Chemical Information Review Document

for

Synthetic and Naturally Mined Gypsum

(Calcium Sulfate Dihydrate) [CAS No. 13397-24-5]

Supporting Nomination for Toxicological Evaluation by the National Toxicology Program

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Abstract

Gypsum is the dihydrate form of calcium sulfate. The word "gypsum," however, is used to describe different phases of the same material, including anhydrite (calcium sulfate, with no water of crystallization), selenite, calcined gypsum, and plaster of Paris. It forms as evaporites from marine waters and is usually found collectively with other mineral deposits such as quartz, sulfur, and clays. Gypsum is also found in lakes, seawater, and hot springs as deposits from volcanic vapors. It is primarily used to manufacture wallboard and plaster for homes, offices, and commercial buildings; it is the most common natural fibrous mineral found indoors. Other applications of gypsum are as a soil additive, as a food and paint filler, and a component of blackboard chalk, medicines, and toothpaste. Humans may therefore be exposed to gypsum via inhalation, ingestion, skin contact, and eye contact. There is concern over the exposure of individuals to gypsum dust in the workplace and home, and this concern has increased in the aftermath of the World Trade Center (WTC) collapse in September 2001. Patients being examined in clinics include office workers, emergency response workers, constructions workers, and public members exposed to dust from the destruction. Analysis of general area and personal breathing zone air samples show that nonasbestos fibers consist mostly of gypsum, fibrous glass, and cellulose. In air and dusts collected from building materials dispersed from the WTC collapse three months later, gypsum was the most common mineral found in outdoor air samples from lower Manhattan. The majority of studies of gypsum workers, however, have reported no lung fibrosis or pneumoconiosis, except when gypsum was contaminated with silica. Gypsum is very soluble in the body. Aerosols of calcium sulfate fibers were quickly cleared from the lungs of rats and guinea pigs via dissolution. Nonpathological findings of subchronic inhalation studies in rats were dependent on the shape of the gypsum fibers. In a chronic inhalation study, calcined gypsum dust produced only minor effects in the lungs of guinea pigs. In carcinogenicity studies, gypsum was weakly tumorigenic. Gypsum induced abdominal cavity tumors in 5% of rats after intraperitoneal injection, carcinomas of the heart and kidney in hamsters after intratracheal administration, and no lung tumors in guinea pigs following inhalation exposure. None of the long-term studies can be considered adequate tests of chronic toxicity or carcinogenicity by modern standards.

Executive Summary

Basis for Nomination

Gypsum (the naturally mined and synthetic form) was nominated by the Mount Sinai-Irving J. Selikoff Center for Occupational and Environmental Medicine and the Operative Plasterers' and Cement Masons' International Association of the United States and Canada for toxicological studies based on widespread human exposure and a lack of well-conducted epidemiology or toxicology studies relevant to assessing the potential for adverse long-term health effects from exposure to gypsum dust. Gypsum is widely used in building materials and human exposure occurs when gypsum is mined, when gypsum is used for manufacturing building materials, when building material is disturbed, especially with power tools for maintenance or renovation, and when buildings are demolished. The nominators state: "Many patients seen in our [New York City] clinic are exposed to gypsum dust in their workplace or in their homes. These patients often have other exposures (asbestos, welding fumes) that make it impossible to attribute any health problems to gypsum by itself. Certain trades are continuously exposed (plasterers, laborers, steamfitters, plumbers, electricians) and have come to us with concern about their exposures. These patients often have other exposures (asbestos, welding fumes) that make it impossible to attribute any health problems to gypsum, by itself. Many office workers, emergency response workers and construction workers and the public were exposed to large amounts of gypsum (as well as other, more toxic substances) in the dust from the burning and collapse of the World Trade Centers [in September 2001]. We see many of these individuals in our clinic, as well."

Nontoxicological Data

<u>Chemical Identification, Physical Properties, and Analysis</u>

The word "gypsum" is used to describe different phases of the same material, including anhydrite (calcium sulfate, with no water of crystallization), selenite, calcined gypsum, and plaster of Paris. According to the National Institute for Occupational Safety and Health (NIOSH) Pocket Guide to Chemical Hazards, gypsum is the dihydrate form of calcium sulfate. It is a naturally occurring mineral consisting of 79% calcium sulfate and 21% water. Gypsum can be identified and analyzed in dust samples by scanning electron microscopy.

<u>Production and Uses</u>

The United States is the main producer of gypsum; it accounted for ~16.4% of the reported global output in 2003. Commercial quantities of gypsum are available from New York, Michigan, Iowa, Kansas, Arizona, New Mexico, Colorado, Utah, and California. In 2004, the estimated U.S. production of crude gypsum was 18.0 million tons. Synthetic gypsum is mainly produced as a byproduct in flue gas desulfurization (FGD) systems. Calcined gypsum is produced domestically from crude gypsum by heating selenite. In the United States, gypsum is primarily used to manufacture wallboard and plaster for homes, offices, and commercial buildings. Other applications of gypsum are as a soil additive, as a food and paint filler, and a component of blackboard chalk, medicines, dental modes, and toothpaste.

<u>Environmental Occurrence and Persistence</u>

Naturally Occurring Gypsum

Gypsum is formed as evaporites from marine waters. It occurs in various forms in nature—gypsite (an impure form in the earth), selenite (flattened and twinned crystals and transparent cleavable masses), alabaster (a translucent and fine grain), and satin spar (a silky and fibrous transparent crystal form)—and in various purities. It is usually found collectively with other mineral deposits such as quartz, halite, sulfur, pyrites, carbonates, and clays. Gypsum is also found in lakes, seawater, and hot springs as deposits from volcanic vapors and sulfate solutions in veins. In the United States, gypsum sources are centered near California, the Great Lakes, and the Texas-Oklahoma area.

Gypsum in Air and Dusts from the World Trade Center (WTC) Collapse
At the WTC disaster site, assessment of general area and personal breathing zone air samples showed that most exposures, including asbestos, did not exceed the NIOSH recommended exposure limits (RELs) or Occupational Safety and Health Administration (OSHA) permissible exposure levels (PELs) [see below]. In samples with concentrations $\geq$0.1 fibers/cm^3 of air, most nonasbestos fibers were found to be gypsum, fibrous glass, and cellulose. Fallen samples collected one and two days after the attack from areas within 0.5 mile of Ground Zero contained particulate matter with <2.5 µm mass median aerodynamic diameter ($PM_{2.5}$) that consisted mostly of calcium-based compounds, including gypsum.

When air and dusts from building materials dispersed from the WTC collapse were collected from November 4 to December 11, 2001, in and around 30 residential buildings in lower Manhattan and from four residential buildings above 59th Street (approximately five miles northeast of the WTC site), gypsum was the most common mineral found in lower Manhattan outdoor air samples. Concentrations found in 40 of 114 respirable fraction PM_4 were estimated at 3 to 14 µg/m^3. Above 59th Street, gypsum concentrations in air were $\leq$5 µg/m^3. Gypsum concentrations in outdoor settled dusts in lower Manhattan were about 0.03 to 27%. In the residential building common areas, gypsum concentrations in settled dusts ranged from about 0.07 to 20%, while in 45 of 57 residences in these buildings, levels ranged from about 0.05 to 30%.

Gypsum in Indoor Environments
Gypsum is stated to be the most common natural fibrous mineral found indoors (20:1 gypsum fibers to asbestos) mainly because of its use in plaster in buildings. In a German study of fibrous dusts from installed mineral wool products in living rooms and workrooms, 134 measurements revealed an average air pollution of 3184 gypsum fibers/m^3.

Human Exposure
Humans may be exposed to gypsum via inhalation, ingestion, skin contact, and/or eye contact. According to the NIOSH National Occupational Exposure Survey (NOES), conducted between 1981 and 1983, an estimated 7,865 workers (1,279 females) were potentially exposed to gypsum dust in eight industries. In a postmortem analysis of subjects in Rome, Italy, with no occupational exposure to mineral dusts, fibrous particles (generally asbestos fibers and small amounts of talc, rutile [aluminum oxide], and calcium sulfate [7778-18-9]) were detected in lung tissue in 16% of subjects. Mineral particle concentrations ranged from 0.7×10^5 to 1.7×10^5 particles/mg, indicating significant accumulations of mineral particles in lungs of persons living in urban areas. In a study of personal exposure to respirable inorganic and organic fibers geometric mean concentrations ranging from 600 to 4700 fibers/m^3 of gypsum fibers were found in European taxi drivers, office workers, retired persons, and schoolchildren.

