure to the individual three SASs at 5 mg/m$^3$ induced transient and, to a lesser degree, very slight histopathological changes and changes in BAL fluids relative to exposure at those SASs at 25 mg/m$^3$. These changes were reversible during the 3-month recovery period. The concentration of 5 mg/m$^3$ can be considered a minimal LOAEL although the investigators did not indicate. None of these changes occurred in rats exposed to 1 mg/m$^3$ of any of the SAS types used. The concentration of 1 mg/m$^3$ was identified as a NOAEL for the three types of SAS tested by the authors. Similar results which identified a NOAEL of 1 mg/m$^3$ for these three SAS types were reported in studies by Arts and Kuper (2003a) and Arts el al. (2003) (both were cited in ECETOC 2006). The NOAEL from the Arts et al. (2007) study, however, is not preferred to develop acute ReVor ESL for amorphous silica since it is based on an exposure duration of 5 d; and the NOAEL is lower than the minimal LOAEL of 10 mg/m$^3$ for Zeofree 80 and the NOAEL of 10 mg/m$^3$ for Ludox colloidal silica identified from the Warheit et al. (1995) study.

3.1.2.3 Supporting Animal Study (Reuzel et al. 1991) In order to find the proper concentration range for their 13-week subchronic inhalation toxicity study, Reuzel et al. (1991) conducted a two-week subacute inhalation study for three amorphous silicas (Aerosil 200, Aerosil R 974 and Sipernat 22S). Aerosil 200 is pyrogenic silica, Aerosil R974 is a surface treated (hydrophobic) pyrogenic silica, and Sipernat 22S is precipitated silica. Particle size distribution was not analyzed and thus, no MMAD and GSD were provided for the tested amorphous silica products in this study. Groups of 10 male and 10 female SPF-bred Wistar rats were exposed for 6 h/d, 5 d/week for two weeks to the following analytical concentrations:

- 0, 17, 44, or 164 mg/m$^3$ Aerosil 200,
- 0, 31, 87, or 209 mg/m$^3$ Aerosil R 974, and
- 0, 46, 170, or 668 mg/m$^3$ Sipernat 22S.

Body weights, food consumption, hematological parameters, organ weights, and gross and microscopic pathology were examined. The results showed that there was a clear dose-response relationship in most of the measured endpoints for all three tested amorphous silicas, and no effects were observed at 17, 31, and 46 mg/m$^3$, respectively, for exposure to Aerosil 200, Aerosil R 974, and Sipernat 22S. While no NOAELs and/or LOAELs were identified from this study, the authors concluded that a NOAEL for Aerosil 200, Aerosil R 974, and Sipernat 22S would be lower than 17, 31, and 46 mg/m$^3$, respectively. The results of this study support the minimal LOAEL of 10 mg/m$^3$ identified from the Warheit et al. (1995) study.

### 3.1.2.4 Supporting Animal Study (Lee and Kelly 1992)

In a 4-week inhalation study, Lee and Kelly (1992) exposed Crl:CD BR rats (25/group) to Ludox colloidal silica at concentrations of 0, 10.1, 50.5, or 154 mg/m$^3$ (analytical concentrations), 6 h/day, 5 d/week for 4 weeks. The MMAD ± geometric standard deviation (GSD) for the 10, 50, and 150 mg/m$^3$ exposure concentrations was 3.7 ± 1.9, 3.3 ± 2.1, and 2.9 ± 2.3 μm, respectively. Five rats were necropsied at the end of the exposure period, and 10 each at 10 d and 3 months post exposure. No pulmonary effects were seen at the lowest concentration of 10 mg/m$^3$. After 4 weeks exposure, lung weights were increased significantly in rats exposed to 50 and 150 mg/m$^3$ Ludox, but lung weights were similar to those of controls at 3 months post exposure. At 50 and 150 mg/m$^3$, there was a concentration-related pulmonary response in the alveolar duct region characterized by silica-dust-laden alveolar macrophages, neutrophilic infiltration, and Type II pneumocyte hyperplasia. Tracheal and mediastinal lymph nodes were enlarged due to the silica-dust-laden alveolar macrophages and tissue hyperplasia. Most particle-laden alvelolar macrophages (AMs) had disappeared and the remaining AMs were aggregated and sharply demarcated at 3 months post exposure. A few aggregates of particle-laden AMs appeared to transform into silicotic nodules comprising macrophages, epithelioid cells, and lymphocytic infiltration in some animals. Some silicotic nodules showed reticular fiber networks with minute collagen fiber deposition. Tracheobronchial lymph nodes were enlarged with aggregates of particle laden AMs and hyperplastic histiocytic cells. A NOAEL of 10 mg/m$^3$ was indentified from this 4-week study. The NOAEL from this study is not preferred to develop acute ReVs and ESLs for amorphous silica since it is based on an exposure duration of 4 weeks.

The results of these acute and subacute animal studies are summarized in the Table 4 below.

**Table 4. Summary of Acute and Subacute Animal Inhalation Studies**

| Study | Animal Strain | Exposure Duration | Type of Silica | NOAEL (mg/m$^3$) | LOAEL (mg/m$^3$) | Response at LOAEL |
|---|---|---|---|---|---|---|
| Warheit et al. (1995) **Key Study** | CD Rats | 6 h/d for 3d | Zeofree 80 10 or 100 mg/m$^3$ | -- | 10 (minimal) | 1. Pulmonary inflammation: transient/mild increased numbers of granulocytes 2. Pulmonary cytotoxicity: transient/mild increases in LDH and total protein levels |
| Warheit et al. (1995) **Key Study** | CD Rats | 6 h/d for 3d | Cristobalite 10 or 100 mg/m$^3$ | -- | 10 | Sustained increases in numbers of granulocytes, NAG, LDH, and protein levels |
| Warheit et al. (1995) **Key Study** | CD Rats | 6 h/d, 5 d/week for 2 or 4 weeks. | Ludox colloidal silica @ 10, 50, or 150 mg/m$^3$ | 10 | 50 | Transient/mild increased numbers of granulocytes |
| Warheit et al. (1995) **Key Study** | CD Rats | 6 h/d, 5 d/week for 2 or 4 weeks. | Ludox colloidal silica @ 10, 50, or 150 mg/m$^3$ | -- | 10 (minimal) | Transient/mild increases in LDH and total protein levels |
| Art et al. (2007) | Male Wistar Rats | 6 h/d for 5 d @ 1, 5, or 25 mg/m$^3$ | Zeosil 45 (precipitat-ed silica) | 1 | 5 (minimal) | Transient and very slight histopathological changes and changes in BAL fluids |
| Art et al. (2007) | Male Wistar Rats | 6 h/d for 5 d @ 1, 5, or 25 mg/m$^3$ | Syloid 74 (silica gel) | 1 | 5 (minimal) | Transient and very slight histopathological changes and changes in BAL fluids |

| Study | Animal Strain | Exposure Duration | Type of Silica | NOAEL (mg/m$^3$) | LOAEL (mg/m$^3$) | Response at LOAEL |
|---|---|---|---|---|---|---|
| Art et al. (2007) | Male Wistar Rats | 6 h/d for 5 d @ 1, 5, or 25 mg/m$^3$ | Cab-O-Sil M5 (pyrogenic silica) | 1 | 5 (minimal) | Transient and very slight histopathological changes and changes in BAL fluids |
| Reuzel et al. (1991) | Wistar Rats | 6 h/d, 5 d/week for 2 weeks | Aerosil 200 @ 0, 17, 44, or 164 mg/m$^3$ | < 17 | 44 | Respiratory distressed, body weight decreased, histopathological changes; there was a clear dose-response relationship |
| Reuzel et al. (1991) | Wistar Rats | 6 h/d, 5 d/week for 2 weeks | Aerosil R 974 @ 0, 31, 87, or 209 mg/m$^3$ | < 31 | 87 | There was a concentration-related increased in lung weights, cellularity, alveolar edema and granulomas of the lungs |
| Reuzel et al. (1991) | Wistar Rats | 6 h/d, 5 d/week for 2 weeks | Sipernat 22S @ 0, 46, 170, or 668 mg/m$^3$ | < 46 | 170 | Similar to those for Aerosil R 974 |
| Lee and Kelly (1992) | Crl:CD BR Rats | 6 h/day, 5 d/week for 4 weeks | Ludox colloidal silica @ 10, 50, and 150 mg/m3 | 10 | 50 | Lung weights increased; alveolar macrophages, neutrophilic infiltration, and Type II pneumocyte hyperplasia; tracheobronchial lymph nodes enlarged; there was a dose-response relationship at 50, and 150 mg/m3 |

