Chemical Information Review Document

for

Silica Flour
(Micronized α-Quartz)
[CAS No. 14808-60-7]

Supporting Nomination for Toxicological Evaluation by the National Toxicology Program

October 2009

National Toxicology Program
National Institute of Environmental Health Sciences
National Institutes of Health
U.S Department of Health and Human Services
Research Triangle Park, NC
http://ntp.niehs.nih.gov/

Abstract

Silica flour, a finely ground crystalline silica, was nominated for toxicological testing via dermal and oral routes of exposure by the National Toxicology Program based on evidence that occupational exposure has been associated with a higher incidence of autoimmune diseases. The general population is exposed dermally to silica flour through its use as an abrasive additive in soaps, skin care products, and paints, and orally exposed through its use in toothpastes and as a filler in numerous pharmaceuticals. Crystalline silica also is used in foundry work and in glass, ceramic, porcelain, tile, and clay production. Numerous case studies and epidemiological studies have shown that exposure to crystalline silica via inhalation or the subcutaneous route produced a variety of adverse effects including cutaneous granulomas, progressive systemic sclerosis, chronic silicosis, chronic obstructive pulmonary disease, chronic renal disease, hyperthyroidism, and scleroderma. The International Agency for Research on Cancer (IARC) stated that there is sufficient evidence in humans for carcinogenicity from inhalation of crystalline silica in the form of quartz or cristobalite from occupational sources. Gene mutations and DNA strand breaks as well as immunological effects have been observed in individuals who were exposed to crystalline silica. The lowest toxic dose in rats published for oral exposure was 120 g/kg and for exposure by intratracheal instillation in mice and rats it was >20 mg/kg and 200-250 mg/kg, respectively. Gastrointestinal effects were seen after oral exposure. Short-term, subchronic, and chronic inhalation studies indicated that quartz produced discrete silicotic nodules, pneumonitis, formation of reactive oxygen species, and cellular proliferation. Quartz silica and DQ12 potentiated the carcinogenicity of benzo[*a*]pyrene and thorotrast (an α-radiation-emitting material). Evidence of naturally occurring contaminants of quartz that appear to antagonize its toxicity also was reported. *In vitro* and *in vivo* studies in mammalian systems showed that crystalline silica was cytotoxic and genotoxic. The IARC concluded that there is sufficient evidence in experimental animals for the carcinogenicity of the crystalline silica polymorphs quartz and cristobalite but limited evidence for the carcinogenicity of tridymite. Other effects observed *in vivo* included increased production of tumor necrosis factor-α, IL-1 macrophage inflammatory protein-2 expression, and lymphokine release, as well as activation of nuclear transcription factor activator protein-1 and lymphocyte proliferation. Crystalline silica also was reported to cause adverse renal effects in test animals and to inhibit some enzymes (e.g., cathepsin B) while inducing others (CYP1A1).

Executive Summary

Basis for Nomination

Silica flour, a finely ground crystalline silica, was nominated for toxicological testing via dermal and oral routes of exposure by a private individual based on evidence that occupational exposure to respirable crystalline silica is associated with a higher incidence of autoimmune diseases. Studies of silica flour to date have focused almost exclusively on respiratory exposures. However, the general population is exposed dermally and orally through the use of silica flour in an array of industrial and consumer products. Insufficient information is available to determine whether oral and dermal exposure to crystalline silica poses a similar health hazard as respiratory exposures.

Nontoxicological Data

Silica exists in crystalline and amorphous forms and in silica rock. Crystalline silica is present in all soils and all types of rocks, and given its lack of solubility in a variety of chemicals, quartz is therefore ubiquitous in the environment. Crystalline silica occurs in different polymorphic forms which include quartz, cristobalite, tridymite, and stichovite. Silica flour is a very finely divided, highly purified form of crystalline silica that consists of particles of up to 100 μm in diameter. Nanosize particles (10-100 nm) may be present in some preparations. Since the mineral sources used for preparing silica and silica flour have varied over time, the concentrations and types of impurities found in test materials also may have changed. Impurities have included calcium oxide, iron oxide, and titanium oxide. Silica flour is very slightly soluble in some alkaline solutions but dissolves completely in alkaline solutions of sodium hydroxide or sodium carbonate. Eight U.S. suppliers of "silica flour fillers" or "silica flour" were identified. Crystalline silica is milled to a fine powder by crushing, grinding, or ball milling to produce the flour. Calcination and flux calcination of diatomite are used to produce cristobalite, a crystalline silica polymorph used in some filtration systems and quartz can be produced by culturing quartz crystals in an autoclave. The silica polymorphs can be converted into other polymorphs under high heat and pressure. The U.S. Environmental Protection Agency's Inventory Update Reporting (IUR) for 1994, 1998, and 2002 listed quartz production at 10,000 to 500,000 pounds. According to the non-confidential 2006 IUR records, the aggregated national production volume for quartz was 500 million to <1 billion pounds. Silica flour is used as an abrasive additive in soaps, skin care products, toothpastes, and paints, and as a filler in a number of pharmaceuticals. It also is used in foundry work and in glass, ceramic, porcelain, tile, and clay production. Additionally, crystalline silica is found as an impurity of amorphous silica and amorphous silica fume. Silica flour, mined or processed as a raw material, is exempt from the Hazard Communication final rule. All other regulatory information pertains to silica.

Human Data

Toxicological data from oral or dermal exposure to silica flour are summarized in this review. Information from studies that used other routes of exposure is included where data from oral or dermal studies were limited or not available. All systemic effects, excluding pulmonary effects, were considered.

One study reported that silica particles placed on the skin surface of study participants were cleared (fell off) with a half-life of 1.5-7.8 hours; the half-life was affected by the amount of body hair on the test site as well as physical movement. A case study reported that long-term ingestion of cristobalite (3 g/day) led to recurring urinary calculi containing minute silica particles in the core. Quartz dissolution is not believed to contribute significantly to clearance in persons with silicosis. Particles deposited in the lung periphery are only slowly and incompletely cleared. Quantification of blood/lymph clearance beyond the pulmonary lymphatics and lymph nodes was not available.

Numerous case histories have described development of cutaneous granulomas after crystalline or amorphous silica was introduced subcutaneously. Crystalline silica particles were found on the skin of

individuals who had progressive systemic sclerosis and known exposure to crystalline silica. Inhalation of respirable crystalline silica is typically associated with chronic silicosis. Other silica-related diseases include pulmonary tuberculosis, chronic obstructive pulmonary disease, chronic renal disease, hyperthyroidism, and scleroderma. The International Agency for Research on Cancer (IARC) stated that there is sufficient evidence in humans for the carcinogenicity of inhaled crystalline silica in the form of quartz and cristobalite from occupational sources. The ingestion of airborne micrometer-sized and larger silica particles may lead to increased risk for extrapulmonary cancers. Genotoxic (e.g., gene mutations and DNA strand breaks) and immunological (e.g., enhanced production of interleukin [IL]-8) effects have been observed in individuals exposed to crystalline silica. Numerous epidemiological studies also indicated that silica exposure can lead to development of renal disease.

Toxicological Data

No reproductive/developmental, initiation/promotion, or cogenotoxicity studies were found.

Chemical Disposition, Metabolism, and Toxicokinetics

After oral administration of silica flour in the diet of white rats, crystals of silica flour were found in a variety of organs, including the myocardium. Comparatively, silica particles were not found in the submucosa, muscularis, or regional lymph nodes of male Wistar rats that were given silica particles via stomach tube. Additionally, silicotic nodules were not found in the liver or spleen. Suckling mice orally gavaged with Percoll microspheres (colloidal silica coated with polyvinylpyrrolidone) had limited amounts of the microspheres in the subepithelial tissue of the villous mucosa and Peyer's patches, mesenteric lymph nodes, and omentum. Percoll was found in the liver and thymic cortex. Inhalation studies indicated that clearance of cristobalite occurred within two weeks after short-term inhalation exposure of rats. Particles moved between alveolar space and lung tissues, and they accumulated in the mediastinal lymph nodes and thymus during the months after exposure.

Studies with nanoscale silica reported that *in vitro* uptake can be regulated by surface charge and cell type. Additionally, *in vivo* studies indicated that particle size plays a role in the excretion rate.

Acute Exposure

The lowest published oral toxic dose was 120 g/kg in rats. The lowest toxic dose for intratracheal (i.t.) exposure was >20 mg/kg in mice and 200-250 mg/kg in rats. Gastrointestinal effects were reported after oral exposure.

In vivo administration of nanoscale silica to mice produced nonspecific focal hemorrhage in the heart and liver; mild toxicity was observed when animals were given micro-sized particles. In a separate study, effects on serum alanine aminotransferase (ALT) activity, IL-6, and tumor necrosis factor-alpha (TNF-α) concentrations were observed with smaller sized nanosilica particles.

Short-Term and Subchronic Exposure

Results from studies of oral or dermal exposure were not available. Discrete silicotic nodules were noted in mice, rats, and hamsters after i.t. instillation of quartz particles. Inhalation exposure caused progressive lesions, pneumonitis, and formation of reactive oxygen species (ROS) and nitrogen species. In rats, the lowest published toxic concentrations ranged from 6.2 mg/m^3 at 6 hours/day for 6 weeks intermittently to 108 mg/m^3 for 6 hours/day for 3 days intermittently. The lowest published toxic doses for exposure by i.t. installation ranged from 240 μg/kg for 12 weeks intermittently to 203 mg/kg for 28 days intermittently.

Adverse liver effects were observed in mice exposed to nanoscale silica. Alterations in ALT levels also were reported.

Chronic Exposure

No studies of oral or dermal exposure to silica flour were available. Inhalation of quartz particles suppressed immune functions and caused cellular proliferation, nodule formation, and alveolar proteinosis in mice and rats. The lowest published toxic concentration for chronic inhalation exposure in rats was 0.74 mg/m^3. Subcutaneous and intraperitoneal (i.p.) injections of Min-U-Sil 5 quartz induced hepatic fibrosis, cirrhosis, and granulomas in nude mice and Syrian golden hamsters.

In rats, fibrogenesis induced by nanoscale silica was reported to be weaker than that induced by microsized particles. Lung/body weight coefficient, hydroxyproline content, and expressions of IL-4 and transforming growth factor-β1 were lower in rats given nanosilica compared those given microsilica.

Synergistic/Antagonistic Effects

No data were available for anticarcinogenic or antigenotoxic effects. Syrian golden hamsters given quartz and benzo[*a*]pyrene (BaP) by i.t. instillation had more respiratory tract tumors than hamsters given BaP alone. A similar interactive effect was observed between Thorotrast and DQ12 in female Wistar rats.

Studies indicate that a naturally occurring quartz contaminant may antagonize its toxicity. Overall, pretreatment of silica particles with aluminum lactate, polyvinylpyridine-N-oxide, and curcumin reduced quartz toxicity. Comparatively, ascorbic acid increased quartz toxicity.

Cytotoxicity

The cytotoxic activity of crystalline silica generally has been related to specific surface area and the interaction of the crystal surface of the particles with biological molecules and cell surfaces. Quartz was cytotoxic at much lower surface-area doses than were low-solubility, low-toxicity particles. Studies indicated that quartz induced apoptosis, generated ROS and oxidative stress, and caused swelling and rupture of lysosomes in animal and human models. In other studies, silica did not produce cytotoxic effects (e.g., did not reduce the viability of BEAS-2B human lung epithelial cells in a mitochondrial reductase assay).

Several studies evaluated the cytotoxic potential of diatomaceous earth and nanoscale silica. These studies showed that diatomaceous earth was cytotoxic and induced ROS. The cytotoxicity of nanosilica was cell-type specific. Nanosilica was shown to increase nitric oxide levels and caspase-3 activity.

Carcinogenicity

No studies of oral or dermal exposure to silica flour were available. The IARC concluded that there is sufficient evidence in experimental animals for carcinogenicity of quartz and cristobalite but that there is limited evidence in experimental animals for carcinogenicity of tridymite. Studies showed a species-dependent effect of quartz which induced pulmonary adenocarcinomas and squamous-cell carcinomas in rats but not in hamsters or mice. Thoracic and abdominal malignant lymphomas, primarily of the histocytic type, were seen in rats after an intrapleural or i.p. injection of suspensions of different types of quartz. Lung tumor incidence was not significantly increased in male A/J mice or in female BALB/cBYJ mice.