Regulatory Status
The NIOSH REL for gypsum is 10 mg/m^3 (total dust—air) and 5 mg/m^3 (respirable fraction—air) as a ten-hour time-weighted average (TWA). The OSHA PELs are 15 and 5 mg/m^3 as an eight-hour TWA, respectively. The American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV) for gypsum (as total dust containing no asbestos and <1% crystalline silica) is 10 mg/m^3 as TWA. In 1992, the Environmental Protection Agency (EPA) established that phosphogypsum (byproduct from a manufacturing process such as for phosphoric acid) must not have a certified average ^{226}Ra concentration >370 becquerel/kg (Bq/kg), restricting its use in most applications.

Toxicological Data
Data from reproductive or developmental toxicity, initiation/promotion, anticarcinogenicity, genotoxicity, or immunotoxicity studies were not available for gypsum dust or fibers.

Human Data

Gypsum is a skin, eye, mucous membrane, and respiratory system irritant. Early studies of gypsum miners did not relate pneumoconiosis with chronic exposure to gypsum. Other studies in humans (as well as animals) showed no lung fibrosis produced by natural dusts of calcium sulfate except in the presence of silica. However, a series of studies reported chronic nonspecific respiratory diseases in gypsum industry workers in Gacki, Poland.

Absorption, Distribution, Metabolism, and Excretion

Unlike other fibers, gypsum is very soluble in the body; its half-life in the lungs has been estimated as minutes. In four healthy men receiving calcium supplementation with calcium sulfate ($CaSO_4 \cdot 1/2H_2O$) (200 or 220 mg) for 22 days, an average absorption of 28.3% was reported.

Health Effects from Occupational Exposures

In a study of 241 underground male workers employed in four gypsum mines in Nottinghamshire and Sussex for a year (November 1976-December 1977), results of chest X-rays, lung function tests, and respiratory systems suggested an association of the observed lung shadows with the higher quartz content in dust rather than to gypsum; the small round opacities in the lungs were characteristic of silica exposure. Prophylactic examinations of workers in a gypsum extraction and production plant (dust concentration exceeded TLV 2.5- to 10-fold) reported no risk of pneumoconiosis due to gypsum exposure, while another study of gypsum manufacturing plant workers reported that chronic occupational exposure to gypsum dust had resulted in pulmonary ventilatory defect of the restrictive form.

Three cases of idiopathic interstitial pneumonia with multiple bullae throughout the lungs were seen in Japanese schoolteachers (lifetime occupation) exposed to chalk; 2/3 of the chalk was made from gypsum and small amounts of silica and other minerals.

Skin Irritation

Coal miners using anhydrite (containing traces of calcium fluoride and hydrofluoric acid) have complained of skin irritation. In ten volunteers, five applications of anhydrite paste (100 mg) or hemihydrate paste (100 mg) to the forearm under occlusion for 24 hours produced mean blood flow values of 18.0 and 14.0%, respectively; controls had a value of 12.1%. The increased blood flow indicated increased irritancy; however, there was no clinical sign of irritation in any subject.

Chemical Disposition, Metabolism, and Toxicokinetics

In rats exposed to an aerosol of anhydrous calcium sulfate fibers (15 mg/m^3) or a combination of milled and fibrous calcium sulfate (60 mg/m^3) six hours per day, five days per week for three weeks, gypsum dust was quickly cleared from the lungs of via dissolution and mechanisms of particle clearance.

In guinea pigs given intraperitoneal (i.p.) injections of gypsum (doses not provided), gypsum was absorbed followed by the dissolution of gypsum in surrounding tissues. In another study, after i.p. injection of gypsum (2 cm^3 of a 5 or 10% suspension in saline) into guinea pigs, which were sacrificed at intervals up to 180 days, most of the dust was found distributed in the peritoneum of the anterior abdominal wall. Gypsum dust produced irregular and clustered nodules, which decreased in size over time.

Several feeding studies in pigs on the bioavailability of calcium in calcium supplements, including gypsum, have been conducted. The bioavailability of calcium in gypsum was similar to that for calcitic limestone, oyster shell flour, marble dust, and aragonite, ranging from 85 to 102%.

Acute Exposure

In mice, the i.p. and intragastric LD_{50} values were 6200 and 4704 mg/kg, respectively, for phosphogypsum (98% $CaSO_4 \cdot H_2O$). For plaster of Paris, the values were 4415 and 5824, respectively. In rats, an intragastric LD_{50} of 9934 mg/kg was reported for phosphogypsum.

Direct administration of WTC $PM_{2.5}$ [mostly composed of calcium-based compounds, including calcium sulfate (gypsum) and calcium carbonate (calcite)] (10, 32, or 100 µg) into the airways of mice produced mild to moderate lung inflammation and airway hyperresponsiveness at the high dose. [It was noted that WTC $PM_{2.5}$ is composed of many chemical species and that their interactions may be related with development of airway hyperresponsiveness.] In female SPF Wistar rats intratracheally (i.t.) instilled with anhydrite dust (35 mg) and sacrificed three months later, an increase in total lipid or hydroxyproline content in the lungs was not observed compared to controls.

Short-term and Subchronic Exposure

In inhalation (nose-only) experiments in which male F344 rats were exposed to calcium sulfate fiber aerosols (100 mg/m^3) for six hours per day, five days per week for three weeks, there were no effects on the number of macrophages per alveolus, bronchoalveolar lavage fluid (BALF) protein concentration, or BALF γ-glutamyl transpeptidase activity (γ-GT). Following three weeks of recovery, nonprotein thiol levels (NPSH), mainly glutathione, were increased in animals. In follow-up experiments, rats were exposed to an aerosol of anhydrous calcium sulfate fibers (15 mg/m^3) or a combination of milled and fibrous calcium sulfate (60 mg/m^3) for the same duration. Calcium levels in the lungs were similar to those of controls; however, gypsum fibers were detected in the lungs of treated animals. Significant increases in NSPH levels in BALF were observed in rats killed immediately after exposure at both doses and in recovery group animals at the higher dose. At 15 mg/m^3, almost all NPSH was lost in macrophages from all treated animals (including those in recovery), but a significant decrease in extracellular γ-GT activity was seen only in recovery group animals. Overall, the findings were "considered to be non-pathological local effects due to physical factors related to the shape of the gypsum fibers and not to calcium sulphate *per se*."

Intratracheal administration of man-made calcium sulfate fiber (2.0 mg) once per week for five weeks resulted in no deaths or significant body weight changes in female Syrian hamsters compared to controls. Inflammation (specifically, chronic alveolitis with macrophage and neutrophil aggregation) was observed in the lung.

Chronic Exposure

In guinea pigs, inhalation of calcined gypsum dust (1.6×10^4 particles/mL) for 44 hours per week in 5.5 days for two years, followed with or without a recovery period of up to 22 months, produced only minor effects in the lungs. There were 12 of 21 deaths over the entire experimental period. These were due to pneumonia or other pulmonary lesions; however, no significant gross signs of pulmonary disease or nodular or diffuse pneumoconiosis became significant. Beginning near 11 months, pigmentation and atelectasis were seen. During the recovery period, four of ten guinea pigs died; two died of pneumonia. Pigmentation continued in most animals but not atelectasis. Low-grade chronic inflammation, occurring in the first two months, also disappeared.

Synergistic/Antagonistic Effects

In rats, i.t. administration of anhydrite (5-35 mg) successively and simultaneously with quartz reduced the toxic effect of quartz in lung tissue. This protective effect on quartz toxicity was also seen in guinea pigs; calcined gypsum dust prevented or hindered the development of fibrosis. Natural anhydrite, however, increased the fibrogenic effect of cadmium sulfide in rats. Additionally, calcined gypsum dust had a stimulatory effect on experimental tuberculosis in guinea pigs.

Cytotoxicity
In Syrian hamster embryo cells, gypsum (up to 10 µg/cm^2) did not induce apoptosis. Negative results were also found in mouse peritoneal macrophages (tested at 150 µg/mL gypsum dust) and in Chinese hamster lung V79-4 cells (tested up to 100 µg/mL).