## 3.1.3 Mode-of-Action (MOA) Analysis

The MOA for respiratory damage following silica exposure appears to be inflammation. Numerous inflammatory mediators have been associated with silica toxicity, including interleukins, tumor necrosis factor-$\alpha$, transforming growth factor $\beta$, 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. The elimination of amorphous silica is relatively fast with limited biopersistence in the lungs, compared to insoluble 'inert' particles like quartz. Based on a physiology-orientated-multicompartmental kinetic model, Stöber *et a.l* (2000) and Koch and Stöber (2001) (both are cited in ECETOC 2006) predicted that the clearance of SAS by dissolution is at least 20 times faster than particulate clearance by macrophages. 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). Exposure of an alveolar epithelial cell line to amorphous silica indicates that inflammatory gene expression may be induced by activation of the activator protein 1 (AP-1) transcription factor. It is assumed that a sufficiently high amount of silica (threshold) is required to activate proinflammatory transcription factors and the subsequent inflammatory cascade (Singal et al. 2005). Therefore, a nonlinear, threshold dose-response was applied for the development of an acute toxicity factor. Importantly, Rabovsky (1997) noted that markers of silica-induced toxicity produced in experimental animals, particularly rats, are similar to those exhibited by humans. Therefore, the findings in rats are relevant to humans.

## 3.1.4 Dose Metric

In the key and supporting studies, data pertaining to exposure concentration of the parent chemical are available. 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.

## 3.1.5 POD for the Key Study

In the acute study conducted by Warheit et al. (1995), rats were exposed to Zeofree 80 amorphous silica for 6 h/d for 3 d. Rats exposed to 10 mg/m$^3$ Zeofree 80 amorphous silica showed signs of mild and transient pulmonary inflammatory response. As discussed in Section 3.1.1.2.1 above, the TD decided to conservatively treat 10 mg/m$^3$ as a minimal LOAEL and the relevant POD.

## 3.1.6 Dosimetric Adjustments

### 3.1.6.1 Default Exposure Duration Adjustments

The concentration ($C_1$) at the 6-h exposure duration ($T_1$) in the key study by Warheit et al. (1995 was adjusted to an adjusted POD ($POD_{ADJ}$) concentration ($C_2$) applicable to a 1-h exposure duration ($T_2$) 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. The TD chose to adjust

the exposure from 6 h/d to 1 h/d rather than adjusting the total duration of exposure in the study over the 3 days of exposure (i.e., 6 h/d for 3 days = 18 h to 1 h) in consideration of protecting against intermittent exposure and the possibility of delayed inflammation.

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

### 3.1.6.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

As noted in Table 3, silica is a solid granule and the study was conducted in rats. 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 target pulmonary region(s). According to Warheit et al. (1995), the MMAD of Zeofree 80 amorphous silica used in their study ranged from 2.4-3.4 μm. The low end (2.4 μm MMAD) and high end (3.4 μm MMAD) of this range were modeled in the MPPD program and are presented for comparison. The particle density is 2.3 g/cm$^3$ (Table 3). The chemical concentration is the POD$_{ADJ}$ of 18.17 mg/m$^3$. The target region for SAS was considered to be the total particle distribution for the TB and pulmonary PU regions. All remaining values used, including the GSD, were default. Once the total particle distribution was determined (Appendix A), the Regional Deposition Dose Ratio (RDDR) was calculated as follows:

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

where: $V_E$ = minute volume

$DF$ = deposition fraction in the target region of the respiratory tract

$NF$ = normalizing factor

$A$ = animal

$H$ = human

RDDR (low end of range) = $[(137.3 \text{ mL/min})/(13,800 \text{ mL/min})] \times [(0.151)/(0.261)] \times [(630,200 \text{ cm}^2)/(3422.5 \text{ cm}^2)] = 1.060$

RDDR (high end of range) = $[(137.3 \text{ mL/min})/(13,800 \text{ mL/min})] \times [(0.148)/(0.271)] \times [(630,200 \text{ cm}^2)/(3422.5 \text{ cm}^2)] = 1.001$

These two RDDRs were then used to dosimetrically adjust from an animal to human POD:

$$POD_{HEC} = POD_{ADJ} \times RDDR \text{ (low)} = 18.17 \text{ mg/m}^3 \times 1.060 = 19.26 \text{ mg/m}^3 = 19,260 \text{ μg/m}^3$$

$$POD_{HEC} = POD_{ADJ} \times RDDR \text{ (high)} = 18.17 \text{ mg/m}^3 \times 1.001 = 18.19 \text{ mg/m}^3 = 18,190 \text{ μg/m}^3$$

The more conservative $POD_{HEC}$ of 18,190 μg/m$^3$ based on RDDR (high) was used to calculate acute ReV and ESL.

## 3.1.7 Critical Effect and Adjustments to the $POD_{HEC}$

### 3.1.7.1 Critical Effect

As indicated in Section 3.1.1.2, 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. 1995) are increases in neutrophil (marker of inflammation) and LDH levels (marker of cytotoxicity) in BAL fluid from male Crl:CD rats exposed to 10 mg/m$^3$ silica for 6 h.

### 3.1.7.2 Uncertainty Factors (UFs)

The MOA by which amorphous silica may produce toxicity is discussed in Section 3.1.2. The default for nonlinear 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 $POD_{HEC}$ of 18.19 mg/m$^3$ from the Warheit et al. (1995) key study:

- 2 for extrapolation from a minimal LOAEL to a NOAEL ($UF_L$), because
  - the effects noted were mild and reversible for amorphous silica, and are less potent than crystalline forms of silica are when exposed to the same level of 10 mg/m$^3$;
  - the effects of enzyme induction, (i.e., LDH, and subcellular proliferation and influx of neutrophils) observed in rats exposed to 10 mg/m$^3$ of Zeofree 80 amorphous silica can be classified also as a NOAEL (see Section 3.1.1.2.1);
  - the level of 10 mg/m$^3$ was a NOAEL for Ludox colloidal silica in the 2 or 4 week study;
  - the default exposure duration adjustment using Haber's Rule with an exponent of 3 tends to be conservative;
  - Therefore, a low to moderate $UF_L$ factor of 2, based on the geometric mean (1.7, rounded to 2) of a $UF_L$ of 1 (NOAEL) and 3 (LOAEL for mild and transient effects), was used for extrapolation from a LOAEL to a NOAEL.
- ECETOC (2010) indicates that no additional interspecies extrapolation ($UF_A$) is needed due to the higher respiratory rate of rodents that leads to a greater respiratory tract burden. The TD applied default dosimetric adjustments using the RDDR to account for toxicokinetic differences. However, a $UF_A$ of 3 is applied to account for toxicodynamic differences.
- 10 for intraspecies variability ($UF_H$), 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.
- 3 for database uncertainty ($UF_D$) was used instead of 10 to account for the lack of acute studies in other species.
- The total UFs applied to the $POD_{HEC}$ were 200.

$$\text{Acute ReV} = POD_{HEC} / (UF_L \times UF_A \times UF_H \times UF_D)$$
$$= 18.19 \text{ mg/m}^3 / (2 \times 3 \times 10 \times 3)$$
$$= 0.09095 \text{ mg/m}^3 \text{ or } 90.95 \text{ µg/m}^3$$

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

The acute ReV of 90.95 µg/m$^3$ was rounded to two significant figures at the end of all calculations. The rounded acute ReV of 91 µg/m$^3$ was then multiplied by 0.3 to calculate the $^{acute}$ESL. At the target hazard quotient (HQ) of 0.3, the $^{acute}$ESL is 27 µg/m$^3$ (Table 5).