Genotoxicity

Overall, the genotoxicity of silica flour has been associated with inflammation, cytotoxicity, and production of ROS. Studies have reported induction of micronuclei, gene mutation, and cellular transformation. The significance of genotoxic effects *in vitro*, which typically were reported for Min-U-Sil 5 or 10 or DQ12, to effects observed *in vivo* is uncertain. Surfactant pretreatment of particles suppressed or delayed genotoxic effects. Evidence suggests an indirect mechanism for DNA damage.

In WIL2-NS cells, nanoscale silica increased the frequency of micronucleated binucleated cells, but no significant increase in DNA strand breakage was observed.

Immunotoxicity

No studies of oral or dermal exposure to silica flour were available. *In vitro* studies indicated that quartz induced production of TNF-α, IL-1, macrophage inflammatory protein-2 expression, and activation of nuclear transcription factor activator protein-1. Comparatively, DQ12 quartz suppressed lymphocyte proliferation and lymphokine release in guinea pig splenic lymphocytes and peritoneal macrophages *in vitro*. Intranasal, i.t., and transoral instillations of silica were associated with a variety of immunotoxic effects (e.g., development of systemic autoimmune disease and enhanced TNF-α and IL-1 production). In female BALB/c mice, subcutaneous injection of silica particles with the antigen 2,4,6-trinitrophenyl coupled to ovalbumin stimulated T-helper-1-cell response.

Other Data

Silica may affect rat liver mitochondrial enzymes, inhibit cathepsin B activity, and modulate cytochrome P450 activity. Additionally, silica produced kidney effects in several species. Male guinea pigs exposed to quartz via drinking water exhibited tubulointerstitial nephritis after exposure for four months. Another study reported that 12 months of exposure to DQ12 did not produce any kidney effects. Intranasal exposure of autoimmune-prone mice to crystalline silica exacerbated development of glomerulonephritis.

Numerous mechanisms of action have been proposed for the toxic effects associated with silica exposure (e.g., cytotoxicity and silicosis). These mechanisms include generation of ROS, induction of cytochrome P450 activity, direct cytotoxicity, and induction of lysosomal damage following phagocytosis. The mechanisms operating *in vitro* may differ from those *in vivo*, and some mechanisms may be species- or organ-specific.

Structure-Activity Relationships

Amorphous silica is generally less toxic than crystalline silica. Since it has greater water solubility, it is cleared more rapidly from the body. Effects observed after inhalation of amorphous silica were milder than those observed for crystalline silica. The IARC considered the available data inadequate for determining the carcinogenic potential of amorphous silica.

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1.0 Basis for Nomination

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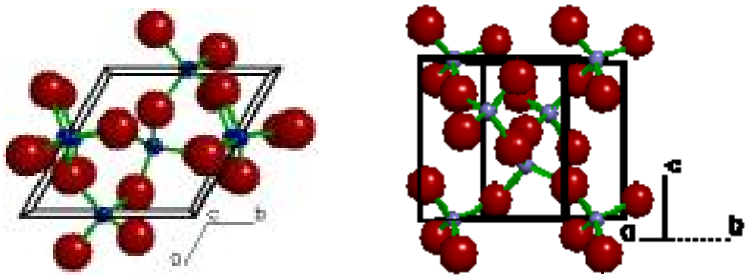
2.0 Introduction

Silica Flour
[14808-60-7]



Silica exists in crystalline forms, amorphous forms, or as silica rocks. Silica flour is the very finely divided, highly purified form of crystalline silica (SiO_2). Crystalline silica occurs naturally in a number of different shapes referred to as polymorphs. These polymorphs include quartz, tridymite, cristobalite, coesite, stishovite, and moganite which, with the exception of stishovite, differ in the orientation and position of the silicon-oxygen tetrahedron (SiO_4), the base unit of most crystalline and amorphous silica. Stishovite has an octahedral structure resulting from silica binding to six oxygen atoms. Quartz, tridymite, and cristobalite can be further subdivided into α and β forms which refer to metastable phases—the α form being the lower-temperature phase and the β form being the higher-temperature phase. The crystalline silica polymorphs can be converted into other polymorphs under conditions of high heat and pressure. In contrast to the orderly arrangement of units in crystalline silica, amorphous silica lacks any overall structure (Castranova and Vallyathan, 2000; IARC, 1997; IPCS, 2000). One natural form of amorphous silica is diatomite (diatomaceous earth [DE], infusorial earth, kieselguhr, tripolite) which is composed of fossilized skeletal remains of diatoms deposited on ocean and lake beds (Budavari, 1996; Registry, 2009a,b,c). Calcination and flux calcination of diatomite is used to produce cristobalite (IARC, 1997).

2.1 Chemical Identification and Analysis

Silica flour (formula; mol. wt. = 60.08 [silicon dioxide]) is also called:

α-Quartz
Agate
Amethyst
Chalcedony
Cherts
Crystalline silica
Crystallized silicon dioxide
D & D
DQ12
Flint
Flintshot
Gold bond R
Ground quartz
Imsil
Micronized quartz
Min-U-Sil
Novaculite
Onyx
Powdered quartz
Quartz
Quartz dust
Quartz silica
Rock crystal
Rose quartz
SF 35
Sand
Sicron F 300
Siderite (SiO2)
Sikron F 100
Sil-Co-Sil
Silica
Silica dust
Silica, crystalline quartz
Silicon dioxide, di- (sand)
Silver bond B
Snowit
TGL 16319
Tiger-eye
W12 (filler)

[Note: DQ12 that is <5 μm is a research standard quartz.]

PubChem CID: 24261 (silicon dioxide)
InChI: InChI=1/O2Si/c1-3-2 (silicon dioxide)
Smiles Notation: O=[Si]=O (silicon dioxide)

Sources: ChemIDplus (undated); PubChem (undated); RTECS (2009a)

2.2 Physical-Chemical Properties

Property	Information	Reference(s)
Physical State	white fine powder	Lindchem Ltd. (2003)
Odor	odorless	Lindchem Ltd. (2003)
Boiling Point (°C)	2230	Lindchem Ltd. (2003)
Melting Point (°C)	161-1720	Lindchem Ltd. (2003)
Flash Point (°C)	not available	Lindchem Ltd. (2003)
Vapor Pressure (mm Hg)	none	Lindchem Ltd. (2003)
Relative Density*	2.65	Lindchem Ltd. (2003)
Water Solubility	insoluble	Lindchem Ltd. (2003)
	~6000 ppm (two species, H_4SiO_4 and $H_6Si_2O_7$)	Wang et al. (2003)
Octanol-water partition coefficient (log K_{OW})	not available	none

*Bulk density varies with particle size. For 200-mesh (75-μm) silica flour, it is 70 lb/ft^3 (Fritz Industries, Inc., undated).

Silica flour contains various sized particles up to 100 μm in diameter. Min-U-Sil is available in uniform size distributions ranging from 5 μm (median diameter = 1.7 μm) to 40 μm (median diameter = 10.5 μm), and Sil-Co-Sil is available in several particle sizes that are ≤100 μm, starting at 40 μm (U.S. Silica Co., undated). DQ12 has a maximum particle size of 5-6 μm

(Robock, 1973). Nanosize particles (10-100 nm) also may be present in some preparations. The mineral sources used for preparation of silica have varied over time. Therefore, the concentrations and types of impurities present in materials that have been tested also may have changed depending on the source (IARC, 1997).

Silica flour is very slightly soluble in alkaline solution but dissolves completely as silicate in alkaline solutions of sodium hydroxide or sodium carbonate at ~673 K (Zarka et al., 1995 patent). Its solubility in 0.1 M sodium chloride solution is ~360 ppm, forming multiple linear, cyclic, and polycyclic silicate species such as $Si(OH)_2O_2Na^-$ and $Si(OH)_5O_2^-$ (Tanaka and Takahashi, 2000a [PMID:10934438], 2000b [PMID:11227564]). In Ringer buffer (physiological salts), the solubility of silica flour is ~10 ppm at 37 ºC. Silica flour solubility is 23.3 ppm in human serum and 24.3 ppm in citrated human plasma (Rahman et al., 1975 [PMID:179135]).

Calcination and flux calcination of DE produces up to 70% crystalline silica, predominantly cristobalite (see **Section 3.0**). The particle sizes are comparable to those of silica flours (~5-10 μm) (e.g., Celite Corporation, 2006).

2.3 Commercial Availability

Silica flour products that are commercially available include Min-U-Sil, Sil-Co-Sil, and DQ12. The number following the name on Min-U-Sil and Sil-Co-Sil represents the maximum particle size (μm). The silicon dioxide content in these products varies but is >98% (e.g., 98.5% for Min-U-Sil 15, 99.5-99.64% for Sil-Co-Sil 52, and 99.8% for Sil-Co-Sil 53). Product impurities include aluminum oxide, calcium oxide, iron oxide, magnesium oxide, potassium oxide, sodium oxide, and titanium dioxide (U.S. Silica Co., undated [select Product Data Index]). Phosphorous oxide also was present in DQ12 (Miles et al., 2008 [PMID:18686105]).

Four U.S. producers of "silica flour fillers" were identified: AGSCO Corporation (Wheeling, IL), Charles B. Crystal Co., Inc. (New York, NY), Nalback Engineering Company (Countryside, IL), and Noah Technologies Corporation (San Antonio, TX) (ICIS, 2009). "Silica flour" suppliers included:

- AGSCO Corporation [Wheeling, IL; Hasbrouck Heights, NJ], also noted above as producing fillers (ThomasNet, 2009)
- Midwest Industrial Products Corporation [Cleveland, OH] (MIPCO, 2008)
- Oglebay Norton Company [Cleveland, OH; Brady, TX] (ThomasNet, 2009)
- Richwood Surface Technologies/Richwood Industries, Inc. [Hawthorne, CA] (ThomasNet, 2009)
- U.S. Silica Company [Berkeley Springs, WV] (U.S. Silica Co., undated)

Calcined, flux-calcined, and natural DE also are available from a variety of sources (e.g., Celite Corporation, 2006; GMZ, Inc., 2007).

Nanoscale Silica

No U.S. producers or commercial products were found for nanocrystalline silica or nanoquartz.

3.0 Production Processes

Crystalline silica is milled to a fine powder (e.g., silica flour) by crushing, grinding, or ball milling of quartz. In addition to mining for natural quartz, quartz may be produced by hydrothermal culturing of quartz crystals in an autoclave (IARC, 1997). Synthetic crystalline silica can be grown under high temperatures and pressure in heavy-duty autoclaves. Keatite, silica W, and porosils are synthetic crystalline silica forms (IARC, 1997; U.S. Bureau of Mines, 1992). It has been noted that not all silica flours are labeled as containing crystalline silica and may in fact be labeled incorrectly at times as amorphous silica (NIOSH, 1981).

The silica polymorphs can be converted into other polymorphs under conditions of high heat and/or pressure. α-Quartz is stable over the temperature and pressures that are observed in the Earth's crust. Tridymite and cristobalite are formed at higher temperatures while coesite and stishovite are formed at higher pressures. The conversion of different metastable forms of the polymorphs (e.g., α and β quartz) occur rapidly, while conversion between polymorphs (e.g., quartz to tridymite) occurs more slowly. The table below shows the temperature ranges for the stability and metastability of different forms of quartz, tridymite, and cristobalite at ambient pressures (IARC, 1997).