Carcinogenicity
In female Sprague-Dawley rats, i.p. injection of natural anhydrite dusts from German coal mines (doses not provided) induced granulomas; whether gypsum was the causal factor was not established. In Wistar rats, four i.p. injections of gypsum (25 mg each) induced abdominal cavity tumors, mostly sarcomatous mesothelioma, in 5% of animals; first tumor was seen at 546 days. In a subsequent experiment using the same procedure, female Wistar rats exhibited the first tumor at 579 days after the last injection. Mean survival of the tumor-bearing rats (5.7% of test group) was 583 days, while mean survival of the test group was 587 days. Tumor types seen were a sarcoma having cellular polymorphism, a carcinoma, and a reticulosarcoma.

Intratracheal administration of man-made calcium sulfate fiber (2.0 mg) once per week for five weeks produced tumors in three of 20 female Syrian hamsters observed two years later. An anaplastic carcinoma was found in the heart, and one dark cell carcinoma was seen in the kidney. Two tumors of unspecified types were observed in the rib.

In guinea pigs, inhalation of gypsum (doses not provided) for 24 months produced no lung tumors.

Other Data
In rats, i.t. administration of gypsum (doses not provided in abstract) from FGD for up to 18 months produced no arterial blood gas changes or indications of secondary heart damage as compared to controls. In another study, a single i.t. dose (25 mg) of flue gas gypsum dust did not produce a pathological reaction when observed for up to 18 months. There were also no signs of developing granuloma of fibrosis of the lungs. Lead quickly accumulated in the femur after injection but was eliminated during the observation period. In the Ames test, the flue gas gypsum dust was negative.

Recently implemented mercury emissions controls on coal-fired power plants have increased the likelihood of the presence of mercury in synthetic gypsum formed in wet FGD systems and the finished wallboard produced from the FGD gypsum. In a study at a commercial wallboard plant, the raw FGD gypsum, the product stucco (beta form of $CaSO_4 \cdot 1/2H_2O$), and the finished dry wallboard each contained about 1 µg Hg/g dry weight. Total mercury loss from the original FGD gypsum content was about 0.045 g Hg/ton dry gypsum processed.

Structure-Activity Relationships
Calcium sulfate (up to 2.5%) was negative in *Salmonella typhimurium* strains TA1535, TA1537, and TA1538 and in *Saccharomyces cerevisiae* strain D4 with and without metabolic activation. In pregnant mice, rats, and rabbits, daily oral administration of calcium sulfate (16-1600 mg/kg bw) beginning on gestation day 6 up to 18 produced no effects on maternal body weights, maternal or fetal survival, or nidation; developmental effects were also not seen.

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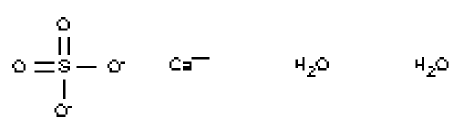
1.0 Basis for Nomination

Gypsum (the naturally mined and synthetic form) was nominated by the Mount Sinai-Irving J. Selikoff Center for Occupational and Environmental Medicine and the Operative Plasterers' and Cement Masons' International Association of the United States and Canada for toxicological studies based on widespread human exposure and a lack of well-conducted epidemiology or toxicology studies relevant to assessing the potential for adverse long-term health effects from exposure to gypsum dust. Gypsum is widely used in building materials and human exposure occurs when gypsum is mined, when gypsum is used for manufacturing building materials, when building material is disturbed, especially with power tools for maintenance or renovation, and when buildings are demolished. The nominators state: "Many patients seen in our [New York City] clinic are exposed to gypsum dust in their workplace or in their homes. These patients often have other exposures (asbestos, welding fumes) that make it impossible to attribute any health problems to gypsum by itself. Certain trades are continuously exposed (plasterers, laborers, steamfitters, plumbers, electricians) and have come to us with concern about their exposures. These patients often have other exposures (asbestos, welding fumes) that make it impossible to attribute any health problems to gypsum, by itself. Many office workers, emergency response workers and construction workers and the public were exposed to large amounts of gypsum (as well as other, more toxic substances) in the dust from the burning and collapse of the World Trade Centers [in September 2001]. We see many of these individuals in our clinic, as well."

2.0 Introduction

Gypsum
[13397-24-5]



ChemIDplus (2004) identifies gypsum as calcium sulfate (according to the database, also called plaster of Paris) and phosphogypsum. According to the National Institute for Occupational Safety and Health (NIOSH) Pocket Guide to Chemical Hazards, gypsum is the dihydrate form of calcium sulfate and plaster of Paris [CAS No. 26499-65-0] is the hemihydrate form (NIOSH, undated-c,d). This is the naming followed by the U.S. EPA ([SRS] undated), Registry (2005), and ChemFinder (2004). Phosphogypsum is given as a synonym for gypsum (RTECS, 2000). It usually designates the byproduct produced from a manufacturing process such as for phosphoric acid (Health Physics Society, 2001; Reed, 1975). Additionally, plaster of Paris is given a separate CAS Registry Number, 26499-65-0 (NIOSH, undated-c; RTECS, 1998; Registry, 2005).

The word "gypsum" is used to describe different phases of the same material, including anhydrite (calcium sulfate, with no water of crystallization), selenite, calcined gypsum, and plaster of Paris (Reed, 1975; Health Council of the Netherlands, Committee on Updating of Occupational Exposure Limits, 2002). This review presents data for gypsum dust and fibers; the terminology used in the original sources was employed. Information and study data relating to oral exposure to gypsum or anhydrous calcium sulfate (including dietary supplements) and the use of gypsum in bone implants is generally not included in this review.

2.1 Chemical Identification and Analysis

2.1.1 Gypsum [13397-24-5]

Gypsum (9CI) ($CaSO_4 \cdot 2H_2O$; mol. wt. = 174.19) is also called:

Calcium(II) sulfate dihydrate
CoCoat T
Crystacal R
Duracal Cement
G 6 (refractory)
G 16 (gypsum)
G 75 (mineral)
GIPS
Gypsite
Gypsum stone
Gypsum sulfate
Hydrated calcium sulfate
Hydrocal
Hydroperm
Landplaster
Mineral white
New Diastone
PE 20A
Phosphogypsum
Primoplast
SK (mineral)
Tiger Kencoat

Sources: ChemFinder (2004); NIOSH (undated-c); Registry (2005); RTECS (2000); U.S. EPA SRS (undated)

PubChem CID = 24948
InChI: 1/Ca.H2O4S.2H2O/c;1-5(2,3)4;;/h;(H2,1,2,3,4);2*1H2/q+2;;;/p-2/fCa.O4S.2H2O/qm;-2;;

2.1.2 Plaster of Paris [26499-65-0]

Plaster of Paris ($CaSO_4 \cdot 1/2H_2O$; mol. wt. = 145.2) is also called:

Calcium sulfate hemihydrate
Crystacal
Dried calcium sulfate
Densite
Densite (gypsum)
FGR
Gypsum hemihydrate
Hemihydrate gypsum
PH 200
Sakura Plaster of Paris B Grade
TA 20
Tiger Stone

Sources: NIOSH (undated-c); Registry (2005); RTECS (1998)

2.1.3 Calcium sulfate [7778-18-9]

Calcium sulfate ($CaSO_4$; mol. wt. = 136.14) is also called:

Anhydrite
Anhydrous calcium sulfate (1:1)
Anhydrous gypsum
Anhydrous sulfate of lime
Drierite
Gibs
Karstenite
Muriacite
Natural anhydrite
Sulfuric acid, calcium salt
Terra Alba
Thiolite

Sources: ChemFinder (2004); ChemIDplus (2004); Registry (2005)

2.1.4 Analytical Methods

Ambient nanometer-sized airborne particles, including sulfur-bearing particles, can be identified and analyzed by a new technique called energy-filtered transmission electron microscopy (EFTEM) (Chen et al., 2005). Gypsum was one of the minerals identified in bulk dust samples collected from Danish offices and analyzed by scanning electron microscopy (Molhave et al., 2000). The components of several crystals (silica, gypsum, brushite, etc.) in urinary stones were identified by polarization microscopy, infrared spectroscopy, X-ray diffraction, electron microscopy, and chemical analysis (Kim, 1982). Suspensions of total dust samples from Portland cement (PC) are quantitatively analyzed by measuring the intensities of X-ray fluorescence for Ca, Si, Fe, and Sr in samples deposited onto Ag membrane filters as well as the attenuation of X-rays from the fluorescing Ag membrane filter. The common crystalline solid phases in dust from PC bulk material and air samples are compared using X-ray diffraction for qualitative confirmation (OSHA, 1991).