**Table 5. Derivation of the Acute ReV and $^{acute}$ESL**

| Parameter | Summary |
|---|---|
| Study | Warheit et al. (1995) |
| Study population | Crl:CD BR rats (male) |
| Study quality | High |
| Exposure Methods | Inhalation exposure to 10 or 100 mg/m$^3$ of Zeofree 80 amorphous silica (MMAD = 2.4-3.4 μm) for 6 h/d for 3 d |
| LOAEL | 10 mg/m$^3$ |
| NOAEL | None |
| Critical Effects | Increased neutrophil and LDH in BAL fluids |
| POD$_{animal}$ | 10 mg/m$^3$ (minimal LOAEL) |
| POD$_{ADJ}$ (extrapolated 1-h concentration) | 18.17 mg/m$^3$ |
| POD$_{HEC}$ | 18.19 mg/m$^3$ (RDDR = 1.001) |
| Total Uncertainty Factors (UFs) | 200 |
| *Interspecies UF* | *3* |
| *Intraspecies UF* | *10* |
| *LOAEL UF* | *2* |
| *Incomplete Database UF* | *3* |
| *Database Quality* | *Moderate* |
| **acute ReV [1 h] (HQ = 1)** | **91 μg/m$^3$** |
| **$^{acute}$ESL [1 h] (HQ = 0.3)** | **27 μg/m$^3$** |

## 3.2. Welfare-Based Acute ESLs

### 3.2.1 Odor Perception

There are no odors associated with silica (Mallinckrodt Chemicals 2006). Therefore, no $^{acute}$ESL$_{odor}$ was developed.

### 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 = 91 µg/m$^3$
- $^{acute}$ESL = 27 µg/m$^3$

The short-term ESL for air permit reviews is the health-based $^{acute}$ESL of 27 µg/m$^3$ (Table 2). The acute ReV of 91 :g/m$^3$ is used as the short-term AMCV for the evaluation of air monitoring data (Table 1).

# Chapter 4 Chronic Evaluation

## *4.1 Noncarcinogenic Potential*

Chronic inhalation exposure to high levels of silica (most commonly crystalline silica) has long been known to cause silicosis. Amorphous silica is less fibrogenic than crystalline silica thus, silicosis has rarely been observed after exposure to pure amorphous silica (IARC 1997, ACGIH 2001). Epidemiological studies do not support that amorphous silicas have any relevant potential to induce fibrosis in exposed workers (ACGIH 2001). Studies on chronic pulmonary toxicological effects of inhaled amorphous silica particles are limited. The limited toxicological database indicates that subchronic and chronic studies in animal exposure to amorphous silica leads to transient pulmonary changes but not to chronic conditions, such as fibrosis or cancer (McLaughlin et al. 1997; Johnston et al. 2000; Warheit 2001; Merget et al. 2002; Greer and Goldsmith 2007).

## 4.1.1 Physical/Chemical Properties

Physical/chemical properties of amorphous silica are discussed in Chapter 3. As with acute exposure, the chronic toxicity of amorphous silica particles is related to particle size. Because markers of pulmonary inflammatory response are generally measured in BAL fluids, which represent both the TB and PU regions of the lung, the chronic 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 (PM$_{10}$).

Human studies for the evaluation of pulmonary effects (e.g., silicosis, chronic bronchitis, emphysema, chronic obstructive pulmonary disease (COPD), and carcinoma) investigating chronic exposures to amorphous silica are sparse. Most of these studies failed to show a significant association between exposure to amorphous silica and lung effects, and to definitively differentiate between crystalline and amorphous silica. Furthermore, most of silica exposures in these studies were contaminated by some amounts of crystalline silica, thus independent effects of amorphous silica cannot be determined (ACGIH 2001; Merget et al. 2002). The intentionally manufactured SAS are without contamination of crystalline silica. There is no evidence of cancer or other long-term respiratory health effects (e.g., silicosis) in workers employed in the

manufacture of SAS. Several SAS of different types (pyrogenic, precipitated and sols) have been evaluated in subchronic and chronic animal studies, using airborne concentrations ranging from 0.5 to 150 mg/m$^3$ (ECETOC 2006). Therefore, animal inhalation studies with intentionally manufactured SAS are used to develop the chronic ReV and ESL. Since no subchronic or chronic studies of non-SAS amorphous silica were available, the developed chronic ReV and ESL for SAS are used for all forms of amorphous and non-crystalline silica as a policy decision. The TD, however, may develop separate chronic toxicity factors for non-SAS forms of amorphous silica if available studies become available. The TD chose the Groth et al. (1981) chronic study that evaluated different forms of SAS as the key study because the study examined multiple pulmonary effects on multiple species with sufficient numbers of animal in each experiment group for multiple forms of amorphous silica exposures. For comparison purpose, the TD also chose subchronic study by Reuzel et al. (1991) as a supporting study because the study showed that the adverse effects caused by these amorphous silica products demonstrated a clear dose-response relationship in most of the measured endpoints.

### 4.1.1.1 Groth et al. (1981) Key Study

Groth et al. (1981) compared the pulmonary toxicity (respiratory impairment and histopathological changes) of inhaled synthetic amorphous fume silica, precipitated silica, and silica gel in rats, guinea pigs, and monkeys. Eighty male Sprague-Dawley rats, 20 male Hartley guinea pigs, and 10 adult male cynomolgus monkeys were exposed to silica dusts at a target concentration of 15 mg/m$^3$ over a period of 5.5 to 6 h/d, 5 d/week, for up to 18 months. MMAD and GSD were not provided in this study. However, the TD determined MMAD and corresponding GSD based on the sampling results of size distribution of particles used in the amorphous silica experiments (see Table 2 of the Groth et al. (1981) study). The particle size fraction (μm) and the corresponding cumulative percentage of particle mass data were plotted on a log-probability graph paper. The calculated MMAD ± GSD are: fume silica (3.2 ± 2.5μm), precipitated silica (3.5 ± 2.5μm), and silica gel (3.9 ± 2.6 μm). An equal number of animals served as controls.

Rats were sacrificed serially after 3, 6, and 12 months of exposure, and guinea pigs and monkeys after 10 to 18 months of exposure. The most significant effect of exposure to the three forms of amorphous silica occurred in monkeys and was confined to the lungs and lymph nodes, which contained large numbers of macrophages and mononuclear cell aggregates, sometimes significantly reducing the size of the bronchiolar lumen. Relatively few or no silica-containing macrophages were seen in the lungs and lymph nodes of rats and guinea pigs exposed to any of the forms of amorphous silica in this study. It is also significant that fume silica induced early nodular fibrosis in the lungs of the monkeys in monkeys exposed to all three forms of amorphous silica for 14 months. In addition, pulmonary function tests were conducted to assess the degree of respiratory impairment. Pulmonary functions, as measured by lung volumes and ventilatory mechanics, were decreased at the end of the study period in monkeys exposed to fume silica and silica gel. The authors noted that respiratory impairment appeared to be most pronounced in fume silica-exposed monkeys. Under the conditions of this experiment, fume silica appeared to

cause more severe pulmonary effects than did either precipitated silica or silica gel. A freestanding LOAEL of 15 mg/m$^3$ amorphous silica for pulmonary effects (i.e., respiratory impairment and histopathological changes) was indentified from this study and was used as the relevant POD to develop the chronic ReV and ESL.