Polymorph	Temperature Stability	Metastability
α-Quartz	up to 573 °C	-
β-Quartz	573-870 °C	>870 °C
β_1-Tridymite	-	up to 117 °C
β_2-Tridymite	-	117-163 °C
α-Tridymite	870-1470 °C	>163 °C
α-Cristobalite	-	up to 200-275 °C
β-Cristobalite	1470-1713 °C	>200-275 °C

Diatomite (amorphous silica) is open-pit mined in the United States and used to produce cristobalite. The process involves calcination of amorphous silica to change its chemical and physical properties and to convert it to crystalline silica, primarily α-cristobalite with traces of tridymite (Crangle, 2008; IARC, 1997). Calcined diatomite consists mostly of varying concentrations of aluminum, iron, and silicon oxides. The calcination process involves heating diatomite to 1200 °C or higher in a rotary furnace. At 600 °C, water has evaporated and iron is oxidized (Registry, 2009b). After diatomite was heated at 900 °C in a platinum 98 bucket for 5 hours, 1.5% crystallization (1% quartz and 0.5% cristobalite) was observed using x-ray diffractometry. Heating at 1200 °C for 5 hours resulted in 49% crystallization (1% quartz and 48% cristabolite) (Elias et al., 2006). Other articles discussed processes for preparing cristobalite-free calcinated diatomite (Antoni et al., 2005; Fischer et al., 2003).

Nanoscale Silica

The first hydrothermal chemical synthesis of nanocrystalline quartz was reported in 2003. Nanoparticles in low yield were size selected after precipitation from basic solutions formed from amorphous silica (fumed or colloidal) under elevated temperatures and pressure. Crystallites with sizes ranging from 10 to 100 nm were obtained (Bertone et al., 2003). Nanosize crystalline silica particles also may be produced from rice husks and *Fusarium oxysporum* fungus (Bansal et al., 2006 [PMID:17061888]) or synthesized by a sol-gel process via a sol-gel,

salt-assisted aero-sol-gel and ultrasonication (Kim et al., 2004 [PMID:15835116], 2007 [PMID:17206810]; Rao et al., 2005 [PMID:15913636]). Particles with diameters from 10 to 20 nm were produced by hydrolysis and hydrothermal aging of tetraethylorthosilicate in an L-lysine solution (Snyder et al., 2007 [PMID:17625899]).

4.0 Production and Import Volumes

In 2003, consumption of ground silica was 221,000 metric tons for ceramic production and 519,000 metric tons for filler (Dolley, 2003). Under the U.S. Environmental Protection Agency's (EPA) Inventory Update Reporting (IUR) for 1994, 1998, and 2002, production of 10,000 to 500,000 pounds of quartz was reported (U.S. EPA, 2009). According to the non-confidential 2006 IUR records, the aggregated national production volume for quartz was 500 million to <1 billion pounds (U.S. EPA, 2006). [It is possible that the 1994-2002 volumes corresponded to synthetic production only and the 2006 volume reported is the total production for quartz sand.] The last worldwide report for the annual production of silica (total quartz sand and gravel) was 100.2×10^6 metric tons (IARC, 1997).

The United States is the largest producer of DE in North America. Between 1970 and 1994, the United States produced 578 to 671 thousand tons of DE (IARC, 1997).

5.0 Uses

Silica flour is used as an abrasive in polishes and cleaning products; an additive in soaps, toothpastes, and paints; as a reinforcing filler in rubber, plastics, paper, wood fillers, and road surfacing materials; and in fillers for a broad range of pharmaceuticals. It also is used in foundry work and in glass, ceramic, porcelain, tile, and clay production. Ground silica sand is used in brick, mortar, concrete, sandpaper, and sandblasting (NTP, 2005). Finely ground quartz crystals are used in some skin-care products, including exfoliants, scar and acne treatments, and corn, callus, and wart removers; mineral-based cosmetics; and hair- and nail-care products (EWG, 2009; Head2Toe Beauty, 2009; Swanson Health Products, 2009). A search of the Environmental Working Group database did not find any products that included "silica flour" as an ingredient.

The major use of diatomite appears to be for calcination. In 2007, 51% of diatomite consumed was used for filtration, most of which was calcined. Calcined diatomite represented 65% of the total filtration market in 2007. It is commonly used to filter beverages such as beer and wine, sugar and sweetener liquors, oils and fats, pharmaceuticals, and water. One well-known use is as an absorbent for nitroglycerin in dynamite (Crangle, 2008). Other applications included use as an additive for cement, as a filler, as an absorbent, and as a constituent of insulation. As a filler, it has been used in paint, paper, asphalt products, and plastic (Household Products Database, 2009; U.S. EPA, 1995).

Nanoscale Silica

Silica nanoparticles have been used in combination with DNA and dendrimers to develop a DNA delivery system for gene therapy and DNA vaccines (Gemeinhart et al., 2005 [PMID:15801794]). Nanoscale silica also is proposed for use in targeted delivery of drugs and bioimaging materials (e.g., Jin et al., 2007 [PMID:17630705]; Moulari et al., 2008 [PMID:18790531]; Nelson et al., 2009 [PMID:19447201]). Luminescent silica nanoparticles have been evaluated for use as a labeling agent for biomedical applications (Jin et al., 2007

[PMID:17630705]). Adding silica nanoparticles to materials such as ceramic-polymer composites and concrete increased their resistance (Maes, 2008; Siejka-Kulczyk et al., 2008).

6.0 Environmental Occurrence and Persistence

Given its lack of solubility in a variety of chemicals, quartz is ubiquitous in the environment and is the second most common mineral in the world (U.S. Bureau of Mines, 1992). All three types of rock—igneous, sedimentary, and metamorphic—contain quartz (the average amount in igneous rock is 12%). Quartz also is a major component of airborne sand and dust (U.S. Bureau of Mines, 1992; IPCS, 2000). Concentrations measured in high-volume filter samples of total suspended particulates in ambient air from 10 U.S. cities ranged from 0 to 15.8 $\mu g/m^3$ (IPCS, 2000). Crystalline silica is present in all soils as a result of rock erosion, crystallization of amorphous silica, or deposition due to transport. Uncalcined DE contains between 0.1 and 4.0% crystalline silica (IARC, 1997).

Wet scrubbers and fabric filters are used to control calciner emissions, but no information was available on the content of cristobalite in calciner emissions or on the control of emissions during other process involved in handling DE (U.S. EPA, 1995). Quartz and cristobalite were quantitated in air samples from Tokyo in 1965, and the concentration of quartz was reported to be ≤0.034 mg/m^3. The concentration of cristobalite and potential sources of airborne silica were not included in the abstract (Sakabe et al., 1965).

7.0 Human Exposure

Dermal and/or oral exposure to quartz, the two routes of primary interest in this review, may occur during the use of a variety of consumer and commercial products, such as cleansers, some skin care products and soaps, art clays and glazes, pet litter, talcum powder, caulk, pharmaceuticals, putty, paint, and mortar. These products contain ≥0.1% crystalline silica (U.S. Bureau of Mines, 1992). Dermal exposure also has occurred from the use of silicea, a homeopathic remedy prepared from flint, quartz, sandstone, and other rocks, to treat a variety of ailments (e.g., acne, breast inflammation, ear infection, and knee conditions). In addition, silicea has been recommended for use in fortifying hair and nails (Los Angeles Chinese Learning Center, undated).

The general public also may be exposed to crystalline silica as an impurity of amorphous silica, such as DE or amorphous silica fume (ECETOC, 2006). Amorphous silica may be added to food as an anti-caking or anti-foaming agent or to pharmaceuticals as an excipient (EFSA, 2004; IARC, 1997). The concentrations of crystalline silica reported in commercially available diatomite filters (e.g., used to filter water, beer, and oils) or fillers (e.g., used in paint, paper, and scouring powders) ranged from 2.0-62.7%. Most of the crystalline silica is cristobalite, which is formed during calcination of diatomite. Uncalcined diatomite contained ≤4.0% crystalline silica compared to 60-70% found in calcined diatomite. Concentrations were lower in "straight calcined" (10-20%) compared to flux calcined products (40-60%), and some commercially available DE contained almost 70% cristobalite (Celite Corporation, 2006; Elias et al., 2006; GMZ, Inc., 2007; IARC, 1997).

Exposure of the general population also may occur by inhalation of ambient air that contains quartz from electrical power generation, agricultural tilling, forest fires, volcanic eruptions, wind

erosion, and dust from travel on paved and unpaved roads (IPCS, 2000). One report noted that the silica and silicate composition in ambient air was similar to that of particles recovered from Peyer's patches in the intestines of individuals who had no history of occupational exposure to silica (Urbanski et al., 1989 [PMID:2548180]).

The greatest risk of human exposure to crystalline silica is occupational, primarily through inhalation. In 2001, it was estimated that approximately two million workers in the United States were exposed to silica, of which 100,000 were exposed to concentrations >0.1 mg/m^3 (Steenland and Sanderson, 2001 [PMID:11282798]). Atmospheric concentrations of silica reported in the workplace and health risks associated with inhalation exposure have been well documented in other reviews (IARC, 1997; IPCS, 2000; NIOSH, 1984a,b; NTP, 2000, 2005) and will not be described here in detail. The types of occupations and operations that have been reported to have the greatest risk of silica exposure include the following: coal mining and milling; DE mining and plant operations (mixing, blending, filling, and packaging); granite quarrying and processing; foundry operations; steel fabrication; stone crushing and related industries; silica flour production; sandblasting operations; construction; plastering; operating painting and paint spraying equipment, laundering and dry cleaning machines, and grinding, abrading, buffing, and polishing machines; janitors and cleaners; ceramic, pottery, and brick manufacturing; and silicon carbide production workers (Infante-Rivard et al., 1994 [PMID:7985648]; Rice et al., 2001).

Nanoscale Silica

Airborne particulate matter ($PM_{2.5}$) collected in Houston and El Paso, TX, had nanoscale crystalline silica aggregated with carbon nanocrystals (Murr et al., 2004a,b). Nanosized silica also was identified in soot emissions from C1 coal combustion. A retrospective cohort study in southwest China is currently evaluating the potential link between household use of C1 coal and lung cancer in non-smoking women (Tian et al., 2008).

8.0 Regulatory Status

Silica flour as a raw material being mined or processed is exempted from the Hazard Communication final rule. For example, operators of silica flour mills are not required to label containers of the raw material (e.g., bins) (MSHA, 2002).

Two U.S. Food and Drug Administration (FDA) guidance documents discussed the use of silica (not silica flour) in medical devices. The draft guidance on the preparation of premarket approval applications for obtaining testicular prostheses stated that silica may be added to silicone elastomers to reinforce them. Since elastomers are soft and prone to degradation and abrasion, individuals may be exposed to silica during placement or use. The guidance noted that while amorphous crystalline is typically used in the production process, there is concern over the presence of crystalline silica impurities and potential conversion of amorphous silica into crystalline silica. Accordingly, the draft guidance noted that abrasion testing and evaluations for the presence of crystalline silica must be performed (U.S. FDA, 1993). Nonbinding recommendations of the FDA suggested amorphous, rather than crystalline, silica be used in the elastomer shell dispersions used in saline-filled or silicone gel-filled breast implants (U.S. FDA, 2006).

Silica and quartz were included in several codified rules that are administered by the FDA (Code of Federal Regulations, 2009). A summary of the rules are provided in the table below. As noted previously, amorphous silica is typically added to foods; however, crystallized silica may be present. No regulations specifically identifying "silica flour" were noted.

Paragraph	Title	Summary
§73.50	Ultramarine blue	This is a color additive which may have silica added to vary shade color.
§74.2053	D&C Black No. 3	The specifications for the color additive D&C include the silica may not be present in more than 5%.
§175.300	Resinous and polymeric coatings	Coatings that are the food-contact surface, that are used in food production, containment, and transport. One of the adjuncts for listed epoxy resins is silane coupled silica which is prepared by the reaction of listed chemicals with microcrystalline quartz.
§176.200	Defoaming agents used in coatings	Silica is listed as a substance that may be used in the formulation of defoaming agents in coatings used for food production, containment, and transport.
§176.210	Defoaming agents used in the manufacture of paper and paperboard	Silica is listed as a substance that may be used in the formulation of defoaming agents that may be used in the manufacturing of paper and paperboard used in food production, containment, and transport.
§177.1200	Cellophane	Silica is listed as a substance that may be added to cellophane, which is to be used in food packaging.
§177.2600	Rubber articles intended for repeated use	Silica is listed as a filler that may be used in preparation of rubber articles that are to be repeatedly used in food production, containment, and transport.
§178.3297	Colorants for polymers	Silica is listed as a substance that may be used to color articles or components of articles intended for use in food production, containment, and transport.
§872.6030	Oral cavity abrasive polishing agent	Silica pumice is listed as a potential abrasive material used in the preparation of an oral cavity abrasive polishing agent.
§872.6660	Porcelain powder for clinical use	This is a device that may include quartz that is to be used for the production of artificial teeth in prosthetic dentistry.