2.2 Physical-Chemical Properties

Property	Information	Reference(s)
	Gypsum [13397-24-5]	
Physical State	white crystalline powder or lumps	IPCS (2004a)
Odor	odorless	NIOSH (undated-c)
Melting Point (°C)	100	Registry (2005)
Density (g/cm^3)	2.3	IPCS (2004a); Registry (2005)
Specific Gravity	2.32	NIOSH (undated-d)
Water Solubility	0.24 g/100 mL @ 25 °C	IPCS (2004a)
Vapor Pressure (mm Hg)	0	NIOSH (undated-d)
	Plaster of Paris [26499-65-0]	
Physical State	fine hygroscopic yellow or white powder	IPCS (2004b); NIOSH (undated-d)
Odor	odorless	NIOSH (undated-d)
Melting Point (°C)	163	IPCS (2004b); Registry (2005)
Density (g/cm^3)	2.76 (_ hemihydrate); 2.63 (_ hemihydrate)	IPCS (2004b)
Specific Gravity	2.5	NIOSH (undated-d)
Water Solubility	0.30 g/100 mL @ 25 °C	IPCS (2004b)
Vapor Pressure (mm Hg)	~0	NIOSH (undated-d)
	Calcium Sulfate [7778-18-9]	
Physical State	white hygroscopic powder or crystal	ChemFinder (2004)
Odor	odorless	ChemFinder (2004)
Melting Point (°C)	1450	Registry (2005) ChemFinder (2004)

Density (g/cm^3)	2.960	Registry (2005) ChemFinder (2004)
Water Solubility	slightly soluble	ChemFinder (2004)

Gypsum is a naturally occurring mineral consisting of 79% calcium sulfate and 21% water (Reed, 1975). The white color of pure gypsum changes to gray, brown, or pink as impurities are added. When heated, gypsum loses 75% of its water, becoming hemihydrate gypsum ($CaSO_4 \cdot 1/2H_2O$), which is easily grounded to a powder commonly called plaster of Paris. When mixed with water, forming a paste or slurry, it dries and sets as a very hard solid. Additionally, as the plaster-water mixture dries, water will chemically recombine with hemihydrate gypsum, and the material will revert back to the original composition of gypsum (Founie, 2003). Further heating to above ~180 °C will produce the anhydrous form, called anhydrous calcium sulfate or anhydrite (Wikipedia, 2005).

Phosphogypsum (byproduct of manufacturing processes) is relatively acidic, contains a small amount of fluoride, and is slightly radioactive. The radium content of phosphogypsum is 20 to 30 picoCuries ^{226}Ra per gram (pCi/g), whereas the radium content of natural gypsum and of most soils and rocks is 1 to 2 pCi/g or less (Florida State University, undated).

2.3 Commercial Availability

Commercial quantities of gypsum are available from New York, Michigan, Iowa, Kansas, Arizona, New Mexico, Colorado, Utah, and California in the United States and in England and Canada (Wikipedia, 2005). In 2003, crude gypsum was mined by 22 companies in the United States at 45 mines in 17 states. Companies that produced ~77% of the total U.S. crude gypsum were U.S. Gypsum Corporation (9 mines), National Gypsum Company (6 mines), Georgia-Pacific Corporation (6 mines), BPB America Inc. (5 mines), and American Gypsum Company (3 mines). Calcining plants that produced ~92% of the national calcined gypsum output were U.S. Gypsum (21 plants), National Gypsum (15 plants), Georgia-Pacific (14 plants), and BPB (6 plants) (Founie, 2003). Calcined gypsum is marketed as plaster or prefabricated products; the plaster is packed in 100-lb bags and sold under various trade names (Reed, 1975).

3.0 Production Processes

Gypsum is produced from deposits found worldwide and is consumed within the country in which it is mined. Synthetic gypsum is mainly produced as a byproduct in flue gas desulfurization (FGD) systems; smaller amounts originate from chemical processes such as acid neutralization processes, citric acid production, sugar production from sugar beets, and titanium dioxide production. Calcined gypsum is produced domestically from crude gypsum (Founie, 2003). It is produced by heating selenite at ~350 °F for one hour. Upon addition of water, plaster of Paris is formed, which then quickly sets and hardens as selenite again. Gypsum for use in cement is crushed to –1/2 inch; it is ground to about 100 mesh for agricultural or filler use (Reed, 1975).

Phosphogypsum is an industrial byproduct from the manufacture of fertilizer (Founie, 2003).

4.0 Production and Import Volumes

In 2003, the latest figures showed that the United States was the lead world producer of gypsum, accounting for ~16.4% of the reported global output (Founie, 2003). During the period between 2001 and 2003, U.S. production of crude gypsum remained fairly constant; values ranged from

15.7 to 16.7 million tons. This was a decrease from the production of 22.4 and 19.5 million tons in 1999 and 2000, respectively. However, estimates for 2004 show an increase with a value of 18.0 million tons. Manufacture of synthetic gypsum has steadily increased: in 1999, 5.2 million tons were produced, while in 2004, an estimated 11.0 million tons were produced. Also in 2004, an estimated 25.5 million tons of calcined gypsum were produced. Imports of crude gypsum [including anhydrite] steadily decreased (9.3 million tons in 1999 to 8.3 million tons in 2003); 10.4 million tons was estimated for 2004. U.S. exports, however, were low with only 130,000 metric tons sent abroad (Founie, 2005; Olson, 2004). Additionally, in 2003, 18 U.S. coal-fired electrical plants produced ~12.0 million tons of synthetic gypsum from FGD system (Founie, 2003).

Since the mid-1980s, the annual production rate of phosphogypsum has ranged from 40 to 47 million metric tons per year; 4.5 tons of phosphogypsum results from the production of a ton of phosphoric acid. As of 1989, the phosphoric acid industry consisted of 21 active facilities that used the wet-acid production process; the majority of these facilities are located in Florida (12), Louisiana (3), and North Carolina (1) (U.S. EPA, 2004).

5.0 Uses

In the United States, gypsum is primarily used to manufacture wallboard and plaster (construction material) for homes, offices, and commercial buildings (Founie, 2003). In 2003, ~90% of U.S. consumption was comprised of these products (Olson, 2004). Gypsum is added to cement to delay setting time. Worldwide, gypsum is used in portland cement, which is employed in concrete for bridges, buildings, highways, and many other structures. It is also used as a soil additive or conditioner for large areas of land in suburban and agricultural regions. High-purity gypsum is used in various industrial operations, including the production of foods, glass, paper, and pharmaceuticals (Founie, 2003). In foods (e.g., tofu and breads), it is a source of calcium; we consume 28 lb of gypsum in our lifetime (Snyder and Russel, undated). It is especially found in traditional (i.e., Chinese herbal) medicines (e.g., Yuan et al., 1999). Gypsum is also used in blackboard chalk, dental modes, surgical casts, paint filler, toothpaste, and molds for casting metals (Wikipedia, 2005).

Synthetic gypsum is used as a substitute for mined gypsum, principally for wallboard manufacturing, agricultural purposes, and cement production (Founie, 2003).

6.0 Environmental Occurrence and Persistence

Naturally Occurring Gypsum

Gypsum is formed as evaporites from marine waters; they are found as orderly stratigraphic beds with limestone and salt (Reed, 1975). Gypsum occurs in various forms in nature—gypsite (an impure form in the earth), selenite (flattened and twinned crystals and transparent cleavable masses), alabaster (a translucent and fine grain), and satin spar (a silky and fibrous transparent crystal form)—and in various purities. It is usually found collectively with other mineral deposits such as quartz, halite, sulfur, pyrites, carbonates, and clays. Gypsum is also found in lakes, seawater, hot springs, deposits from volcanic vapors, and sulfate solutions found in narrow channels in rock or earth (Oakes et al., 1982; Wikipedia, 2005). For example, in the interaction of lava from Hawaii's Kilauea volcano with sea water, which yields large clouds of mist known as LAZE, airborne fibers were detected in one of five LAZE plume (beach) samples at a concentration of 0.16 fibers/cm^3. These fibers were composed largely of hydrated calcium sulfate, similar in morphology to gypsum [exact identification could not be made in all cases] (Kullman et al., 1994).