### 4.1.1.2 Reuzel et al. (1991) Supporting Study

Based on the results of concentration-finding subacute studies as discussed in Section 3.1.2.1, Reuzel et al. (1991) conducted a subchronic inhalation study of three amorphous silica products (Aerosil 200, Aerosil R 974 and Sipernat 22S). Groups of 70 male and 70 female SPF-bred Wistar rats were exposed to target concentrations of 0, 1, 6, or 30 mg/m$^3$ for Aerosil 200; one concentration of 30 mg/m$^3$ for Aerosil R 974 or Sipernat 22S for 6 h/d, 5 d/week for 13 weeks. Particle size distribution was not analyzed and thus, no MMAD and GSD were provided for the tested amorphous silica products in this study. After the exposure period, 20 rats/sex/group were sacrificed. In addition, 10, 10, 10 and 20 rats/sex/group was sacrificed after 13, 26, 39 and 52 weeks of exposure, respectively. Body weights, hematological parameters, organ weights, and gross and microscopic pathology were examined. The results showed that the adverse effects caused by these amorphous silica products demonstrated a clear dose-response relationship in most of the measured endpoints. At the end of the exposure period, the following effects were noted:

- Body weight gain was statistically significant lower in male rats exposed to 30 mg/m$^3$ Aerosil 200 or Sipernat 22S compared to the control group.
- Neutrophil counts were found higher in most exposure groups, but was only statistically significant in rats exposed to 30 mg/m$^3$ Aerosil 200.
- The increases of lung weight and lung collagen contents were statistically significant in all treated groups except those exposed to 1 mg/m$^3$ Aerosil 200.
- In addition, rats exposed to Aerosil 200 or Aerosil R 974 developed granulomatous lesions in the lungs, but no silicosis was observed.
- Rats exposed to 30 mg/m$^3$ Aerosil 200 induced the most severe changes in the lungs and these changes were only partly reversed during the post-exposure period.
- Aerosil R 974 and the lower levels (6 or 30 mg/m$^3$) of Aerosil 200 resulted in less severe and mostly reversible changes.
- Exposure to 30 mg/m$^3$ Sipernat 22S or 1 mg/m$^3$ Aerosil 200 induced rather mild and quickly reversible lung changes.
- The results of this study showed a clear dose-response relationship for pulmonary inflammatory responses and changes in the lungs for rats exposed to Aerosil 200.

While microscopic changes in the lungs were observed in rats exposed to 1 mg/m$^3$ Aerosil 200 amorphous silica, the effects (characterized by the accumulation of alveolar macrophages and neutrophil influx but not in other measured endpoints) are rather mild. In addition, the changes induced by all three types of amorphous silica regressed more-or-less quickly within one year

after the end of exposure. Importantly, no induction of silicotic nodules/silicosis was observed in rats exposed to all three tested amorphous silica products. Therefore, the TD considers the level of 1 mg/m$^3$ an NOAEL and the level of 6 mg/m$^3$ a LOAEL for subchronic pulmonary effects. The corresponding, actual mean concentrations for the target concentrations of 1 and 6 mg/m$^3$ were $1.3 \pm 0.1$ and $5.9 \pm 0.2$ mg/m$^3$, respectively. The subchronic LOAEL of 5.9 mg/m$^3$ identified from this study is in agreement with the freestanding LOAEL of 15 mg/m$^3$ from the Groth et al. (1981) chronic study. For comparison purposes, the subchronic NOAEL of 1.3 mg/m$^3$ for pulmonary toxicity was also used as the relevant POD to develop the chronic ReV and ESL for amorphous silica.

## 4.1.2 Other Study (Rosenbruch 1992)

Rosenbruch (1992) examined effects of chronic inhalation exposure of amorphous silica. Groups of male Wistar rats were exposed to an average measured concentration of 10.9 mg/m$^3$ of amorphous quartz glass (VP 203-006, n=15, 99 % value of the particle size = 2 μm), 11.1 mg/m$^3$ of crystalline quartz (DQ-12, n=15, 99 % value of the particle size = 1.6 μm), or filtered air (n = 10) for 7 h/d, 5 d/week for 12 months. Morphological and morphometric changes of lung associated lymph nodes were studied. The results showed that both amorphous and crystalline silica can lead to severe lymph node fibrosis. The proportion of lymph node changes, however, was focally slight reactions after amorphous quartz glass (VP 203-006), but severe fibrosis after crystalline quartz (DQ-12) exposure. A freestanding LOAEL of 10.9 mg/m$^3$ for amorphous quartz glass was identified from this study. The LOAEL is in agreement with those identified from the Groth et al. (1981) key study. While the LOAEL of 10.9 mg/m$^3$ is lower than that identified by Groth et al. (1981), the LOAEL was not used to develop the chronic ReV and ESL for amorphous silica because the Rosenbruch (1992) study only examined one animal specie for one form of amorphous silica exposure.

## 4.1.3 MOA Analysis

The MOA for respiratory damage following chronic amorphous silica exposure appears to be chronic inflammation (characterized by the accumulation of alveolar macrophages and neutrophil influx in the lung and lymph nodes). The chronic inflammation can subsequently lead to respiratory impairment and histopathological changes pathological changes in the lungs such as decreased lung functions, granulomatous lesions, or less likely nodular fibrosis. Potential mechanisms of inflammation induced by silica are discussed in section 3.1.2. As with acute inflammation, it is assumed that a sufficiently high amount of silica is required to initiate and sustain the chronic inflammation. Therefore, a nonlinear, threshold dose-response is assumed for the development of pulmonary effects.

## 4.1.4 Dose Metric

As described in Section 3.1.3, in the key and supporting chronic or subchronic studies, data on exposure concentration of the parent chemical are available. 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.

## 4.1.5 PODs for Key and Supporting Studies

In the chronic study by Groth et al. (1981), rats, guinea pigs and monkeys were exposed to synthetic amorphous fused silica, precipitated silica, and silica gel at a target concentration of 15 mg/m$^3$ over a duration of 5.5 to 6 h/d, 5 d/week, for up to 18 months. The freestanding chronic LOAEL of 15 mg/m$^3$ respiratory amorphous silica for pulmonary effects was used as the relevant POD.

In the subchronic supporting study by Reuzel et al. (1991), rats were exposed to an analytical concentration of 1.3 mg/m$^3$ Aerosil 200 amorphous for 6 h/d for 13 weeks and showed signs of mild and transient inflammatory response and other pulmonary effects. As discussed in Section 4.1.1.2 above, the TD considers 1.3 mg/m$^3$ the subchronic NOAEL and the relevant POD.

The reported LOAEL of 10.9 mg/m$^3$ from the supporting study by Rosenbruch (1992) was similar to the LOAELs identified from both the aforementioned key studies. The critical effects noted in animals are considered relevant to humans.

## 4.1.6 Dosimetric Adjustments

### 4.1.6.1 Exposure Duration Adjustments

According to Section 4.3.2 of the ESL Guidelines (TCEQ 2006), the chronic POD of 15 mg/m$^3$ (Groth et al. 1981) and subchronic POD of 1.3 mg/m$^3$ (Reuzel et al. 1991) were adjusted from discontinuous exposure (6 h/d for 5d/wk) to a continuous exposure concentration using the following dosimetric adjustments:

Groth et al. (1981) key study:

$$POD_{ADJ} = POD \times D/24 \times F/7$$
$$POD_{ADJ} = 15 \text{ mg/m}^3 \times 6/24 \times 5/7$$
$$POD_{ADJ} = 2.678 \text{ mg/m}^3$$

Reuzel et al. (1991) supporting study:

$$POD_{ADJ} = 1.3 \text{ mg/m}^3 \times 6/24 \times 5/7$$
$$POD_{ADJ} = 0.2321 \text{ mg/m}^3$$

Where: $POD_{ADJ}$ = POD from an animal study, adjusted to a continuous exposure duration
POD = POD from an animal study, based on a discontinuous exposure duration
D = exposure duration, hours per day
F = exposure frequency, days per week4.1.6.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

### 4.1.6.2.1 POD$_{ADJ}$ from Groth et al. (1981) Key Study

The deposition fraction of amorphous silica was calculated for each key study using the MPPD program. The MMAD of the fume silica, which produced most pronounced effects among the three testing amorphous silica products, was 3.2 μm with a GSD of 2.5. The particle density is 2.3 g/cm$^3$ (Table 2) and the chemical concentration is the POD$_{ADJ}$ of 2.678 mg/m$^3$. The target region for SAS was considered to be the total particle distribution for the TB and PU regions. All remaining values used were default. Once the total particle distribution was determined, the RDDR of 0.739 was calculated and then used to dosimetrically adjust from an animal POD to a POD$_{HEC}$ (Appendix B).