Recommended limits for inhalation exposure have been established for silica. According to the American Conference of Governmental Industrial Hygienists, the threshold limit value for respireable crystalline silica is 0.025 mg/m^3 (time weighted average [TWA]). Recommended exposure limits (RELs) of 0.05 mg/m^3 for quartz and 6 mg/m^3 for amorphous silica, including DE, were established by NIOSH based on a 10-hour TWA. The OSHA PEL for quartz was set at 10 mg/m^3/(% respireable SiO_2+2) and for amorphous silica at 80 mg/m^3/(% respireable SiO_2+2). TLV-TWAs for inhalable and respireable particulate fractions of 10 and 3 mg/m^3, respectively, were recommended for occupational exposure to natural (uncalcined) DE containing no asbestos and <1 % crystalline silica (OSHA, 2004; RTECS, 2009a,b).

European Union Scientific Committee Regulations

Silica is listed in the European Inventory of Existing Commercial Chemical Substances. It is not classified in Annex I of Directive 67/548/EEC (index of dangerous substances), Annex I of Regulation (EC) No. 689/2008 (list of chemicals subject to export notification), or the European Priority List under Council Regulation (EEC) No. 793/93 (Export and Import of Dangerous Chemicals); however, it may be included in a group entry. It is listed in the Organization for

Economic Co-operation and Development List of High Production Volume Chemicals (ChemPortal, 2006).

9.0 Toxicological Data

9.1 General Toxicology

The following sections summarize toxicological data related to dermal or oral exposures to silica flour and nanoscale silica. [Note: The cited authors' terms (i.e., quartz, DQ12, etc.) are used.] Information from studies of other routes of exposure (e.g., inhalation) is included where particularly relevant or when data from dermal or oral exposure was not available. All systemic endpoints, excluding pulmonary effects, were considered.

9.1.1 Human Data

Chemical Disposition, Metabolism, and Toxicokinetics

Silica particles (3 or 10 μm diameter) labeled with a fluorescence tag and deposited topically on human skin were cleared (fell off) with a half-life of 1.5-7.8 hours. Factors that affected the clearance rate were the amount of hair present at the loading site and physical movement (Hession et al., 2006 [PMID:16249045]).

A case study reported that long-term ingestion of cristobalite (3 g/day) led to recurring urinary calculi containing minute silica particles in the core (Leusmann et al., 1986 [PMID:3026031]).

Quartz dissolution was not believed to contribute significantly to clearance or biological activity in persons with silicosis. Particles deposited in the lung periphery were only slowly and incompletely cleared, likely due to macrophage cytotoxicity (Stöber, 1999 [PMID:10380170]). Blood/lymph clearance beyond the pulmonary lymphatics and lymph nodes was not reported. However, blood/lymph transport following inhalation exposure was indicated by the presence of silica in organs other than the lung or gastrointestinal tract (e.g., liver, spleen, or bone marrow) and in the remote lymphatics and nodes (Slavin et al., 1985 [PMID:3980008]).

Acute, Subchronic, and Chronic Exposures

Numerous case studies have described development of cutaneous granulomas after crystalline or amorphous silica was accidently introduced subcutaneously by tattooing, injection, or surgical procedures that may have involved the embedding of glass, sand, or soil (Mowry et al., 1991 [PMID:1850974]). Crystalline silica particles (1-90 μm diameter) were identified in the skin of individuals with progressive systemic sclerosis and known exposure to crystalline silica based on a 16-year history of using scouring powder that contained crystalline silica (Mehlhorn et al., 1990a [PMID:2177697], 1990b [PMID:2165341]). It also was suggested that some cases of cutaneous sarcoidosis could be due to silica contamination in mineral powder such as talc (Vincent et al., 2004 [PMID:15536384]).

Inhalation of respirable crystalline silica is typically associated with chronic silicosis, usually a nodular pulmonary fibrosis. Numerous case reports of silicosis in workers occupationally exposed to silica quartz are available. Other silica-related diseases included pulmonary tuberculosis, chronic obstructive pulmonary disease such as bronchitis and emphysema, chronic renal disease, hyperthyroidism, and scleroderma. Additional adverse effects or complications in workers with silicosis who likely had been exposed to quartz dust included cancer of the

nasopharynx or pharynx, esophagus, stomach, intestines, peritoneum, liver, pancreas, bladder, lymphatic or hematopoietic system, skin, and bone; however, evidence of an association with exposure to quartz dust was not clear (IPCS, 2000). The NIOSH Hazard Review entitled "Health Effects of Occupational Exposure to Respirable Crystalline Silica" provides a review of publications through March 1999 (NIOSH, 2002).

Several studies have correlated employment at a DE mining and processing facility with development of adverse health effects (e.g., Hughes et al., 1998). Results from a study of workers (n = 492) at one facility showed that total cristobalite exposure and total dust exposure correlated with the International Labor Office scoring system for chest radiographs (Harber et al., 1998 [PMID:9467117]). One study described the presence of pneumoconiosis in an individual that worked in a beer production plant. The patient's history indicated that he was exposed to DE and mineral asbestos dusts (Mendez Vargas et al., 1987).

Carcinogenicity

Lung cancer was associated with occupational exposure to inhaled quartz (IPCS, 2000). According to the IARC, there is sufficient evidence in humans of carcinogenicity from inhaled crystalline silica in the form of quartz and cristobalite from occupational sources (IARC, 1997).

Persons exposed to airborne micrometer-sized and larger silica particles may ingest them after inhalation, during open-mouthed breathing, or from hand-to-mouth contact (particles larger than ~10 μm are likely to be swallowed after mucociliary clearance), resulting in contact with the gastrointestinal tract. At least 17 occupational epidemiological studies reported moderately elevated risk for extrapulmonary cancers among persons with high silica exposure, and 11 of the studies found increased risk of cancers of the gastrointestinal tract and associated organs, including the esophagus, stomach, salivary glands, and digestive organs (e.g., Fillmore et al., 1999 [PMID:10361596]; Finkelstein and Verma, 2005 [PMID:15597359]; Yu et al., 2005 [PMID:15578719]; Zheng et al., 1996 [PMID:8760587]).

The relationship between crystalline silica exposure and lung cancer death was evaluated in a cohort study of 2342 white males that worked at a DE mining and processing facility in Lompoc, CA. Results showed that there was a dose-related increase in cancer deaths among individuals without radiological silicosis. Overall, lung cancer excess was larger among individuals with radiological silicosis than individuals without silicosis (Checkoway et al., 1999). Using different exposure-response models, Rice and colleagues (2001) showed that exposure to respirable crystalline silica was a significant predictor of lung cancer death. Using the REL (0.05 mg/m^3), the predicted excess lifetime risk for cancer death ranged from 8.6 to 18 out of 1000 individuals, based on 45 years of crystalline silica exposure. [Noted: Based on information provided in the cited sources, it is presumed that the populations evaluated in the two studies are the same.] Information submitted to the U.S. EPA indicates that asbestos exposure may play a role in lung cancer deaths among workers exposed to crystalline silica (IDPA, 1994, 1996).

Genotoxicity

In lung tumors from workers with silicosis, p53 gene mutations were reported (Liu et al., 2000 [PMID:10905501]). DNA strand breaks were observed in lymphocytes of foundry and pottery workers, (Basaran et al., 2003 [PMID:12768610]). Additionally, sister chromatid exchanges

(SCE) and chromosomal aberrations (CA) in human lymphocytes *in vivo* were reported (IPCS, 2000).

Immunotoxicity

It was suggested that uncontrolled immune responses induced by inhalation of crystalline silica particles play a key role in the development of silicosis and lung cancer (Huaux, 2007 [PMID:17351471]). There is a possible link between immune activation by occupational exposure to quartz and the following diseases: scleroderma, rheumatoid arthritis, polyarthritis, mixed connective tissue disease, SLE, Sjogren's syndrome, polymyositis, and fibrositis (IPCS, 2000). A high incidence of scleroderma was reported in scouring-powder manufacturers in Spain. A possible link has also been proposed between silica exposure and small-vessel vasculitis (e.g., Wegener granulomatosis) (Parks et al., 1999).

In vitro, Min-U-Sil 5 enhanced production of interleukin-8 (IL-8) in normal human bronchial epithelial cells (Veranth et al., 2007). Incubation of lipopolysaccharide (LPS)-primed human peripheral blood mononuclear cells with Min-U-Sil 5 resulted in caspase-1-dependent release of IL-1β. Phagocytosis of quartz particles was shown to induce inflammation via activation of the NALP3 inflammosome (Hornung et al., 2008 [PMID:18604214]). Exposure to DQ12 quartz resulted in persistent upregulation of IL-8 and depletion of the nuclear transcription factor NFκB inhibitor IκBα in A549 human lung epithelial cells *in vitro* (Monteiller et al., 2007 [PMID:17409182]; Schins et al., 2002a [PMID:12034310]).

Renal Toxicity

Numerous epidemiological studies have evaluated kidney effects associated with silica exposure. The International Programme on Chemical Safety stated that epidemiological studies indicated that there was an association between development of renal disease and occupational exposure to crystalline silica dust (IPCS, 2000). Associations between silica exposure and kidney effects also were reviewed by the IARC (1997). While silica exposure was not proposed to be associated with a number of kidney effects in 17 cases of pulmonary silicosis, the authors did propose that the development of acute focal glomerulophephritis was related (Slavin et al., 1985 [PMID:3980008]). More recent studies provided conflicting evidence of an association between silica exposure and renal disease or cancer development. A review by Steenland (2005 [PMID:15940719]) showed that there was excess risk of end-stage kidney disease (5.1%, based on male background rates) and renal disease (1.8%) based on the data from one and three cohorts, respectively. An earlier study by Steenland and colleagues (2001 [PMID:11416778]) evaluated a cohort of 4626 silica-exposed industrial sand workers. An excess mortality from renal disease (standardized mortality ratio [SMR] = 2.61) and chronic renal disease (SMR = 1.61) was reported. An excess incidence of end-stage renal disease, especially glomerulonephritis (SMR = 3.85) also was seen. An association between occupational silica exposure and kidney cancer was described in Vermont granite workers (Attfield and Costello, 2004 [PMID:14748044]). Comparatively, a study of German porcelain production workers indicated that renal cancer or non-malignant renal disease was not associated with employment (Birk et al., 2009 [PMID:19225421]). Similar conclusions were reported from an analysis of 2670 employees of the North American sand industry (McDonald et al., 2005).

9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

No studies via dermal exposure were available.

Silica particles (50-300 mg) given to male Wistar rats by stomach tube were not found in the submucosa, muscularis, or regional lymph nodes 10 or 41 weeks after administration. Additionally, no silicotic nodules were found in the liver or spleen (González Huergo and Rojo Ortega, 1991 [PMID:1665076]). In dogs and rabbits administered silica dust intragastrically, urinary concentrations of silica increased but blood concentrations did not vary significantly (JECFA, 1974).

White rats were administered silica flour in their diet for six to eight weeks (approximately 60 to 100 g silica flour was consumed over the study period). Animals were then administered normal diets for four to ten days prior to necropsy. Sections of ileum were examined with ordinary and polarized light. Results showed that silica flour entered the intestinal epithelium, likely by phagocytosis, then, after entering the villi, moved into the blood system. Silica flour crystals were dispersed throughout the body (e.g., myocardium and brain) (Reimann et al., 1965). [Note: Figures of crystals in the systemic organs were not provided in the paper. Results were only presented in the text.]