At the base of the Guadalupe Mountains in Texas are white dunes of gypsum, formed from the evaporation of seas (Miller, 2005). These dunes of gypsum are also found in neighboring New Mexico; gypsum beds up to 100 feet thick were reported. In the United States, gypsum sources are centered near California, the Great Lakes, and the Texas-Oklahoma area, although gypsum beds are also found in other states such as Iowa and Utah, up to 200 feet thick (Reed, 1975).

<u>Gypsum in Air and Dusts from the World Trade Center (WTC) Collapse</u>

At the WTC disaster site, assessment of general area and personal breathing zone air samples showed that most exposures, including asbestos, did not exceed the NIOSH recommended exposure limits (RELs) or Occupational Safety and Health Administration (OSHA) permissible exposure levels (PELs) [see Section 8.0]. In samples (n=25) with concentrations ≥0.1 fibers/cm^3 of air, most nonasbestos fibers were found to be gypsum, fibrous glass, and cellulose (McKinney et al., 2002). Fallen samples collected one and two days after the attack from areas within 0.5 mile of Ground Zero contained particulate matter with <2.5 µm mass median aerodynamic diameter ($PM_{2.5}$) that were alkaline and mostly of calcium-based compounds, including calcium sulfate (gypsum) and calcium carbonate (calcite), arising from crushed building materials such as cement and wallboard (Gavett, 2003; McGee et al., 2003).

When air and dusts from building materials dispersed from the WTC collapse were collected from November 4 to December 11, 2001, in and around 30 residential buildings in lower Manhattan and from four residential buildings above 59th Street (approximately five miles northeast of the WTC site), gypsum was the most common mineral found in lower Manhattan outdoor air samples. Concentrations found in 40 of 114 respirable fraction PM_4 (particulate matter of mass median diameter 4 µm) were estimated at 3 to 14 µg/m^3. (The X-ray diffraction method used to determine a broad range of constituents gave only semiquantitative results for gypsum; thus, values were reported as estimates.) Frequencies of gypsum occurrence were 33 of 105 PM_{10} samples and 24 of 101 PM_{100} samples. Above 59th Street, gypsum concentrations in air were ≤5 µg/m^3 (WTC Environmental Assessment Working Group, 2002; see also Jeffery et al., 2003).

Gypsum concentrations in outdoor settled dusts in lower Manhattan were about 0.03 to 27%. In the residential building common areas (23 of 26 samples), gypsum concentrations in settled dusts ranged from about 0.07 to 20%. In 45 of 57 residences in these buildings, gypsum dust concentrations ranged from about 0.05 to 30%. The estimated maximum gypsum concentration above 59th Street was 4% (WTC Environmental Assessment Working Group, 2002).

<u>Gypsum in Indoor Environments</u>

Gypsum is stated to be the most common natural fibrous mineral found indoors (20:1 gypsum fibers to asbestos) mainly because of its use in plaster in buildings (Hoskins, 2001). In a German study of fibrous dusts from installed mineral wool products in living rooms and workrooms, 134 measurements revealed an average air pollution of 3184 gypsum fibers/m^3; 20% of those with a diameter of >1µm were from construction materials (Anonymous, 1994).

7.0 Human Exposure

Humans may be exposed to gypsum via inhalation, ingestion, skin contact, and/or eye contact (NIOSH, undated-c). The same exposure routes exist for plaster of Paris (NIOSH, undated-d). It was estimated that healthy individuals exposed to ~425 µg WTC $PM_{2.5}/m^3$ air [see Section 6.0] for eight hours would receive a dose comparable to that of mice receiving 100 µg [see Section 9.1.3], which could lead to lung inflammation, airway hyperresponsiveness, and cough (Gavett, 2003; Gavett et al., 2003).

According to the NIOSH National Occupational Exposure Survey (NOES), conducted between 1981 and 1983, an estimated 7,865 workers (1,279 females) were potentially exposed to gypsum dust in eight industries (NIOSH, undated-a). For plaster of Paris, an estimated 60,066 employees (7,948 females) were exposed in 16 industries (NIOSH, undated-b). Analysis by specific occupations is also available.

When fragments of lung tissue were taken postmortem from the upper lobe of the right lung of 60 subjects who had resided in Rome, Italy, with no occupational exposure to mineral dusts, fibrous particles (generally asbestos fibers and small amounts of talc, rutile [aluminum oxide], and calcium sulfate [7778-18-9]) were detected in 16% of subject. Mineral particle concentrations ranged from $0.7x10^5$ to $1.7x10^5$ particles/mg, indicating significant accumulations of mineral particles in lungs of persons living in urban areas (Albedi et al., 1990). In a study of personal exposure to respirable inorganic and organic fibers, geometric mean concentrations of 597, 1046, 1965, and 3722 fibers/m^3 of gypsum fibers (length >5 µm) were found in European taxi drivers, office workers, retired persons, and schoolchildren, respectively. Levels of gypsum fiber with a length between 2.5 and 5 µm were higher: 1729, 1406, 3010, and 4725 fibers/m^3, respectively (Schneider et al., 1996).

8.0 Regulatory Status

The NIOSH REL for gypsum and plaster of Paris is 10 mg/m^3 (total dust—air) and 5 mg/m^3 (respirable fraction—air) as a ten-hour time-weighted average (TWA). The OSHA PELs are 15 and 5 mg/m^3 as an eight-hour TWA, respectively (NIOSH, undated-c,d; RTECS, 2000). The American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV) for gypsum and plaster of Paris (as total dust containing no asbestos and <1% crystalline silica) is 10 mg/m^3 as TWA (IPCS, 2004a,b).

In 1992, the Environmental Protection Agency (EPA) established that phosphogypsum not have a certified average ^{226}Ra concentration >370 becquerel/kg (Bq/kg); this restricted its use in most applications including agricultural and construction purposes. It is therefore stockpiled in stacks (Health Physics Society, 2001; U.S. EPA, 2004).

9.0 Toxicological Data

9.1 General Toxicology

Both gypsum and plaster of Paris are skin, eye, mucous membrane, and respiratory system irritants. Other symptoms humans may exhibit from exposure are coughing, sneezing, or rhinorrhea (NIOSH, undated-c,d). Early studies of gypsum miners did not relate pneumoconiosis with chronic exposure to gypsum (Forbes et al., 1950; Gardner, 1938; Riddell, 1934; Schepers and Durkan, 1955; all cited by Oakes et al., 1982). Other studies in humans (as well as animals) showed no lung fibrosis produced by natural dusts of calcium sulfate except in the presence of silica (e.g., Burilkov and Michailova-Dotschewa, 1990, and Einbrodt, 1988). However, a series of studies reported chronic nonspecific respiratory diseases in gypsum industry workers in Gacki, Poland (Owsinski and Dolezal, 1972). Results of more recent human exposure studies to gypsum dust/fiber are presented below.

9.1.1 Human Data

Absorption, Distribution, Metabolism, and Excretion

Unlike other fibers, gypsum is very soluble in the body with an estimated half-life in the lungs in the range of several minutes (Hoskins, 2001). In healthy men receiving calcium sulfate supplementation ($CaSO_4 \cdot 1/2H_2O$; 220 mg orally), average absorption was 28.3% (Rao and Rao, 1974).

Health Effects from Occupational Exposures

Plasterers and Construction Workers

Numerous case-control studies have been conducted regarding a possible association between cancer risk and occupations, including plasterers and construction workers (exposures to crystalline silica, man-made mineral fibers, polycylic aromatic hydrocarbons, etc.) (e.g., Arndt et al., 1996, Bruske-Hohlfeld et al., 2000, and Milne et al., 1983). A statistically significant increase in risks for lung cancer, asbestosis, other non-malignant respiratory diseases, and benign neoplasms was observed among plasterers potentially exposed to toxic materials such as plaster of Paris, silica, fiberglass, talc, and 1,1,1-trichloroethylene. Plasterers were also found to have the highest risk of liver cancer (Bouchardy et al., 2002; Okuda et al., 1989; Stern et al., 2001; Zahm et al., 1989).

Workers in the Gypsum Industry

In a study of 241 underground male workers employed in four gypsum mines in Nottinghamshire and Sussex for a year (November 1976-December 1977), results of chest X-rays, lung function tests, and respiratory systems suggested an association of the observed lung shadows with the higher quartz content in dust rather than to gypsum. The small round opacities in the lungs were characteristic of silica exposure (Oakes et al., 1982).