$$POD_{HEC} = POD_{ADJ} \text{ x RDDR (low)} = 2.678 \text{ mg/m}^3 \text{ x } 0.739 = 1.98 \text{ mg/m}^3$$

### 4.1.6.2.2 POD$_{ADJ}$ from Reuzel et al. (1991) Supporting Study

Particle size distribution was not analyzed and thus, no MMAD and GSD were provided for the tested amorphous silica products in the Reuzel et al. (1991) study. The MMAD of amorphous silica tested in most reported animal inhalation exposure studies range from 1.8 to 3.9 μm with GSD ranging from 1.9 to 2.6 (Groth et al. 1981; Warheit et al. 1995; Arts et al. 2007; Lee and Kelly 1992; Lewinson et al. 1994; Pratt 1983). The TD used the three MMADs with GSD (3.7 ± 1.9, 3.3 ± 2.1, and 2.9 ± 2.3 μm) reported in Lee and Kelly (1992) for Ludox colloidal silica (see Section 4.1.2.1) as surrogate MMAD and GSD values to model the total particle distribution for the TB and PU regions and to calculate the corresponding RDDRs (Appendix C). The calculated RDDRs for the MMAD (± GSD) of 3.7 (± 1.9), 3.3 (± 2.1), and 2.9 (± 2.3) μm are 0.735, 0.735, and 0.715, respectively. These RDDRs are in agreement with the RDDR of 0.739 modeled based on data from Groth et al. (1981). The lowest RDDR of 0.715 was conservatively used to dosimetrically adjust the POD$_{ADJ}$ of 0.232 mg/m$^3$.

$$POD_{HEC} = POD_{ADJ} \text{ x RDDR} = 0.232 \text{ mg/m}^3 \text{ x } 0.715 = 0.169 \text{ mg/m}^3$$

## 4.1.7 Critical Effect and Adjustments to the POD$_{HEC}$

### 4.1.7.1 Critical Effect

Data from animal noncarcinogenic key and supporting studies suggest that chronic inflammatory response is the most sensitive endpoint for exposure to amorphous silica (see Section 4.1.1 and 4.1.2).

### 4.1.7.2 UFs

The following UFs were applied to the POD$_{HEC}$ of 1.98 mg/m$^3$ from the chronic study by Groth et al. (1981):

- a UF$_L$ of 10 for the extrapolation from LOAEL to NOAEL,
- a UF$_H$ of 10 for intraspecies variability to account for potential sensitive human subpopulations, such as those with existing pulmonary inflammation due to other causes,

- a $UF_A$ of 3 for interspecies variability because a default dosimetric adjustment using the RDDR was conducted to account for toxicokinetic differences between animals and humans but not toxicodynamic differences, and
- a $UF_D$ of 1 was used because multiple species with sufficient numbers of animal in each experiment group were studied.
- The total UF = 300.

The following UFs were applied to the $POD_{HEC}$ of 0.169 mg/m$^3$ derived from the subchronic study series by Reuzel et al. (1991):

- a $UF_H$ of 10 for intraspecies variability,
- a $UF_A$ of 3 for interspecies variability because a default dosimetric adjustment was conducted to account for toxicokinetic differences between animals and humans but not toxicodynamic differences,
- a $UF_{Sub}$ of 3 instead of 10 for extrapolation from subchronic to chronic exposure was used because subchronic exposure to the most toxic amorphous silica (i.e., Aerosil 200) only cause mild and reversible inflammatory responses, and the subchronic NOAEL is much lower than a subchronic NOAEL reported by Lee and Kelly (1992) or other chronic LOAELs reported by Groth et al. (1981) and Rosenbruch (1992), and
- a $UF_D$ of 1 was used because multiple species with sufficient numbers of animal in each experiment group were studied, and a dose-response relationship was observed.
- The total UF = 100.

## 4.1.8 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:

Groth et al. (1981):

$$\text{Chronic ReV} = POD_{HEC} / (UF_L \times UF_A \times UF_H \times UF_D) = 1.98 \text{ mg/m}^3 / (10 \times 3 \times 10 \times 1)$$
$$= 0.00660 \text{ mg/m}^3 \text{ or } 6.60 \text{ µg/m}^3$$

Reuzel et al. (1991):

$$\text{Chronic ReV} = POD_{HEC} / (UF_{Sub} \times UF_A \times UF_H \times UF_D) = 0.169 \text{ mg/m}^3 / (3 \times 3 \times 10 \times 1) =$$
$$0.0017 \text{ mg/m}^3 \text{ or } 1.7 \text{ µg/m}^3$$

The chronic ReV of 1.7 µg/m$^3$ derived from the Reuzel et al. (1991) key study is lower than that derived from the Groth et al. (1981) key study. However, the chronic ReV of 1.7 µg/m$^3$ is based on a NOAEL of 1.3 mg/m$^3$ identified from a subchronic exposure study which is not preferred to develop ReVs and ESLs for the following reasons:

- the NOAEL of 1.3 mg/m$^3$ is not supported by a NOAEL of 10 mg/m$^3$ indentified from another subchronic exposure study by Lee and Kelly (1992);

- the Reuzel et al. (1991) study was a 13-week subchronic study;

- Particle size distribution was not analyzed and thus, no MMAD and GSD were provided for the tested amorphous silica products in the Reuzel et al. (1991) study;

- the chronic ReV of 1.7 µg/m$^3$ is lower than the chronic ReV of 2 µg/m$^3$ for crystalline silica (TCEQ 2009). Since amorphous silica is less fibrogenic than crystalline silica and silicosis has rarely been observed after exposure to amorphous silica (IARC 1997), the chronic ReV of 1.7 µg/m$^3$ derived from the Reuzel et al. (1991) key study may be too conservative.

Based on this, the TD chose not to use the chronic ReV of 1.7 µg/m$^3$ to develop the $^{chronic}$ESL$_{nonlinear(nc)}$. While the ReV of 6.60 µg/m$^3$ is based on a freestanding LOAEL, it is based on a chronic exposure study and is preferred to develop the ReV and ESL. Additionally, the LOAEL is consistent with those LOAELs identified from other chronic exposure studies. Therefore the TD chose the ReV of 6.60 µg/m$^3$ derived from a LOAEL by Groth et al. (1981). Rounding the results from the key study to two significant figures at the end of all calculations yields a chronic ReV of 6.6 µg/m$^3$. At the target HQ of 0.3, the $^{chronic}$ESL$_{nonlinear(nc)}$ is 2.0 µg/m$^3$ (Table 6).

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

| Parameter | Summary |
|---|---|
| Study | Groth et al. (1981) |
| Study Population | 80 male Sprague-Dawley rats, 20 male Hartley guinea pigs, and 10 adult male cynomolgus monkeys |
| Study Quality | High |
| Exposure Method | Whole body animal inhalation exposure to silica dusts at 15 mg/m$^3$ for 5.5 to 6 h/d, 5 d/week, for 13 to 18 months |
| LOAEL | 15 mg/m$^3$ (target concentration) |
| NOAEL | N/A |
| Critical Effects | Pulmonary effects such as chronic inflammation, respiratory impairment, and decrese in pulmonary function. |
| POD | 15 mg/m$^3$ (freestanding LOAEL) |
| Extrapolation to continuous exposure (POD$_{ADJ}$) | 2.679 mg/m$^3$ |
| POD$_{HEC}$ | 1,980 μg/m$^3$ (RDDR = 0.739) |
| Total UFs | 300 |
| *Interspecies UF* | *3* |
| *Intraspecies UF* | *10* |
| *LOAEL UF* | *10* |
| *Subchronic to chronic UF* | *N/A* |
| *Incomplete Database UF* | *1* |
| *Database Quality* | *High* |
| **chronic ReV (HQ = 1)** | **6.6 μg/m3** |
| **$^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3)** | **2.0 μg/m3** |

## *4.2 Carcinogenic Potential*

Several SAS types demonstrated no mutagenic activity in *Salmonella typhimurium* or *Escherichia coli* in the presence and/or absence of metabolic activation, using standard plate incorporation or spot test methods (ECETOC 2006). 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). IARC concluded that there is inadequate evidence in humans for the carcinogenicity of amorphous silica and SAS. Amorphous silica is not classifiable as to its carcinogenicity to humans (Group 3) (IARC 1997). Based on experimental data and guidance in USEPA's Guidelines for Carcinogenic Risk Assessment (2005), the TD concludes there is inadequate information to assess carcinogenic potential via inhalation. Because the available data are inadequate to assess carcinogenicity in humans via the inhalation route, the $^{chronic}ESL_{linear(c)}$ was not developed.