Suckling mice were orally gavaged for 7 days with Percoll microspheres (colloidal silica coated with polyvinylpyrrolidone; mean diameter = 20-30 nm). Translocation studies indicated limited amounts of the microspheres were present in the subepithelial tissue of the villous mucosa and Peyer's patches, mesenteric lymph nodes, and omentum. Percoll also was found in the liver and thymic cortex (Matsuno et al., 1983 [PMID:6300397]; Sigma-Aldrich, 1998).

Rat lung clearance of cristobalite primarily occurred within two weeks after short-term inhalation exposure. Particles moved between alveolar space and lung tissues and the concentration in the alveolar space fluctuated depending on the macrophage population. During the months after exposure particles accumulated in the mediastinal lymph nodes and thymus. Kidney, spleen, liver, and blood had negligible concentrations of silica (Absher et al., 1992 [PMID:1327732]).

In vitro studies using macroscopically normal areas of bowel from patients with Crohn's disease, ulcerative colitis, or colonic carcinoma showed that silicates could be collected in human gut-associated lymphoid tissue (GALT). Ultrastructural localization studies indicated that the silicates were present in phagolysosomes of macrophages in GALT (Powell et al., 1996). Another *in vitro* study reported that cristobalite was selectively bound by serum protein apolipoprotein-A1 (Barrett et al., 1999 [PMID:10581205]).

Nanoscale Silica

The effect of surface charge on cellular uptake of mesoporous nanosilica into human mesenchymal stem and 3T3-L1 cells was evaluated. The uptake *in vitro* was regulated by a threshold positive surface charge and was cell specific (Chung et al., 2007 [PMID:17397919]). Nanosilica (50, 100, and 200 nm diameter) injected intravenously (i.v.) into mice was observed in macrophages of the liver and spleen for four weeks. The smaller size particles were excreted in urine and feces (via bile) more quickly than the larger particles (Cho et al., 2009 [PMID:19397964]).

9.1.3 Acute Exposure

The lowest published toxic dose by oral exposure was 120 g/kg in the rat. Gastrointestinal effects (specifically, hypermotility, diarrhea, and other not specified changes) were reported. Lowest published toxic/lethal concentrations/doses for exposure by inhalation, intratracheal (i.t.) instillation, implantation, or i.v. also were reported in the mouse, rat, and rabbit. The lowest lethal doses following exposure via i.t. instillation was >20 mg/kg for mice and 200-250 mg/kg for rats (RTECS, 2009a).

Nanoscale Silica

Three days after 7-week-old Balb/c mice were fed 2.5 g nanosilica (10-20 nm), histopathological examination revealed a nonspecific focal hemorrhage in the heart and liver; the spleen, stomach, and intestine were not affected. Mild toxicity also was observed when mice were given micro-sized particles (45 μm). There was a nonspecific focal hemorrhage in the heart, focal hemorrhage in the liver and spleen, and a nil lesion in the stomach and intestine (Cha and Myung, 2007).

A study of 8-week-old Balb/c mice injected i.v. with nanosilica (70, 300, or 1000 nm [SP70, SP300, or SP1000]; 10-100 mg/kg) reported that SP70 produced degenerative necrosis of hepatocytes in the liver at the 30 mg/kg dose; no abnormal changes were seen in the spleen, kidney, or lung. SP300 and SP1000 produced no toxicity. This was confirmed by the increase seen in serum alanine aminotransferase (ALT) activity with SP70 at 30 mg/kg (levels were 35-fold higher than control values) while no effect on ALT activity was seen with SP300 or SP1000 at any dose. ALT, as well as serum levels of IL-6 and tumor necrosis factor-alpha (TNF-α), were dose-dependently increased in mice treated with SP70 (Nishimori et al., 2009a [PMID:19232391]).

9.1.4 Short-Term and Subchronic Exposure

No studies via dermal exposure were available. A study of nanosilica given orally to mice is described below in the Nanoscale Silica section. An oral study in guinea pigs is presented in **Section 9.8** (Effects on Kidneys).

In mice, rats, and hamsters, i.t. instillation of quartz particles caused discrete silicotic nodules in the lungs. Inhalation exposure resulted in progressive lesions and pneumonitis. Additionally, in rats, quartz given by either route induced formation of reactive oxygen species (ROS) (including hydroxyl radicals) and reactive nitrogen species (IPCS, 2000). The following table presents the lowest published toxic concentrations reported by the Registry of Toxic Effects of Chemical

Substances for subchronic inhalation exposure of mice, guinea pigs, and hamsters (RTECS, 2009a):

Species	Dose/Duration	Effects
mouse	1475 μg/m^3 / 8 hr/d × 21 wk (int)	lung, thorax, and respiration
mouse	4932 μg/m^3 / 24 hr/d × 39 wk (cont)	endocrine (changes in spleen weight); immunological (allergic)
mouse	160 mg/kg / 2 wk (int)	blood (changes in serum composition [e.g., bilirubin]); immunological (allergic)
guinea pig	28 mg/m^3 / 3 wk (int)	lung, thorax, or respiration; biochemical (enzyme inhibition, induction or change in blood or tissue levels)
hamster	3 mg/m^3 / 6 hr/d × 78 wk (int)	lung, thorax, or respiration

Abbreviations: cont = continuous; d = day(s); hr = hour(s); int = intermittent; wk = week(s)

In rats, the lowest published toxic concentrations ranged from 6.2 mg/m^3 for intermittent inhalation 6 hours/day for 6 weeks, to 108 mg/m^3 for intermittent inhalation 6 hours/day for 3 days. The lowest published toxic dose for i.t. exposure ranged from 240 μg/kg (12 weeks intermittent exposure) to 203 mg/kg (28 days intermittent exposure). Observed effects included changes in the lung, thorax, or respiration; blood effects (e.g., changes in spleen); biochemical effects (e.g., enzyme inhibition or induction); and immunological effects, including allergic response (RTECS, 2009a).

Nanoscale Silica

Balb/c and C57BL/6J mice fed nanoscale silica (30 nm, 140 g silica/kg) for 10 weeks had higher levels of ALT compared to controls or mice fed microsilica (30 μm). Silica content in the livers from all treated mice looked almost the same, but nanosilica fed mice had fatty liver patterns (So et al., 2008 [PMID:19198457]).

In 8-week-old Balb/c mice, i.v. injection of 70 nm-sized silica particles (10 or 30 mg/kg) every 3 days for 4 weeks dose-dependently induced denaturation of hepatocytes. Histological analysis also revealed hepatic microgranulation and splenic megakaryocyte accumulation; liver fibrosis was induced, as evidenced by the significant increase in hydroxyproline (1.6- and 3.5-fold over controls at 10 and 30 mg/kg, respectively) and collagen content. Serum ALT levels were elevated but no abnormal changes were seen in the kidney, lung, brain, or heart (Nishimori et al., 2009a [PMID:19232391], 2009b [PMID:19341796]).

9.1.5 Chronic Exposure

No studies via dermal or oral exposure were available.

In mice and rats, inhalation of quartz particles suppressed immune functions and caused cellular proliferation, nodule formation, and alveolar proteinosis (IPCS, 2000). The lowest published toxic concentration for chronic (two-year intermittent) inhalation exposure in rats was 0.74 mg/m^3; effects were observed in the lungs, thorax, and respiration (RTECS, 2009a). Hepatic fibrosis, cirrhosis, and granulomas were observed in nude mice and Syrian golden hamsters 12 months after subcutaneous or intraperitoneal (i.p.) injection of Min-U-Sil 5 quartz (3.5 and 1.6 g/kg body weight, respectively); effects were seen in all of the mice and hamsters 12 and 3 months after dosing, respectively (Williams and Knapton, 1996 [PMID:8621163]).

One 90-day animal study (species and methodology were not provided) showed that ingestion of DE did not produce any adverse health effects (IUCLID, 2000).

Nanoscale Silica

The effect of nanosilica on fibrogenesis was reported to be weaker than that of microsilica. The lung/body weight coefficient, hydroyproline content, and expressions of IL-4 and transforming growth factor-β1 were significantly lower in Wistar rats 1 and 2 months after i.t. instillation of nanosilica (20 mg) compared results from rats given microsilica. Additionally, Stage 1 cellular nodules were seen in the group given nanosilica compared to Stage II, II+ and Stage II+, III silicotic nodules observed in the group given microsized particles (Chen et al., 2004 [PMID:15807405]).

9.1.6 Synergistic/Antagonistic Effects

No studies of anticarcinogenic or antigenotoxic effects were available.

Synergistic/Antagonistic Effects of Silica Flour

Syrian golden hamsters given Min-U-Sil or Sil-Co-Sil quartz with benzo[*a*]pyrene (BaP) by i.t. instillation had more respiratory tract tumors than hamsters given BaP alone (IPCS, 2000). Intravenous injection of Thorotrast (α-radiation-emitting material) had an interactive effect on pulmonary carcinogenicity in female Wistar rats exposed to DQ12 quartz by inhalation; tumors of the liver and spleen also were observed (IARC, 1997; IPCS, 2000).

Synergism/Antagonism of Silica Flour-Induced Effects

Quartz (5 and 15%) naturally occurring in coal-mine dust was less fibrogenic than quartz artificially mixed with low quartz content coal-mine dust in the same proportion, suggesting that naturally occurring contaminants may antagonize quartz toxicity (IARC, 1997). A naturally occurring quartz with occluded crystal surfaces was less inflammatory than DQ12 in rats exposed by i.t. instillation (Miles et al., 2008 [PMID:18686105]). Pretreatment of DQ12 quartz with aluminum lactate greatly reduced the ability of quartz to cause pulmonary inflammation in rats exposed by i.t. instillation (IARC, 1997).

Pretreatment of DQ12 quartz with aluminum lactate or polyvinylpyridine-*N*-oxide (PVNO) greatly reduced its ability to generate hydroxyl radicals, prevented DNA damage, and inhibited particle uptake in A549 human lung epithelial cells *in vitro* (Schins et al., 2002b [PMID:12230410]). PVNO also inhibited *in vitro* adsorption of human high-density lipoprotein (HDL) by three different fibrogenic α-quartz samples. Comparatively, PVNO inhibited low-density lipoprotein absorption by two of the α-quartz samples but enhanced absorption by the third sample (Bogatu and Contag, 2005 [PMID:16320625]). Treatment with aluminum lactate reduced the effects of DQ12 quartz on cell viability, apoptosis, and TNF-α production in NR8383 rat alveolar macrophages (Attik et al., 2008 [PMID:18803060]). Curcumin (a polyphenol found in turmeric) reduced the cytotoxicity and inflammatory effects of DQ12 quartz in rat lung cells, but not its genotoxic effects. [Note: Curcumin itself caused oxidative DNA damage] (Li et al., 2008 [PMID:18001810]). Ascorbic acid increased Min-U-Sil 5 quartz-induced release of TNF-α from rat aleveolar macrophages (Scarfi et al., 2009). Scarfi and colleagues (2009) also stated that previous studies indicated that ascorbic acid pretreatment

increased quartz-induced cytotoxicity and cyclooxygenase-2 expression in RAW 264.7 cells (IARC, 1997).

9.1.7 Cytotoxicity

Cytotoxicity of crystalline silica particles generally has been related to specific surface area and the interaction of the crystal surface with biological molecules and cell surfaces. Freshly fractured surfaces are more reactive than aged surfaces (IPCS, 2000). DQ12 quartz was cytotoxic to human alveolar epithelial A549 cells at much lower surface-area doses than other low-solubility, low-toxicity particles at the same mass dose (Monteiller et al., 2007 [PMID:17409182]). Rat lung epithelial cells *in vitro* were more sensitive than human lung epithelial cells to the toxic effects of DQ12 quartz (Schins et al., 2002a [PMID:12034310]).

Following is a list and brief description of cytotoxicity studies in human cells *in vitro* and animal cells *in vivo* and *in vitro*.