Prophylactic examinations of workers in a gypsum extraction and production plant (dust concentration exceeded TLV 2.5- to 10-fold) reported no risk of pneumoconiosis due to gypsum exposure. Occupational dust bronchitis was observed in four cases; death due to chronic non-specific lung disease was 5.3%, not exceeding the average for the corresponding age and sex collective in the general population (Burilkov and Michailova-Dotschewa, 1990). In another study of gypsum manufacturing plant workers (n=50), chronic occupational exposure to gypsum dust resulted in pulmonary ventilatory defect of the restrictive form (Moustafa et al., 1994 abstr.).

Schoolteachers

Three cases of idiopathic interstitial pneumonia with multiple bullae throughout the lungs were seen in Japanese schoolteachers (lifetime occupation) exposed to chalk; 2/3 of the chalk was made from gypsum and small amounts of silica and other minerals (Ohtsuka et al., 1995).

Skin Irritation

Coal miners using anhydrite (containing traces of calcium fluoride and hydrofluoric acid) for filling in gaps between rocks and beams have complained of skin irritation. When the hemihydrate was used as a substitute, which was less alkaline than anhydrite paste, a significant decrease in the condition was reported. In ten volunteers, five applications of anhydrite paste (100 mg) or hemihydrate paste (100 mg) to the forearm under occlusion for 24 hours produced mean blood flow values of 18.0 and 14.0%, respectively; controls had a value of 12.1%. The increased blood flow indicated increased irritancy; however, there was no clinical sign of irritation in any subject (Lachapelle et al., 1984).

9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

In rats exposed to an aerosol of anhydrous calcium sulfate fibers (15 mg/m^3) or a combination of milled and fibrous calcium sulfate (60 mg/m^3) six hours per day, five days per week for three weeks, gypsum dust was quickly cleared from the lungs via dissolution and mechanisms of particle clearance (Clouter et al., 1997, 1998; both cited by Health Council of the Netherlands, Committee on Updating of Occupational Exposure Limits, 2002).

In guinea pigs given intraperitoneal (i.p.) injections of gypsum (doses not provided), gypsum was absorbed followed by the dissolution of gypsum in surrounding tissues (Greim, 1996; cited by Health Council of the Netherlands, Committee on Updating of Occupational Exposure Limits, 2002). In another study, after i.p. injection of gypsum (2 cm^3 of a 5 or 10% suspension in saline) into guinea pigs, which were sacrificed at intervals up to 180 days, most of the dust was found distributed in the peritoneum of the anterior abdominal wall. Gypsum dust produced irregular and clustered nodules, which decreased in size over time, leaving brown pigment which ultimately disappeared (Miller and Sayers, 1936, 1941).

Several studies in pigs on the bioavailability of calcium in calcium supplements, including gypsum, have been conducted. The animals were fed calcium-supplemented diets for up to 42 days. The bioavailability of calcium in gypsum was similar to that for calcitic limestone, oyster shell flour, marble dust, and aragonite, ranging from 85 to 102% (e.g., see Ross et al., 1984, and Fialho et al., 1992).

9.1.3 Acute Exposure

In mice, the i.p. and intragastric (gavage) LD_{50} values were 6200 and 4704 mg/kg, respectively, for phosphogypsum (98% $CaSO_4 \cdot H_2O$). For plaster of Paris, the values were 4415 and 5824, respectively. In rats, an intragastric LD_{50} of 9934 mg/kg was reported for phosphogypsum (Khodykina et al., 1996).

In mice, direct administration of WTC $PM_{2.5}$ [mostly composed of calcium-based compounds, including calcium sulfate (gypsum) and calcium carbonate (calcite); see Section 6.0] (100 µg) into the airways produced mild to moderate lung inflammation and airway hyperresponsiveness to methacholine that was similar to that from a standard ambient air PM sample and greater than that from toxic residual oil fly ash sample. Lower doses (10 and 32 µg) did not induce significant inflammation or hyperresponsiveness; inhalation of WTC $PM_{2.5}$ (11 mg/m^3) also had no such effects (Gavett, 2003; Gavett et al., 2003). [It was noted that WTC $PM_{2.5}$ is composed of many chemical species and that their interactions may be related with development of airway hyperresponsiveness (McGee et al., 2003).]

In female SPF Wistar rats intratracheally (i.t.) instilled with anhydrite dust (35 mg) and sacrificed three months later, an increase in total lipid or hydroxyproline content in the lungs was not observed compared to controls (Breining et al., 1990).

9.1.4 Short-term and Subchronic Exposure

In inhalation (nose-only) experiments in which male F344 rats were exposed to calcium sulfate (fiber) aerosols (100 mg/m^3) for six hours per day, five days per week for three weeks, there were no effects on the number of macrophages per alveolus, bronchoalveolar lavage fluid (BALF) protein concentration, or BALF γ-glutamyl transpeptidase activity (γ-GT). Following three weeks of recovery, nonprotein thiol levels (NPSH), mainly glutathione, were increased in animals (Clouter et al., 1996; cited by Health Council of the Netherlands, Committee on Updating of Occupational Exposure Limits, 2002). In follow-up experiments, rats were exposed to an aerosol of anhydrous calcium sulfate fibers (15 mg/m^3) or a combination of milled and fibrous calcium sulfate (60 mg/m^3) for the same duration. Calcium levels in the lungs were similar to those of controls; however, gypsum fibers were detected in the lungs of treated animals. Significant increases in NSPH levels in BALF were observed in rats killed immediately after exposure at both doses and in the three-week recovery group animals at the higher dose. At 15 mg/m^3, almost all NPSH was lost in macrophages from all treated animals (including those in recovery), but a significant decrease in extracellular γ-GT activity was seen only in recovery group animals. At 60 mg/m^3, γ-GT activity in lung macrophages was significantly increased; this was hypothesized as a "compensatory response" to the loss of NPSH. Overall, the findings were "considered to be non-pathological local effects due to physical factors related to the shape of the gypsum fibers and not to calcium sulphate *per se*" (Clouter et al., 1997, 1998; both cited by Health Council of the Netherlands, Committee on Updating of Occupational Exposure Limits, 2002).

Intratracheal administration of man-made calcium sulfate fiber (2.0 mg) once per week for five weeks resulted in no deaths or significant body weight changes in female Syrian hamsters compared to controls. Inflammation (specifically, chronic alveolitis with macrophage and neutrophil aggregation) was observed in the lung (Adachi et al., 1991).

9.1.5 Chronic Exposure

In guinea pigs, inhalation of calcined gypsum dust aerosol (average size=5 µm [range 1-40 µm]; dose=1.6×10^4 particles/mL) for 44 hours per week in 5.5 days for two years, followed with or without a recovery period of up to 22 months, produced only minor effects in the lungs. There were 12 of 21 deaths over the entire experimental period. These were due to pneumonia or other pulmonary lesions; however, no significant gross signs of pulmonary disease or nodular or diffuse pneumoconiosis became significant. Beginning near 11 months, pigmentation and atelectasis (and later diffuse cellular reaction without fibrosis) were seen. During the recovery period, four of ten guinea pigs died; two died of pneumonia. Pigmentation continued in most animals but not atelectasis, although diffuse cellular proliferation was seen. Low-grade chronic inflammation, occurring in the first two months, also disappeared (Schepers et al., 1955).

9.1.6 Synergistic/Antagonistic Effects

In rats, i.t. administration of anhydrite (5-35 mg) successively and simultaneously with quartz reduced the toxic effect of quartz in lung tissue—specifically, total lipid and hydroxyproline content. With increasing anhydrite concentration, a decrease in foam cell content with an increase in the number of histiocytic nodules was observed (Breining et al., 1990; Rosmanith and Breining, 1988). This antagonistic (protective) effect on quartz toxicity was also seen in guinea pigs; calcined gypsum dust prevented or hindered the development of fibrosis (Schepers et al., 1955).

Natural anhydrite, however, increased the fibrogenic effect of cadmium sulfide in rats (Brammertz and Breining, 1992). Additionally, calcined gypsum dust had a stimulatory effect on experimental tuberculosis in guinea pigs (Schepers et al., 1955).

9.1.7 Cytotoxicity

In Syrian hamster embryo cells, gypsum (up to 10 $\mu g/cm^2$) did not induce apoptosis (Dopp et al., 1995; cited by Health Council of the Netherlands, Committee on Updating of Occupational Exposure Limits (2002). Negative results were also found in mouse peritoneal macrophages (tested at 150 µg/mL gypsum dust) and in Chinese hamster lung V79-4 cells (tested up to 100 µg/mL) (Chamberlain et al., 1982).