## 4.3. Welfare-Based Chronic ESL

Since there are no data indicating that plants are harmed by exposure to amorphous 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 ReV = 6.6 µg/m$^3$
- $^{chronic}ESL_{nonlinear(nc)}$ = 2.0 µg/m$^3$

The long-term ESL for air permit reviews is the health-based $^{chronic}ESL_{nonlinear(nc)}$ of 2.0 µg/m$^3$ (Table 2). The chronic ReV of 6.6 µg/m$^3$ is used as the long-term ACMV for the evaluation of air monitoring data (Table 1).

# Chapter 5 References

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## *5.2 Other Studies and Documents Reviewed by the TD*

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# Appendix A. MPPD Program Output for Key Study-Warheit et al. (1995)

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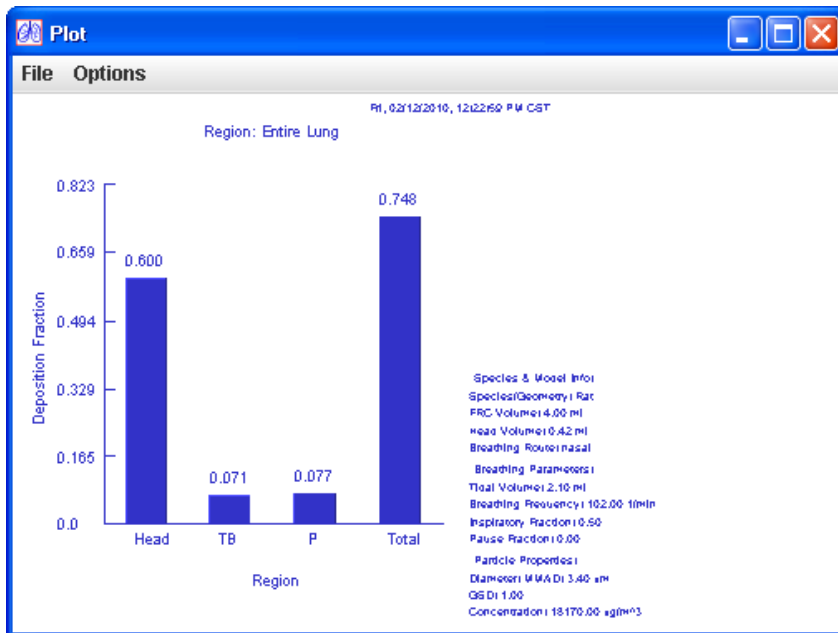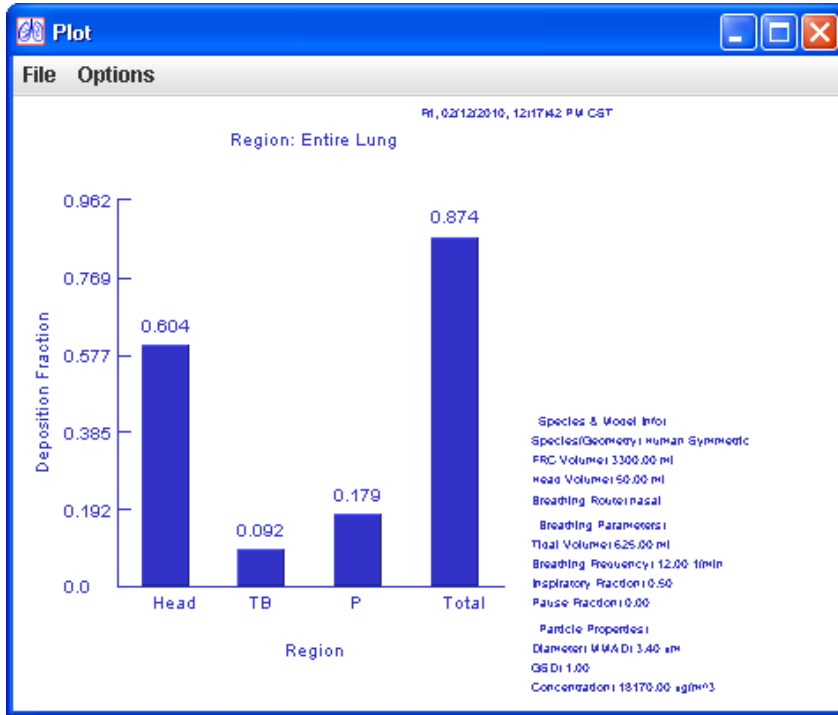
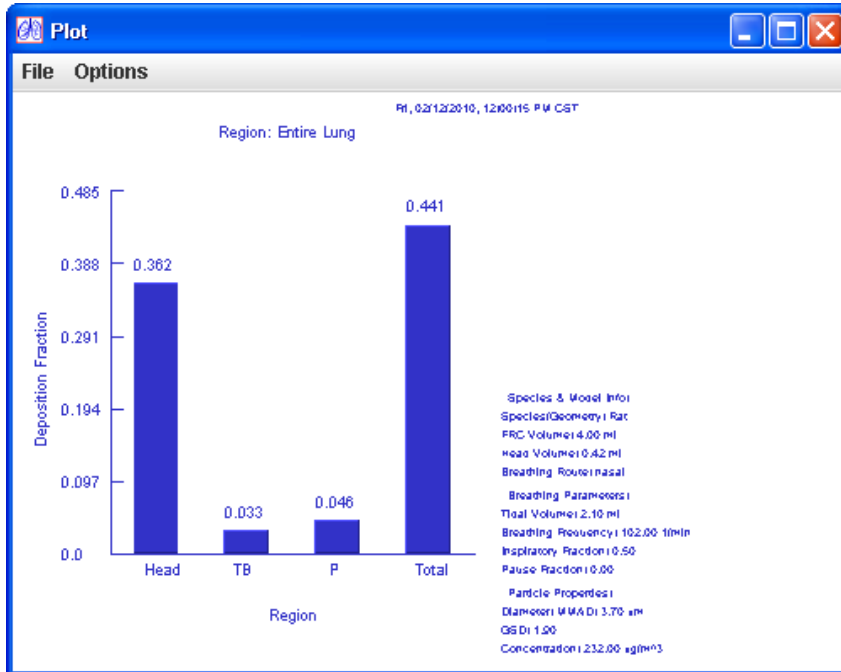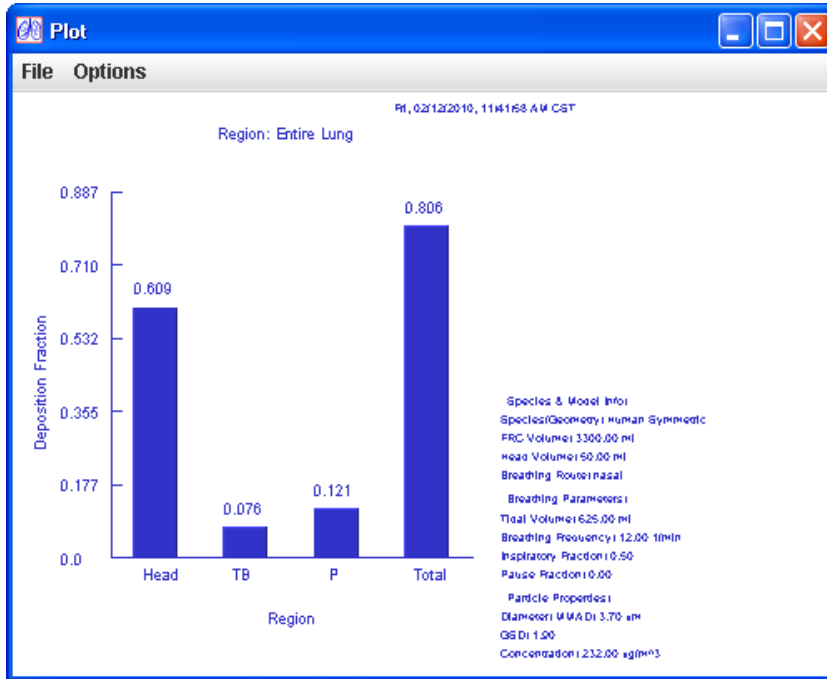**2. MPPD Program Output for Warheit et al. (1995) – low end of range**