Human Studies (*in vitro*)

- Min-U-Sil 5 quartz induced apoptosis and generation of ROS in cultured human aortic endothelial cells (Santarelli et al., 2004 [PMID:15242185]).
- Extracellular ROS were generated in culture medium incubated with DQ12 particles; the particle-free supernatant then induced intracellular ROS in normal human bronchial epithelial cells at concentrations equivalent to those observed in cells exposed directly to quartz (Deshpande et al., 2002).
- DQ12 quartz was cytotoxic and induced oxidative stress in A549 lung epithelial cells (Monteiller et al., 2007 [PMID:17409182]).
- Min-U-Sil 5 quartz did not reduce the viability of BEAS-2B human lung epithelial cells in a mitochondrial reductase assay (Veranth et al., 2007).
- Min-U-Sil 5 quartz did not induce oxidative stress in human blood serum in an assay of the ferric reducing ability of serum (Rogers et al., 2008 [PMID:18593597]).

Animal Studies (*in vivo* and *in vitro*)

- In three studies, i.t. instillation of rats with Min-U-Sil induced apoptosis in lung cells recovered by lavage (IPCS, 2000).
- Cultures of lung fragments from neonatal mice that had been exposed to silica flour exhibited effects resembling those seen with chronic silicosis induced by inoculation or inhalation of silica (Yoshihara and Yew, 1978 [PMID:214331]).
- DQ12 quartz was cytotoxic in rat lung epithelial cells *in vitro* (Schins et al., 2002a [PMID:12034310]).
- DQ12 quartz phogocytized by NR8383 rat alveolar macrophages *in vitro* decreased cell viability and induced apoptosis (Attik et al., 2008 [PMID:18803060]).
- Phagocytosis of Min-U-Sil 5 quartz particles by mouse bone-marrow-derived macrophages *in vitro* resulted in rupture of lysosomes and leakage of lysosomal contents into the cytosol (Hornung et al., 2008 [PMID:18604214]).
- Cristobalite and quartz induced dose-dependent cytotoxicity and morphological transformations in Syrian hamster embryo (SHE) cells *in vitro* (Elias et al., 2000 [PMID:10963957]).

Diatomaceous Earth

The cytotoxic potential of five forms of DE was evaluated in SHE cells. The forms included untreated DE, DE heated to 900 °C, DE heated to 1200 °C, a commercially available DE product (Chd), and a finer fraction (<10 μm) of the product (Chd-F). DE, Chd, and Chd-F decreased

cellular proliferation and colony-forming efficiency in a dose-dependent manner. Heating of the particles led to induction of transforming ability, which was proposed to be related to the transformation of DE to cristobalite (Elias et al., 2006). These results are supported by earlier studies by Elias and colleagues (2000 [PMID:10963957]). DE also induced formation of ROS in human phagocytic cells (Stratta et al., 2001 [PMID:11327392]). Studies in mouse peritoneal macrophages reported that both uncalcined and calcined DE samples, which have lower cristobalite content, were more cytotoxic than the flux calcined DE samples. Additionally, the cytotoxic activity of the flux calcined samples was similar to cristobalite (Bye et al., 1984).

Nanoscale Silica

The following information is from studies of nanoscale silica toxicity:

- Nanoscale silica was not cytotoxic to human mesothelioma MSTO-211H, mouse fibroblast 3T3, U937, or human mesenchymal stem cells but was cytotoxic to RAW 264.7, WIL2-NS, WS1, CCD-996sk, MRC-5, MKN-28, and HT-29 cells (Brunner et al., 2006 [PMID:16903273]; Chang et al., 2007 [PMID:17410806]; Chung et al., 2007 [PMID:17397919]; Dutta et al., 2007; Lin et al., 2006 [PMID:17112558]; Lucarelli et al., 2004 [PMID:15627643]; Wang et al., 2007a [PMID:17285640]; Waters et al., 2009 [PMID:19073995]).
- Conflicting results were observed in cytotoxicity studies of nanosilica in A549 and HEK293 cells. One study reported inflammatory responses were increased in A549 cells, as well as in L-132 (normal) cells, without extensive cell death. A second study showed that nanoscale silica was cytotoxic to A549 cells while another one reported minimal cytotoxicity in A549 and HEK293 cells, as well as in Huh-7, A-172, and MKN-1 cells (effect was not dose dependent) (Cha and Myung, 2007; Chang et al., 2007 [PMID:17410806]; Choi et al., 2009 [PMID:19181388]). A recent study, reported that nanosilica induced dose-dependent cytotoxicity in HEK293 cells and attributed it to increased oxidative stress (Wang et al., 2009 [PMID:19401228]).
- In human neuroblastoma SK-N-SH cells, a mesoporous silica nanomaterial, MCM-41, was more cytotoxic than two of its functionalized analogs, AP-T (which has grafted aminopropyl groups) and MP-T (which has grafted mercaptopropyl groups) or spherical silica nanoparticles. The toxicity of the silica nanospheres, which have the lowest surface area, and AP-T were similar, suggesting that particle shape may play a role in cytotoxicity (Di Pasqua et al., 2008 [PMID:18279965]).
- Nanoscaled quartz (mean size = 14 nm) induced pro-inflammatory stimulation as noted by enhanced release of IL-8, and impairment of proliferative activity in human dermal microvascular endothelial cells (Peters et al., 2004 [PMID:15332593]).

9.2 Reproductive and Teratological Effects

No studies via dermal, oral, or inhalation exposures were available.

9.3 Carcinogenicity

No studies via oral or dermal exposures were available.

According to the IARC, there was sufficient evidence in experimental animals for the carcinogenicity of quartz and cristobalite administered by inhalation or various routes of injection. Evidence in experimental animals for the carcinogenicity of tridymite was limited (IARC, 1997). Inhalation or i.t. instillation of quartz in rats induced pulmonary adenocarcinomas and squamous cell carcinomas but pulmonary tumors were not seen in hamsters or mice. Thoracic and abdominal malignant lymphomas, primarily of the histocytic type, were seen in rats given a single intrapleural or i.p. injection of suspensions of several types of quartz. The incidence of lung tumors was not significantly increased in male A/J mice (lung

adenoma assay) or in an inhalation study in BALB/cBYJ female mice (IPCS, 2000). Subcutaneous or i.p. injection of Min-U-Sil 5 quartz induced liver cell carcinomas in nude mice but not in Syrian golden hamsters (Williams and Knapton, 1996 [PMID:8621163]).

9.4 Initiation/Promotion Studies

No studies via dermal, oral, or inhalation exposures were available.

9.5 Genotoxicity

Although results from different studies have sometimes been conflicting, genotoxicity of silica flour generally has been associated with inflammation, cytotoxicity, and production of ROS (especially hydroxyl radicals). Study results have varied depending on the different types of quartz tested (e.g., Cakmak et al., 2004 [PMID:15031953]; Seiler et al., 2004 [PMID:15031954]). The relevance of *in vitro* genotoxicity test results to *in vivo* studies is still uncertain. Most of the *in vitro* studies have tested Min-U-Sil 5 or 10 or DQ12. In some studies, surfactant pretreatment of particles suppressed or delayed genotoxic effects (IPCS, 2000). No-effect levels for genotoxicity of DQ12 quartz in the rat lung were higher than those reported for fibrogenicity (Seiler et al., 2004 [PMID:15031954]). Since quartz particles do not penetrate the cell nucleus, evidence suggests an indirect mechanism for the observed DNA damage, which may involve the mitochondrial electron transport chain (Li et al., 2007 [PMID:17239409]). The table on the next page is a summary of test results for crystalline silica quartz.

Nanoscale Silica

Treatment of WIL2-NS (human B-cell lymphoblastoid) cells with nanoscale silica induced hprt mutations at the highest dose (120 μg/mL). A dose-dependent increase in the frequency of micronucleated binucleated cells also was observed. No significant increase in DNA strand breaks was seen (Wang et al., 2007a [PMID:17285640]; 2007b).

9.6 Cogenotoxicity

No studies via dermal, oral, or inhalation exposures were available.

9.7 Immunotoxicity

No studies via oral or dermal exposures were available.

In vitro studies indicate that DQ12 enhances TNFα production in rat alveolar macrophages (Attik et al., 2008 PMID:18803060]; Huaux et al., 1995 [PMID:7747285]). IL-1 production, after LPS stimulation, also was increased in rat alveolar macrophages after DQ12 administration (Huaux et al., 1995 [PMID:7747285]). Quartz increased macrophage inflammatory protein-2 expression in rat lung and alveolar type II epithelial cells (Driscoll et al., 2001 [PMID:11764986]). Comparatively, DQ12 quartz suppressed lymphocyte proliferation and lymphokine release in guinea pig splenic lymphocytes and peritoneal macrophages *in vitro* (Surcel et al., 1987 [PMID:2828466]). Freshly fractured crystalline silica (particle size ≤10 μm) induced protein kinase C (PKC)-dependent activation of nuclear transcription factor activator protein-1 (AP-1) via mitogen-activated protein kinase (MAPK) pathways in JB6 mouse epithelial cells (Ding et al., 2006). Crystalline silica (particle size <5 μm) activation of NFκB in RAW 264.7 mouse macrophages was dependent upon tyrosine phosphorylation of IκBα and p65 NFκB by Src tyrosine kinase (Kang et al., 2006).

The following table summarizes test results for crystalline silica quartz from studies included in the IPCS (2000) report and other sources:

Endpoint	Test System	Exposure	Results	Reference
DNA Damage				
8-OHdG	Wistar rat, male	i.t. instillation	Elevated in lung tissue DNA	IPCS (2000); Seiler et al., 2004 [PMID:15031954])
8-OHdG	Wistar rat, male	i.t. instillation	Negative in peripheral blood leukocyte DNA	IPCS (2000)
8-OHdG	Human A549 lung epithelial cells	*in vitro*	Elevated in DNA extracts	Schins et al., 2002a [PMID: 12034310]
8-OHdG	Rat lung epithelial cells	*in vitro*	Elevated in DNA extracts	Li et al., 2007 [PMID:17239409]; Schins et al., 2002a [PMID: 12034310]
Strand breaks	Human Hel 299 embryonic lung cells & A549 lung epithelial cells	*in vitro*	Positive	Cakmak et al., 2004 [PMID:15031953]; IPCS (2000) ; Schins et al., 2002a [PMID: 12034310]
Strand breaks	Rat pulmonary alveolar macrophages	*in vitro*	Positive	Gao et al., 2000 [PMID:10884165]
Strand breaks	Rat lung epithelial cells	*in vitro*	Positive	Li et al., 2007 [PMID:17239409]; Schins et al., 2002a [PMID: 12034310]
Strand breaks	Chinese hamster V79 lung cells	*in vitro*	Positive	IPCS (2000)
DNA binding	Isolated DNA	*in vitro*	Positive	IPCS (2000)
DNA binding	Calf thymus DNA	*in vitro*	Positive	IPCS (2000)
Micronucleus				
MN	Wistar rat, male - alveolar macrophage	not given	Positive	IPCS (2000)
MN	Human Hel 299 embryonic lung	*in vitro*	Positive	IPCS (2000)
MN	SHE cells and V79 cells	*in vitro*	Positive	IPCS (2000)
MN	Chinese hamster ovary cells	*in vitro*	Positive	Hart and Hesterberg, 1998 [PMID:9467118]
MN	Albino mice	not given	Negative	IPCS (2000)
MN	SHE cells	*in vitro*	Negative	IPCS (2000)
Gene Mutations				
hprt gene	Rat alveolar epithelial cells	not given	Positive	IARC, 1997; IPCS (2000)
p53 gene	Wistar rat, female	i.t. installation	Positive - lung tissue	Seiler et al., 2004 [PMID:15031954]
p53 gene	Rat	i.t. installation	Negative - lung tissue	Ishihara et al., 2002 [PMID:11825659]
hprt gene	Rat RLE-6TN alveolar epithelium	*in vitro*	Negative	IPCS (2000)

Endpoint	Test System	Exposure	Results	Reference
Sister Chromatid Exchange				
SCE	Chinese hamster V79 lung cells	*in vitro*	Negative	IPCS (2000)
SCE	Human lymphocytes	*in vitro*	Negative	IPCS (2000)
Chromosomal Aberrations				
CA	SHE cells and V79 cells	*in vitro*	Negative	IPCS (2000)
CA	Human Hel 299 embryonic lung	*in vitro*	Negative	IPCS (2000)
Cellular Transformation				
Neoplastic transform.	Human embryonic lung cells	*in vitro*	Positive	Shen et al., 2006 [PMID:16125882]
Neoplastic transform.	BALB/3T3/ mouse embryo cells	*in vitro*	Positive	IPCS (2000)
Neoplastic transform.	SHE cells	*in vitro*	Positive	IPCS (2000)
Neoplastic transform.	Fetal rat lung epithelial cells	*in vitro*	Weakly positive	IPCS (2000)
Other				
Aneuploidy	SHE cells and V79 cells	*in vitro*	Negative	IPCS (2000)
Metabolic cooperation	Chinese hamster V79 lung cells	*in vitro*	Negative	IPCS (2000)

In vitro studies reported that DE and quartz increased IL-12 production in human phagocytic cells (Stratta et al., 2001 [PMID:11327392]). Additional studies showed that DE was cytotoxic to a mouse monocyte-macrophage tumor cell line. When compared to crystalline silica, DE was classified as having "intermediate toxicity" (Fenoglio et al., 2000).