9.2 Reproductive and Teratological Effects

No data were available.

9.3 Carcinogenicity

In female Sprague-Dawley rats, i.p. injection of natural anhydrite dusts from German coal mines (doses not provided) induced granulomas; whether gypsum (or other unknown components) was the causal factor was not established (Greim, 1996; cited by Health Council of the Netherlands, Committee on Updating of Occupational Exposure Limits, 2002). In Wistar rats, four i.p. injections of gypsum (25 mg each) induced abdominal cavity tumors, mostly sarcomatous mesothelioma, in 5% of animals; first tumor was seen at 546 days (Pott et al., 1974). In a subsequent experiment using the same procedure, female Wistar rats exhibited the first tumor at 579 days after the last injection. Mean survival of the tumor-bearing rats (5.7% of test group) was 583 days, while mean survival of the test group was 587 days. Tumor types seen were a sarcoma having cellular polymorphism, a carcinoma, and a reticulosarcoma (Pott et al., 1976).

Intratracheal administration of man-made calcium sulfate fiber (average diameter=1.0 µm, average length=17.8 µm; dose=2.0 mg/animal) once per week for five weeks produced tumors in three of 20 female Syrian hamsters observed two years later. An anaplastic carcinoma was found in the heart, and one dark cell carcinoma was seen in the kidney. Two tumors of unspecified types were observed in the rib (Adachi et al., 1991).

In guinea pigs, inhalation of gypsum (doses not provided) for 24 months produced no lung tumors (Schepers, 1971).

9.4 Initiation/Promotion Studies

No data were available.

9.5 Anticarcinogenicity
No data were available.

9.6 Genotoxicity
No data were available.

9.7 Cogenotoxicity
No data were available.

9.8 Antigenotoxicity
No data were available.

9.9 Immunotoxicity
No data were available.

9.10 Other Data
Flue Gas Gypsum

In rats, i.t. administration of gypsum (doses not provided in abstract) from FGD by the limestone and lime hydrate process for up to 18 months produced no arterial blood gas changes or indications of secondary heart damage as compared to controls (Einbrodt et al., 1988). In another study, a single i.t. dose (25 mg) of flue gas gypsum dust did not produce a pathological reaction when observed for up to 18 months. There were also no signs of developing granuloma of fibrosis of the lungs. Concentrations of aluminum, chromium, and nickel were not increased in the lungs, kidneys, or livers. Lead quickly accumulated in the femur after injection but was eliminated during the observation period. In the Ames test, the flue gas gypsum dust was negative (Bartmann, 1986 diss.).

Recently implemented mercury emissions controls on coal-fired power plants increased the likelihood of the presence of mercury in synthetic gypsum formed in wet FGD systems and the finished wallboard produced from the FGD gypsum. Mercury emissions during the wallboard production thermal processes of drying and calcining are also expected. In a study at a commercial wallboard plant, the raw FGD gypsum, the product stucco (beta form of $CaSO_4 \cdot 1/2H_2O$), and the finished dry wallboard each contained about 1 µg Hg/g dry weight. Total mercury loss from the original FGD gypsum content was about five percent or about 0.045 g Hg/ton dry gypsum processed (Marshall et al., 2005).

10.0 Structure-Activity Relationships
In the PubChem database, anhydrite [CID = 115280] is listed as a similar compound to gypsum. Anhydrite (i.e., calcium sulfate without water of crystallization) was reviewed by the Health Council of the Netherlands, Committee on Updating of Occupational Exposure Limits in 2002. Calcium sulfate (up to 2.5%) was negative in *Salmonella typhimurium* strains TA1535, TA1537, and TA1538 and in *Saccharomyces cerevisiae* strain D4 with and without metabolic activation. In pregnant mice, rats, and rabbits, oral administration of calcium sulfate (16-1600 mg/kg bw) daily beginning on gestation day 6 up to 18 produced no effects on maternal body weights,

maternal or fetal survival, or nidation; developmental effects were also not seen (Health Council of the Netherlands, Committee on Updating of Occupational Exposure Limits, 2002).

11.0 Online Databases and Secondary References

11.1 Online Databases

National Library of Medicine Databases (TOXNET)
ChemIDplus
EMIC and EMICBACK
HSDB
IRIS

STN International Files

AGRICOLA	IPA
BIOSIS	MEDLINE
BIOTECHNO	NIOSHTIC
CABA	NTIS
CANCERLIT	Registry
EMBASE	RTECS
ESBIOBASE	TOXCENTER

TOXCENTER includes toxicology data from the following files:

Aneuploidy	ANEUPL*
BIOSIS Previews® (1969-present)	BIOSIS*
CAplus (1907-present)	CAplus
International Labour Office	CIS*
Toxicology Research Projects	CRISP*
Development and Reproductive Toxicology	DART®*
Environmental Mutagen Information Center File	EMIC*
Epidemiology Information System	EPIDEM*
Environmental Teratology Information Center File	ETIC*
Federal Research in Progress	FEDRIP*
Health Aspects of Pesticides Abstract Bulletin	HAPAB
Hazardous Materials Technical Center	HMTC*
International Pharmaceutical Abstracts (1970-present)	IPA*
MEDLINE (1951-present)	MEDLINE
Pesticides Abstracts	PESTAB*
Poisonous Plants Bibliography	PPBIB*
Swedish National Chemicals Inspectorate	RISKLINE
Toxic Substances Control Act Test Submissions	TSCATS*

*These are also in TOXLINE. Missing are TOXBIB, NIOSHTIC®, NTIS.

National Archives and Records Administration
Code of Federal Regulations (CFR)

In-House Databases
Current Contents on Diskette®

The Merck Index, 1996, on CD-ROM

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Appendix A: Units and Abbreviations

ºC = degrees Celsius
µg/L = microgram(s) per liter
µg/m^3 = microgram(s) per cubic meter
µg/mL = microgram(s) per milliliter
µM = micromolar
BALF = bronchoalveolar lavage fluid
EPA = Environmental Protection Agency
FGD = flue gas desulfurization
g = gram(s)
g/mL = gram(s) per milliliter
γ-GT = γ-glutamyl transpeptidase
h = hour(s)
i.p. = intraperitoneal(ly)
i.t. = intratracheal(ly)
kg = kilogram(s)
L = liter(s)
lb = pound(s)
LC = liquid chromatography
LC_{50} = lethal concentration for 50% of test animals
LD_{50} = lethal dose for 50% of test animals
LD = low dose
M = male(s)
MD = mid dose
mg/kg = milligram(s) per kilogram
mg/m^3 = milligram(s) per cubic meter
mg/mL = milligram(s) per milliliter
min = minute(s)
mL/kg = milliliter(s) per kilogram
mm = millimeter(s)
mM = millimolar
mmol = millimole(s)
mmol/kg = millimoles per kilogram
mo = month(s)
mol = mole(s)
mol. wt. = molecular weight
NIOSH = National Institute for Occupational Safety and Health
n.p. = not provided
NPSH = nonprotein thiol levels
NTP = National Toxicology Program
OSHA = Occupational Safety and Health Administration
PEL = permissible exposure limit
$PM_{2.5}$ = particulate matter with <2.5 µm mass median aerodynamic diameter
PM_4 = particulate matter of mass median diameter 4 µm
PM_{10} = particulate matter of mass median diameter 10 µm
PM_{100} = particulate matter of mass median diameter 100 µm

ppb = parts per billion
ppm = parts per million
REL = relative exposure limit
TWA = time-weighted average
WTC = World Trade Center

Appendix B: Description of Search Strategy and Results

A preliminary PubMed (free MEDLINE) search was done on July 27, 2004, using the search statement: gypsum OR calcium(w)(sulfate OR sulphate) OR plasterer*. A total of 98 records were retrieved.