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

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

where: $V_E$ = minute volume

DF = deposition fraction in the target region of the respiratory tract

NF = normalizing factor

A = animal

H = human

RDDR (low end of range) = [(137.3 mL/min)/(13,800 mL/min)] x [(0.151)/(0.261)] x [(630,200 cm$^2$)/(3422.5 cm$^2$)] = 1.060

RDDR (high end of range) = [(137.3 mL/min)/(13,800 mL/min)] x [(0.148)/( 0.271)] x [(630,200 cm$^2$)/( 3422.5 cm$^2$)] = 1.001

## Appendix B. MPPD Program Output for Key Study- Groth et al. (1981)
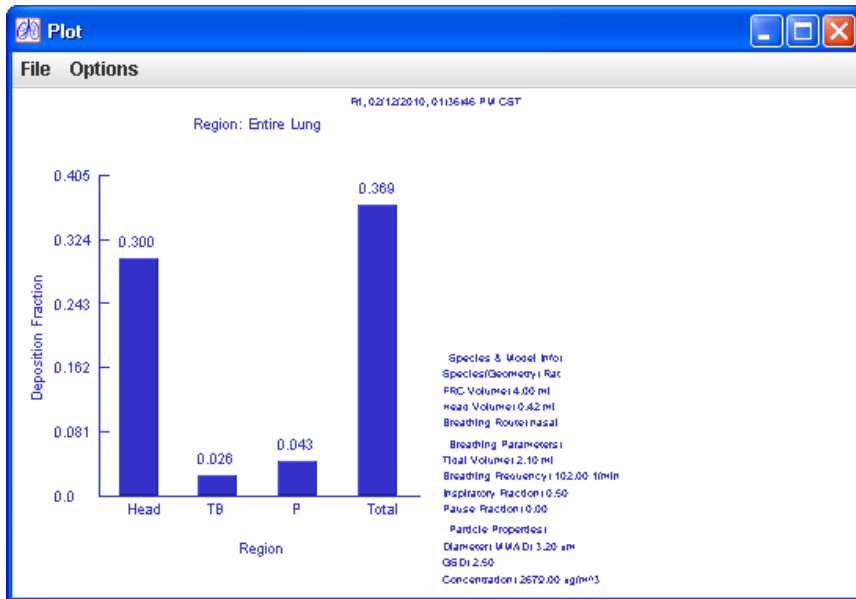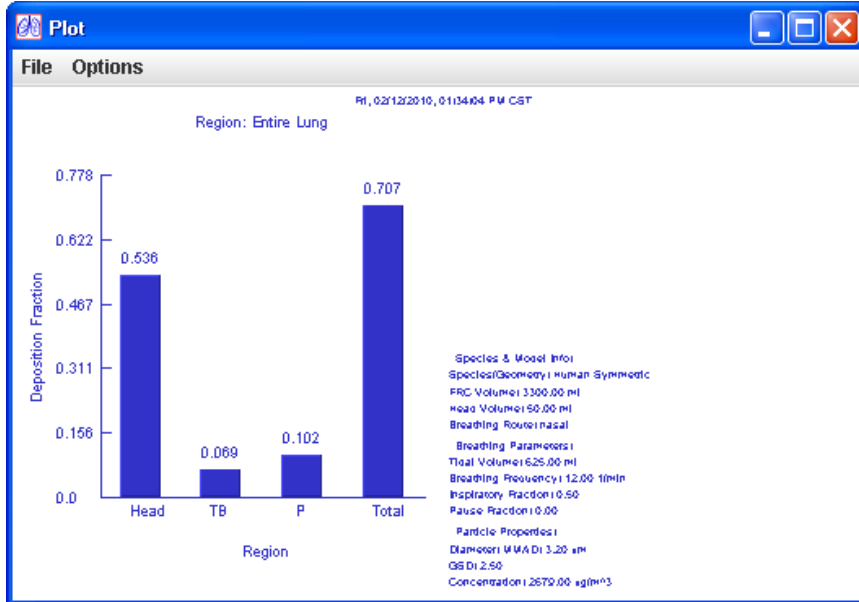




The deposition fractions of TB and P determined from the MPPD program above were then used to calculate the RDDR for each of the supporting studies.

$$RDDR = [(137.3 \text{ mL/min})/(13{,}800 \text{ mL/min})] \times [(0.069)/(0.171)] \times [(630{,}200 \text{ cm}^2)/(3422.5 \text{ cm}^2)] = 0.739$$