Intranasal administration of crystalline silica to New Zealand mixed mice resulted in systemic autoimmune disease (e.g., Brown et al., 2003). Concentrations of immunoglobulin G1 in the bronchoalveolar lavage fluid decreased and TNFα increased. The numbers of B1a B and CD4+ T cells found in the superficial cervical lymph nodes were greater in silica-treated mice (Brown et al., 2004 [PMID:15204774]). Instillation (i.t.) of DQ12 in rats enhanced TNF-α and IL-1 production in phagocytes present in broncheoalveolar lavage samples collected after LPS stimulation (Huaux et al., 1995 [PMID:7747285]). *In vivo* exposure to Min-U-Sil 5 by transoral instillation induced an acute inflammatory response in wild-type mice but not in mice lacking the IL-1 receptor (Hornung et al., 2008 [PMID:18604214]). Silica has an adjuvant effect on production of antibodies to T-dependent antigens (Mancino et al., 1984 [PMID:6319293]; Parks et al., 1999). In female BALB/cf mice, subcutaneous injection of silica particles with the antigen 2,4,6-trinitrophenyl coupled to ovalbumin stimulated a T-helper-1-cell response (van Zijverden et al., 2000 [PMID:11032768]).

9.8 Other Data

Effects on Protein and Enzyme Expression and Activity

For roles of enzymes in proposed mechanisms of action, see Modes of Action below.

A silica solution corresponding to 10 μg/cm^3 damaged rat liver mitochondrial enzymes *in vitro* (JECFA, 1974). Incubation of bovine alveolar macrophages with DQ12 quartz resulted in loss of cathepsin B activity, dependent on phagosome-lysosome fusion (Patzold et al., 1993 [PMID:8277518]). Cytochrome P450 1A1 (CYP1A1) was induced by short-term *in vitro* exposure of epithelial type II cells to DQ12 quartz, but significant upregulation of CYP1A1 was not observed in female Wistar rats exposed *in vivo* by i.t. instillation until 180 days after exposure (Becker et al., 2006 [PMID:16547697]).

Cristobalite minimally decreased endothelin-1 mRNA in human lung epithelial cells A549 but did not affect edothelin A receptor gene expression. Additionally, endothelin-1 expression was negatively correlated to 3-nitrotyrosine levels (which correlated with nitric oxide formation) (Chauhan et al., 2003 abstr.).

Effects on Kidneys

Silica can produce adverse kidney effects in different species (e.g., laboratory rodents and dogs) (Cha et al., 1999 [PMID:10441901]). Evidence of tubulointerstitial nephritis was observed in male guinea pigs that were exposed to silicon-containing compounds (magnesium trisilicate BP, crushed quartz, and crushed Arran granite) via drinking water (250 mg/L) for four months. Guinea pigs that received granite did not form kidney lesions. Animals given magnesium trisilicate exhibited the most severe lesions while those observed in quartz-dosed animals were less severe (Dobbie and Smith, 1982 [PMID:6278583]). Kidney effects were not seen after inhalation exposure to DQ12 quartz for up to 12 months (Rosenbruch et al., 1990 [PMID:2161666]). [Note: Information was obtained from abstract; article is in German.]

Brown and colleagues (2003, 2005) showed that intranasal exposure to crystalline silica exacerbated development of glomerulonephritis in male and female autoimmune-prone New Zealand mixed mice.

Modes of Action

A number of contributory mechanisms of cellular damage by quartz particles have been described in the literature; however, these mechanism(s) are not completely understood. It is thought that the biological response to quartz particles depends primarily on the surface of the particle. It has been suggested that close contact between quartz and carbon or metals could modify the nature of the surface sites, thereby affecting the biological response. It has also been proposed that strong adsorption of HDL to quartz particles may play a role in the induction of fibrosis (Bogatu and Contag, 2005 [PMID:16320625]). Different mechanisms also may be operating *in vivo* compared to *in vitro*. Likewise, mechanisms responsible for cytotoxic may differ from those that cause inflammatory responses, genetic effects, and/or carcinogenicity. Species- or organ-specific mechanisms also may be a factor (e.g., Williams and Knapton, 1996 [PMID:8621163]).

Several different mechanisms have been proposed for the development of silicosis. Recent studies suggested that the inflammatory response to quartz particles is triggered by lysosomal damage following phagocytosis. Leakage of lysosomal contents results in activation of the NALP3 inflammosome and induction of inflammatory mechanisms, leading to silicosis and associated diseases (Hornung et al., 2008 [PMID:18604214]). Additional proposed mechanisms of cellular damage and silicosis have included (1) direct cytotoxicity, (2) induction of apoptosis and subsequent phagocytosis by macrophages to regulate the evolution of inflammation and fibrosis, (3) stimulation of alveolar macrophages resulting in the release of cytotoxic enzymes or oxidants or inflammatory factors that recruit polymorphonuclear leukocytes that can release cytotoxins, and (4) stimulation of alveolar macrophages to release factors that initiate fibroblast production and collagen synthesis (Castranova and Vallyathan, 2000). Oxidant formation induced by DQ12 also was observed in human bronchial epithelial cells (Deshpande et al., 2002).

The adjuvant effect of silica has been proposed as a mechanism for silica-related autoimmune diseases (Parks et al., 1999). In relation to cytotoxicity *in vitro*, a possible relationship between grinding of silica (which generates Si and SiO radicals and hydroxyl radicals when in aqueous solution) and lipid peroxidation has been reported (Castranova and Vallyathan, 2000).

An inflammation-based mechanism for carcinogenicity of quartz has been hypothesized. Another mechanism thought to be involved in lung tumorogenesis related to crystalline silica exposure is activation of host defenses such as clearance mechanisms and anti-oxidant defenses. Oxidants generated from quartz surface and direct genotoxic effects also have been described as potential mechanisms involved in carcinogenicity (IARC, 1997). Ding and colleagues (2006) proposed that generation of ROS results in PKC-dependent activation of AP-1 and transcription factors via MAPK pathways, leading to cell proliferation, genetic changes, and neoplastic transformation. It also has been suggested that quartz may act as a co-carcinogen through its ability to induce CYP1A1 expression (Becker et al., 2006 [PMID:16547697]).

Additional studies *in vitro* noting potential mechanisms of silica toxicity are listed here:

- *In vitro* studies in NR8383 rat alveolar macrophages have shown that phagocytosis of DQ12 quartz particles is an actin-dependent process specifically involving the Fcγ receptor (Haberzettl et al., 2007 [PMID:17375287], 2008 [PMID:18390832]).
- Studies with RAW 264.7 mouse macrophages *in vitro* have demonstrated that contact of quartz with the plasma membrane, in the absence of phagocytosis, induces membrane lipid peroxidation, TNF-α release, and cell death. It has been suggested that this mechanism acts synergistically with ROS production after phagocytosis to activate the macrophage response (Scarfi et al., 2009).
- An oxidative mechanism was suggested for the hemolytic activity of silica particles. Using bovine erythrocytes, the mechanism of Min-U-Sil-induced hemolysis was shown to involve hydrogen peroxide as the active intermediate. Hemolysis was decreased by the addition of catalase (Razzaboni and Bolsaitis, 1990). An earlier study had reported that chemical interactions between silicate dusts and plasma membranes of erythrocytes were involved in hemolysis (Singh et al., 1983).

10.0 Structure-Activity Relationships

Amorphous silica has been studied considerably more than crystalline silica and is generally less toxic. It is more soluble in water and therefore cleared more rapidly from the body. In inhalation studies, it induced inflammation, fibrosis, and silicosis, but the effects were much less severe than those reported for crystalline silica. The IARC considered the data to be inadequate for determining the carcinogenicity of amorphous silica (IARC, 1997). In a study comparing the effects of DE and crystalline silica in SHE cells *in vitro*, DE had less ability to generate hydroxyl radicals. DE reduced cell proliferation and colony-forming efficiency but did not induce neoplastic transformation (Elias et al., 2006).

11.0 Online Databases and Secondary References Searched

11.1 Online Databases

National Library of Medicine Databases

PubMed

ChemIDplus – chemical information database that provides links to other databases such as CCRIS, DART, GENE-TOX, HSDB, IRIS, and TRI. A full list of databases and resources searched are available at http://www.nlm.nih.gov/databases/.

STN International Files

AGRICOLA	IPA
BIOSIS	MEDLINE
CABA	PASCAL
EMBASE	Registry
FROSTI	TOXCENTER
FSTA	

Information on the content, sources, file data, and producer of each of the searched STN International Files is available at http://www.cas.org/support/stngen/dbss/index.html.

Government Printing Office

Code of Federal Regulations (CFR)

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Appendix A: Units and Abbreviations

ºC = degrees Celsius
μg/cm^3 = microgram(s) per cubic centimeter
μg/kg = microgram(s) per kilogram
μg/L = microgram(s) per liter
μg/m^3 = microgram(s) per cubic meter
μg/mL = microgram(s) per milliliter
μm = micrometer(s)
ALT = alanine aminotransferase
AP-1 = activator protein-1
BALF = bronchoalveolar lavage fluid
BaP = benzo[*a*]pyrene
Chd = commercially available DE product
Chd-F = commercially available DE product's finer fraction
DE = diatomaceous earth
EC = European Community
EEC = European Economic Community [*now part of the EC; existed between 1958 and 1993*]
EPA = Environmental Protection Agency
FDA = U.S. Food and Drug Administration
g = gram(s)
g/kg = gram(s) per kilogram
GALT = gut-associated lymphoid tissue
HDL = high-density lipoprotein
IARC = International Agency for Research on Cancer
IL = interleukin
i.p. = intraperitoneal(ly)
IPCS = International Programme on Chemical Safety
i.t. = intracheal(ly)
IUR = Inventory Update Reporting
i.v. = intravenous(ly)
K = kelvin
lb = pound(s)
LPS = lipopolysaccharide
MAPK = mitogen-activated protein kinase
mg/kg = milligram(s) per kilogram
mg/m^3 = milligram(s) per cubic meter
mL/kg = milliliter(s) per kilogram
mm = millimeter(s)
mol. wt. = molecular weight
NIOSH = National Institute for Occupational Safety and Health
nm = nanometer(s)
OSHA = Occupational Safety and Health Administration
PEL = permissible exposure limit
pg/mL = picogram(s) per milliliter
PKC = protein kinase C

PMID = PubMed identification
ppm = parts per million
PVNO = polyvinylpyridine-*N*-oxide
REL = recommended exposure limit
ROS = reactive oxygen species
SCE = sister chromatid exchange
SHE = Syrian hamster embryo
SLE = systemic lupus erythemotosus
SMR = standardized mortality ratio
TLV = threshold limit value
TNF-α = tumor necrosis factor-alpha
TWA = time-weighted average

Appendix B: Description of Search Strategy and Results

Update on Silica Flour – March and April 2009

STN International database files MEDLINE, CABA, AGRICOLA, BIOSIS, IPA, TOXCENTER, PASCAL, FSTA, FROSTI, and EMBASE were searched simultaneously on March 27, 2009. The emphasis was on oral and dermal routes of exposure for silica flours (which by definition are crystalline silicas) with publication dates limited to the period 2005-2009 and on nanoparticulate crystalline silica with no limitations as to route or time period. The approximate numbers of record titles examined per database and the records that were selected for printing in full were as follows:

Database	Record Titles Examined	Records Selected
MEDLINE	67	23
CABA	7	-
AGRICOLA	14	1
BIOSIS	18	1
IPA	1	-
TOXCENTER	47	4
PASCAL	164	8
FSTA	2	-
FROSTI	3	-
EMBASE	12	-
Total	**335**	**37**

With so few pertinent results resulting from the fee-based search, subsequent Internet searches (Google Scholar and PubMed) looked for experimental studies that used Min-U-Sil 5, DQ12 (DQ-12), or Standard Reference Material (SRM) 1878 or SRM 1878a. In addition, ultrafine and many words containing nano were tried in combinations with silica, silicon oxide, silicon dioxide, and quartz. When several toxicity studies were noted that used amorphous nanosilica while looking for crystalline nanosilica studies, the scope was broadened to include their results. The terminologies for the amorphous nanosilicas are very broad, and it is unlikely that our search results on physiological/toxicity studies are comprehensive. Internet searches identified producers of amorphous nanosilica and additional producers/suppliers of silica flour, but did not identify any commercial products containing crystalline nanosilica. Synthetic crystalline silica nanoparticles were used in an animal study. One U.S. producer may supply silicon oxide nanocrystals for research purposes (American Elements).