Simultaneous searches of files MEDLINE, CANCERLIT, NIOSHTIC, AGRICOLA, CABA, BIOTECHNO, EMBASE, ESBIOBASE, BIOSIS, IPA, TOXCENTER, and NTIS on STN International were done on August 25 and 31, 2005. The history of the online search session is reproduced below.

```
L1         6566 S 7778-18-9
L2        11577 S 13397-24-5 OR 26499-65-0
L3         8365 S (CA OR CALCIUM)(W)(SULFATE OR SULPHATE)
L4         2769 S (CA OR CALIUM)(6A)(SULFATE? OR SULPHATE?)
L5        18010 S (CA OR CALCIUM)(6A)(SULFATE? OR SULPHATE?)
L6        14981 S (CA OR CALCIUM)(3A)(SULFATE? OR SULPHATE?)
L7        19754 S GYPSUM
L8         3273 S PHOSPHOGYPSUM OR ANHYDRITE
L9          175 S PLASTERER?
L10       29224 S L1 OR L2 OR L3 OR L7 OR L8 OR L9
L11          59 S (L10 AND (DENTAL OR DENTIST? OR BONE? OR IMPLANT?)) AND TOXIC?
                SET DUPORDER FILE
L12          41 DUP REM L11 (18 DUPLICATES REMOVED)
L13          41 SORT L12 1-41 TI
                SAVE L13 X270BONESTOX/A
L14       29165 S L10 NOT L11
L15       28837 S L14 NOT (RADON OR RA(W)226 OR 226(W)RA OR 222(W)RN)
L16       27983 S L15 NOT (RADIATION OR EMANAT? OR IRRADIAT?)
L17       27964 S L16 NOT IRRADN
L18       27712 S L17 NOT (FISH OR DAPHNIA OR MOLLUS? OR CRUSTACEA?)
L19       27711 S L18 NOT (AQUATIC(6A)(BIOTA OR FLORA OR FAUNA))
L20        1167 S L19 AND ((AIR OR ATMOSPHER?)(6A)(POLLUT? OR MONITOR? OR EMISSION?)
L21          19 S L19 AND BREATH
L22         159 S L19 AND (CHRONIC? OR SUBCHRONIC? OR (14 OR 102 OR 104 OR 13)
L23        2837 S L19 AND (MONTH? OR YEAR? OR 90(W)DAY?)
L24         301 S L19 AND (LUNG OR LUNGS OR PULMONARY OR FIBROTIC OR FIBROSIS
L25         422 S L19 AND (BRONCH? OR ALVEOL? OR RESPIR? OR CLARA OR COPD OR EPIDEMIOL?)
L26         947 S L19 AND (METAB? OR URIN? OR EXCRET? OR CLEARANCE OR BIOAVAIL?)
L27        1403 S L19 AND (CYTOTOX? OR PROLIFER? OR VITRO OR INCUBAT? OR CULTUR?)
L28         518 S L19 AND (BLOOD? OR PLASMA? OR IMMUN? OR SERUM OR LYMPH?)
L29          56 S L19 AND (HYPERSENSITIV? OR ALLERGEN? OR HAPTEN?)
L30         332 S L19 AND (REPRODUCTI? OR DEVELOPMENTAL? OR TERAT?)
L31          44 S L19 AND (PREGNAN? OR FETAL? OR FOETAL? OR FETUS? OR FOETUS?)
L32          29 S L19 AND (EMBRYO? OR PLACENTA? OR GESTAT?)
L33          66 S L19 AND (MUTANT? OR MUTAT? OR MUTAGEN? OR GENOTOX? OR GENETIC(6A)TOXIC)
L34         887 S L19 AND (CARCINO? OR CANCER? OR TUMOR? OR TUMOUR? OR PATHO?)
L35          98 S L19 AND (PRENEOPLAS? OR HYPERPLAS? OR NEOPLAS?)
L36        6008 S L19 AND (EPIDEMIOL? OR HUMAN? OR MINER? OR WORKER? OR HYGIENE)
L37           0 S L19 AND (SALMONELLA AND AMES AND HPRT AND MICRONUCLE? OR COMET(W)ASSAY)
L38          29 S L19 AND (SALMONELLA OR AMES OR HPRT OR MICRONUCLE? OR COMET(W)ASSAY OR UDS OR SCE)
L39          78 S L19 AND (CASE(W)CONTROL OR PROSPECTIVE)
L40         272 S L19 AND (ENZYM? OR CARDIOVASCULAR OR CARDIAC OR HEART OR ARTER?)
L41        6931 S L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27
L42        6931 S L20-L35
L43        7063 S L42 OR L38-L40
L44           0 S EPIMIOL? AND L19
L45         130 S EPIDEMIOL? AND L19
L46        1834 S HUMAN? AND L19
L47        4124 S MINER? AND L19
L48          33 S (MINER OR MINERS) AND L19

=> S L19 AND OCCUPATIONAL(W)DISEASE?
   9 FILES SEARCHED...
L49          93 L19 AND OCCUPATIONAL(W)DISEASE?
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=> S L19 AND (WORKER? AND DISEASE?)
   9 FILES SEARCHED...
L50        103 L19 AND (WORKER? AND DISEASE?)

=> S L19 AND (CELL(W)SIGNALING OR ATHERO?)
L51          2 L19 AND (CELL(W) SIGNALING OR ATHERO?)

=> S L19 AND (INHAL? OR INTRATRACHEAL? OR ENDOTRACHEAL?)
L52        133 L19 AND (INHAL? OR INTRATRACHEAL? OR ENDOTRACHEAL?)

=> S L43-L46 OR L48-L52
L53       7935 (L43 OR L44 OR L45 OR L46) OR (L48 OR L49 OR L50 OR L51 OR L52)

=> DUP REM L53
PROCESSING IS APPROXIMATELY  39% COMPLETE FOR L53
PROCESSING IS APPROXIMATELY  72% COMPLETE FOR L53
PROCESSING COMPLETED FOR L53
L54        5571 DUP REM L53 (2364 DUPLICATES REMOVED)
                ANSWERS '1-1181' FROM FILE MEDLINE
                ANSWERS '1182-1185' FROM FILE CANCERLIT
                ANSWERS '1186-1301' FROM FILE NIOSHTIC
                ANSWERS '1302-1509' FROM FILE AGRICOLA
                ANSWERS '1510-2887' FROM FILE CABA
                ANSWERS '2888-2937' FROM FILE BIOTECHNO
                ANSWERS '2938-3286' FROM FILE EMBASE
                ANSWERS '3287-3400' FROM FILE ESBIOBASE
                ANSWERS '3401-4157' FROM FILE BIOSIS
                ANSWERS '4158-4165' FROM FILE IPA
                ANSWERS '4166-4999' FROM FILE TOXCENTER
                ANSWERS '5000-5571' FROM FILE NTIS

=> S L54 NOT (SOIL? OR FERTILI?)
  11 FILES SEARCHED...
L55       3562 L54 NOT (SOIL? OR FERTILI?)

=> DUP REM L55
PROCESSING COMPLETED FOR L55
L56        3562 DUP REM L55 (0 DUPLICATES REMOVED)
                ANSWERS '1-1150' FROM FILE MEDLINE
                ANSWERS '1151-1154' FROM FILE CANCERLIT
                ANSWERS '1155-1267' FROM FILE NIOSHTIC
                ANSWERS '1268-1338' FROM FILE AGRICOLA
                ANSWERS '1339-1599' FROM FILE CABA
                ANSWERS '1600-1640' FROM FILE BIOTECHNO
                ANSWERS '1641-1973' FROM FILE EMBASE
                ANSWERS '1974-2047' FROM FILE ESBIOBASE
                ANSWERS '2048-2349' FROM FILE BIOSIS
                ANSWERS '2350-2357' FROM FILE IPA
                ANSWERS '2358-3049' FROM FILE TOXCENTER
                ANSWERS '3050-3562' FROM FILE NTIS

=> S L56 AND HUMAN?
   6 FILES SEARCHED...
  11 FILES SEARCHED...
L57       1231 L56 AND HUMAN?

=> DUP REM L57
PROCESSING COMPLETED FOR L57
L58        1231 DUP REM L57 (0 DUPLICATES REMOVED)
                ANSWERS '1-871' FROM FILE MEDLINE
                ANSWER '872' FROM FILE CANCERLIT
                ANSWERS '873-888' FROM FILE NIOSHTIC
                ANSWERS '889-903' FROM FILE CABA
                ANSWERS '904-918' FROM FILE BIOTECHNO
                ANSWERS '919-1046' FROM FILE EMBASE
                ANSWERS '1047-1052' FROM FILE ESBIOBASE
                ANSWERS '1053-1137' FROM FILE BIOSIS
                ANSWERS '1138-1216' FROM FILE TOXCENTER
                ANSWERS '1217-1231' FROM FILE NTIS
```