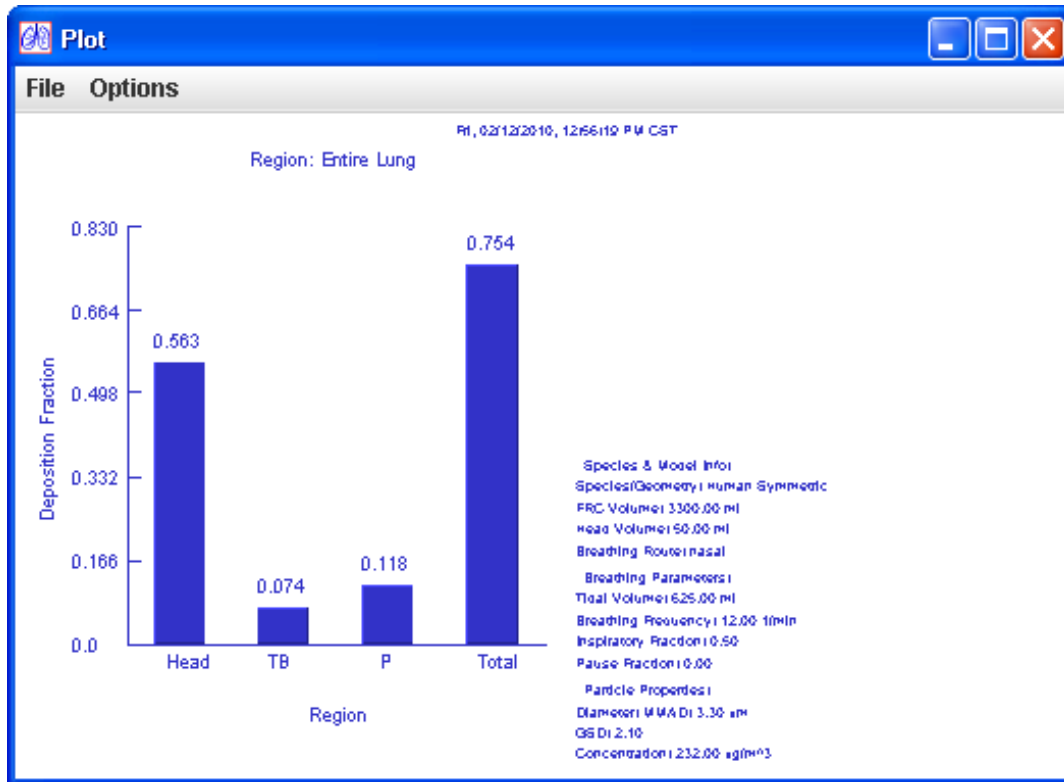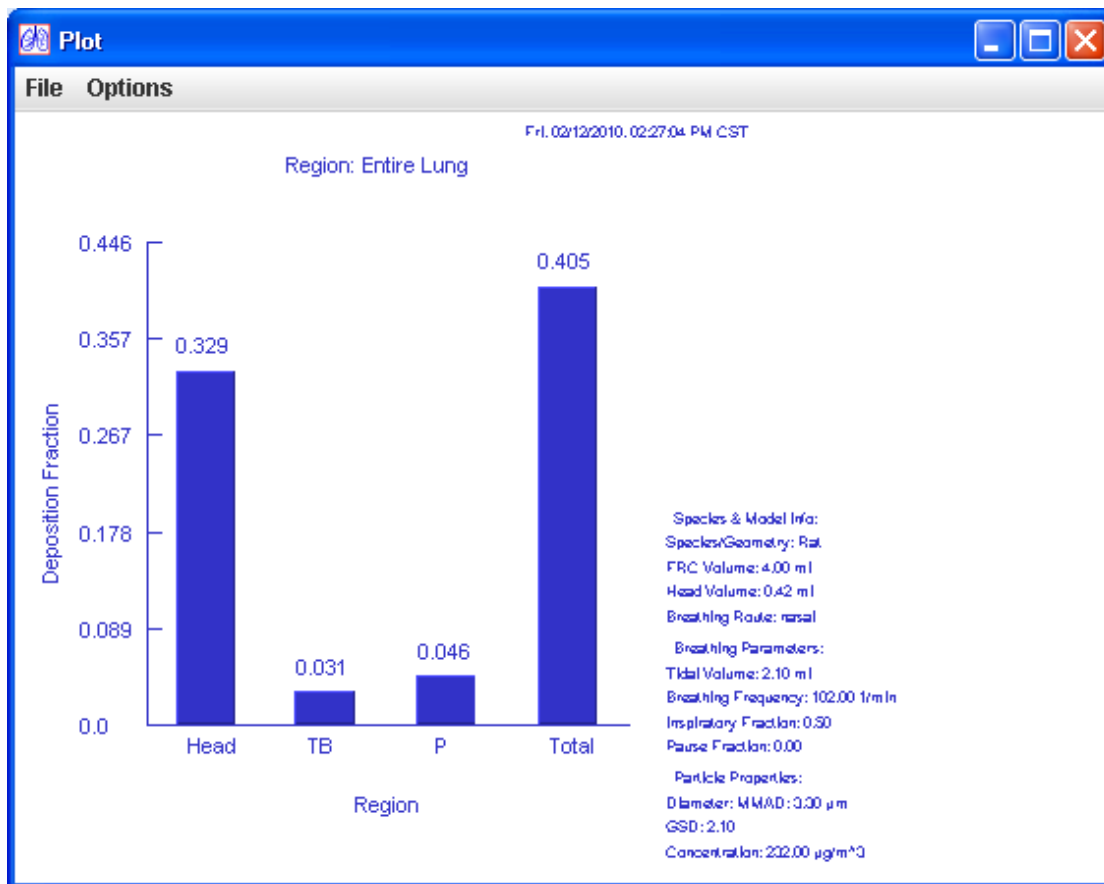## Appendix C. MPPD Program Output for Key Study- Lee and Kelly (1992)

**1. MMAD = 3.7 μm and GSD = 1.9:**
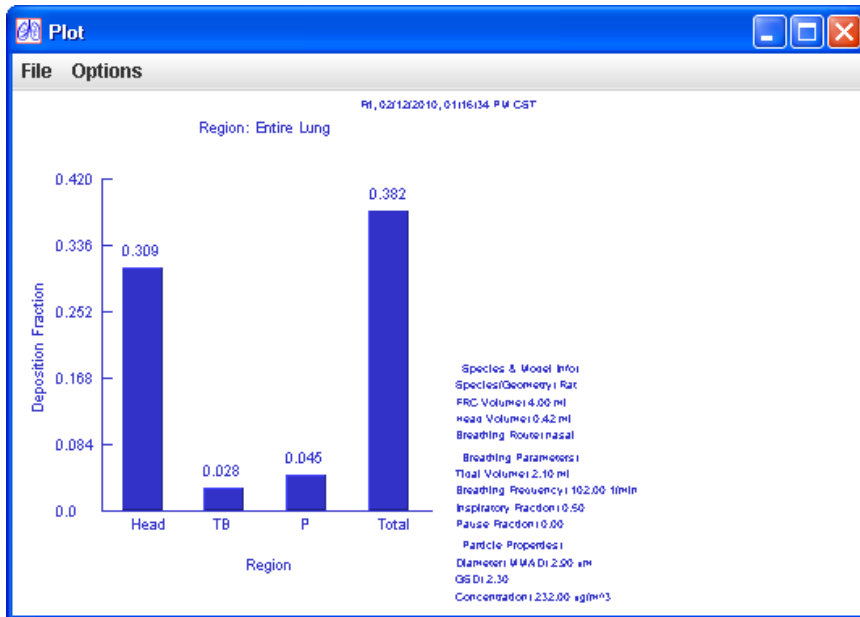
The deposition fractions determined from the MPPD program above were then used to calculate the RDDR for each of the supporting studies.

RDDR = [(137.3 mL/min)/(13,800 mL/min)] x [(0.079)/(0.197)] x [(630,200 cm$^2$)/(3422.5 cm$^2$)] = 0.735
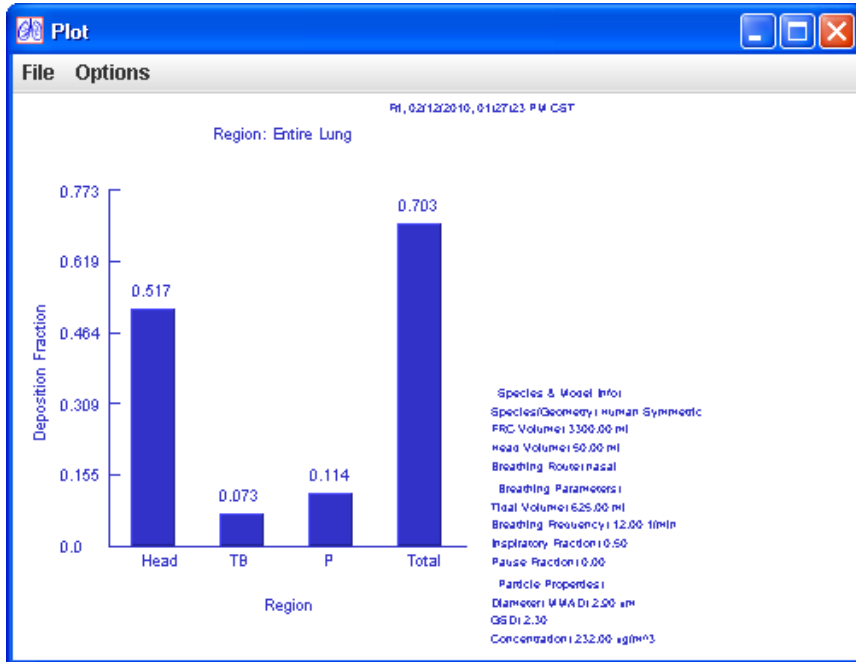
**2. MMAD = 3.3μm and GSD = 2.1:**

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

$$RDDR = [(137.3 \text{ mL/min})/(13,800 \text{ mL/min})] \times [(0.077)/(0.192)] \times [(630,200 \text{ cm}^2)/(3422.5 \text{ cm}^2)] = 0.735$$

**3. MMAD = 2.9μm and GSD = 2.3:**

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

$$\text{RDDR} = [(137.3 \text{ mL/min})/(13,800 \text{ mL/min})] \times [(0.073)/(0.187)] \times [(630,200 \text{ cm}^2)/(3422.5 \text{ cm}^2)] = 0.715$$