The history of the STN International online session is reproduced below:

```
L1          250 S (SILICA OR QUARTZ OR CRISTABOLITE OR CRISTOBOLITE OR TRIDYMITE(W)FLOUR?
L2           71 S (MICRONIZED)(W)(SILICA OR QUARTZ OR CRISTABOLITE OR CRISTOBOLITE OR
                TRIDYMITE)
L3          156 S ULTRAFINE(W)(SILICA OR QUARTZ OR CRISTABOLITE OR CRISTOBOLITE OR
                TRIDYMITE)
L4          477 S L1-L3
L5            0 S SILICON(W)DIOXIDE(W)FLOUR?
L6           33 S SIO2(W)FLOUR?
L7          508 S L4 OR L6
L8           60 S L2 NOT SILICA(W)GEL
L9          497 S L1 OR L3 OR L6 OR L8
L10         807 S L9 OR MIN(W)U(W)SIL
L11           3 S L10 AND DRINKING(W)WATER
L12           6 S L10 AND ORAL?
L13           4 S L10 AND FOOD?
L14           0 S L10 AND GAVAGE?
L15           4 S L10 AND SKIN
L16           0 S L10 AND (DERMAL? OR CUTANEOUS? OR DERMABRASION OR MICRODERMASION)
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L17           0 S MICRONIZED(W)ROSE(W)QUARTZ
L18           0 S L10 AND GASTROINTESTINAL?
L19           0 S L10 AND BIOAVAILAB?
L20           5 S L10 AND INGEST?
L21         869 S L10 OR MICROCRYSTALLINE(W)(SILICA OR QUARTZ OR CRISTABOLITE OR
                  CRISTOBOLITE OR TRIDYMITE)
L22          14 S L21 AND (DRINKING OR ORAL? OR BEVERAGE? OR FOOD? OR GAVAGE? OR SKIN OR
                  DERMAL? OR CUTANEOUS? OR DERMABRASION OR MICRODERMABRASION)
L23           0 S MICROCRYSTALLINE(W)ROSE(W)QUARTZ
                  SET DUPORDER FILE
L24          11 DUP REM L22 (3 DUPLICATES REMOVED)
L25          11 SORT L24 1-11 TI
L26         153 S L21 AND (2005-2009)/PY
L27          14 S L26 AND (INHAL? OR INTRATRACHEAL?)
L28          38 S L26 AND (LUNG? OR PULMONARY)
L29          42 S L27 OR L28
                  SAVE L29 X300NULUNG/A
L30           0 S L26 AND (NONLUNG OR NON(W)LUNG)
                  DELETE X300NULUNG/A
L31          15 DUP REM L29 (27 DUPLICATES REMOVED)
L32          15 SORT L31 1-15 TI
L33         111 S L26 NOT L29
L34          14 S L33 AND (?TOXIC? OR GENOTOXIC? OR IMMUN?)
L35           4 DUP REM L34 (10 DUPLICATES REMOVED)
L36          97 S L33 NOT L34
L37          59 DUP REM L36 (38 DUPLICATES REMOVED)
L38          59 SORT L37 1-59 TI
                  SAVE L37 X300NUMISC/A
L39          41 S "CRYSTALLINE SILICA" AND NANO?
L40        3285 S (QUARTZ OR CRISTOBOLITE OR CRISTABOLITE OR TRIDYMITE) AND NANO?
L41         641 S (QUARTZ OR CRISTOBOLITE OR CRISTABOLITE OR TRIDYMITE)(6A)NANO?
L42          38 S (QUARTZ OR CRISTOBOLITE OR CRISTABOLITE OR TRIDYMITE)(W)NANO?
L43          16 S NANOCRYSTALLINE(W)SILICA OR SILICA(W)NANOCRYSTAL?
L44         381 S SILICA(W)NANO? AND CRYSTAL?
L45         178 S SILICA(6A)NANO?(6A)CRYSTAL?
L46          87 S SILICA(3A)NANO?(3A)CRYSTAL?
L47         256 S NANOSILICA?
L48         426 S L39 OR L42 OR L43 OR L46 OR L47
L49          43 S L48 AND (?TOXIC? OR CYTOTOXIC? OR GENOTOXIC?)
L50          33 S L48 AND (INHAL? OR INTRATRACHEAL? OR PULMONARY OR LUNG?)
L51          27 S L48 AND VITRO
L52          39 S L48 AND (HUMAN OR RATS OR MICE OR HAMSTER? OR RABBIT? OR GUINEA(W)PIG?)
L53          58 S L49 OR L50 OR L51 OR L52
L54          29 DUP REM L53 (29 DUPLICATES REMOVED)
L55          29 SORT L54 1-29 TI
L56         368 S L48 NOT L53
L57         281 DUP REM L56 (87 DUPLICATES REMOVED)
L58           2 S L57 AND IMMUN?
L59         208 S L57 NOT (AMORPHOUS OR FUME? OR GEL OR PRECIPITATED)
L60           0 S L59 AND COSMETIC?
L61           1 S L59 AND (SKIN OR SCRUB OR CLEANS?)
L62         208 DUP REM L59 (0 DUPLICATES REMOVED)
L63         208 SORT L62 1-208 TI
                  SAVE L63 NANOSIO2MISC/A
L64           9 S L48 AND REVIEW/DT
L65           5 DUP REM L64 (4 DUPLICATES REMOVED)
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Searches for Silica Renal Toxicity and Diatomite – September 2009

PubMed was searched on September 9, 2009, for kidney effects. The emphasis was on oral and dermal routes of exposure for silica. The search term "silicon dioxide" was used to search the National Library of Medicine's MeSH headings. The subheadings of "adverse effects," "poisoning," "toxicity," and "urine" were selected. PubMed entries were then searched for those with the selected specifications. The MeSH heading search was then combined with the terms "renal," "kidney," and "neph*" to search for effects associated with kidneys. A total of 159 entries were obtained and 58 entries were selected for further review based on titles.

PubMed and the Internet in general were searched intermittently between September 9 and 17, 2009, to find appropriate calcined diatomite and cristobalite reference sources for the nontoxicological sections of the report. The earlier searches were preliminary to formulating the search strategy for the entries on calcined diatomite and cristobalite in the toxicological portions of the report.

STN International databases MEDLINE, AGRICOLA, CABA, IPA, BIOSIS, TOXCENTER, FSTA, FROSTI, EMBASE, ESBIOBASE, and BIOTECHNO were searched simultaneously on September 10, 2009, with an attempt to focus on human and animal studies. Approximately 250 full records were selected for retrieval from the 1291 search results. Studies that were not selected included those on analytical methods, insecticidal and other common uses, and use in composites. MEDLINE with 123 records and TOXLINE with 70 records dominated the selections. BIOSIS selections comprised a distant third at 29 records. While subject-coding the results, the searcher coded 48 records to be eliminated from further consideration (e.g., review articles in foreign languages or reviews that were too old to be helpful). The history of the online session with database tallies is reproduced below:

```
                ACTIVATE X300DENAMES/Q
               ---------
L1              QUE  DIATOMITE OR KIESELGUHR OR KIESELGUR
L2              QUE  68855-54-9 OR 61790-53-2 OR 91053-39-3
L3              QUE  (DIATOMACEOUS OR INFUSORIAL)(W)(EARTH? OR SILICA)
L4              QUE  (L1 OR L2 OR L3)
               ---------
L5         11547 S L4
L6           533 S L5 AND (CRYSTALLINE OR CALCIN?)
L7           405 S L5 AND (LUNG OR LUNGS OR PNEUMOCONIOSIS OR INHAL? OR WORKER?)
L8           328 S L5 AND (EPIDEMIOL? OR OCCUPATION? OR SILICOSIS OR SILICOTIC?)
L9           969 S L5 AND (CANCER? OR COHORT? OR MORTALITY OR EXPOSURE?)
L10          177 S L5 AND CRISTOBALITE
L11          660 S L5 AND (CANCER? OR COHORT? OR MORTALITY)
L12         1389 S L6-L8 OR L10 OR L11
L13        10158 S L5 NOT L12
L14          312 S L13 AND (RATS OR RAT OR MICE OR MOUSE OR HAMSTER? OR GUINEA(W)PIG?)
L15          753 S L13 AND (RABBIT? OR DOGS OR HUMAN? OR MAN OR MEN OR PATIENT?)
L16         1019 S L14 OR L15
L17          470 S L16 NOT (METHOD? OR ABSORBENT? OR FILTER? OR FILTRATION?)
L18            6 S CRISTABOLITE
L19            1 S CRISTOBOLITE
L20         1519 S CRISTOBALITE
L21         1526 S L18-L20
L22          474 S L21 AND (EPIDEMIOL? OR WORKER? OR OCCUPATION? OR HUMAN? OR MEN OR
                 WOMEN)
L23          347 S L21 AND (RATS OR RAT OR MICE OR MOUSE OR HAMSTER? OR GUINEA(W)PIG?)
L24          360 S L21 AND (RABBIT? OR DOGS OR HUMAN? OR MAN OR MEN)
L25          762 S L22-L24
L26         1859 S L12 OR L17
L27          452 S L25 AND (INHAL? OR LUNG OR LUNGS OR PNEUMO?)
L28          121 S L25 AND (CYTOTOX? OR CLEARANCE OR GASTRIC OR GASTROINTESTINAL)
L29          128 S L25 AND (STOMACH OR LIVER OR SPEEN OR LYMPH?)
L30          145 S L25 AND (CANCER? OR UROLITHIASIS OR CALCULI OR SARCOIDOSIS)
L31          533 S L27-L30
L32         2273 S L26 OR L31
                 SET DUPORDER FILE
L33         1291 DUP REM L32 (982 DUPLICATES REMOVED)
             271 ANSWERS '1-271' FROM FILE MEDLINE
              80 ANSWERS '272-351' FROM FILE AGRICOLA
             114 ANSWERS '352-464' FROM FILE CABA
               4 ANSWERS '465-468' FROM FILE IPA
             209 ANSWERS '469-677' FROM FILE BIOSIS
             480 ANSWERS '678-1157' FROM FILE TOXCENTER
              33 ANSWERS '1158-1190' FROM FILE FSTA
               7 ANSWERS '1191-1197' FROM FILE FROSTI
              87 ANSWERS '1198-1284' FROM FILE EMBASE
               7 ANSWERS '1285-1291' FROM FILE ESBIOBASE
L34         1291 SORT L33 1-1291 TI
                 SAVE L34 X300DETI2/A
```