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Health Assessment Document for Talc

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CONTENTS

CONTENTS (continued)

TABLES

PREFACE

This health assessment on talc was prepared for the Office of Health and Environmental Assessment to serve as a source document for EPA use. In the development of the assessment document, the scientific literature has been inventoried, key studies have been evaluated, and summary/conclusions have been prepared so that the chemical's toxicity and related characteristics are qualitatively identified. Observed effect levels and other measures of dose-response relationships are discussed, where appropriate, so that the nature of the adverse health responses is placed in perspective with observed environmental levels. The relevant literature for this document has been reviewed through early 1991.

Any information regarding sources, emissions, ambient air concentrations, and public exposure has been included only to give the reader a preliminary indication of the potential presence of this substance in the ambient air. While the available information is presented as accurately as possible, it is acknowledged to be limited and dependent in many instances on assumption rather than specific data. This information is not intended, and, therefore, should not be used, as an exposure assessment by which to estimate risk to public health.

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1. SUMMARY

Concern surrounding the adverse health effects of asbestos on the general population has stimulated interest in the potential health effects of other natural and man-made fibers. The health effects of talc, a nonfibrous silicate mineral with multiple consumer uses, are discussed in this document. Additional concern over talc exposure is associated with the possible presence of asbestos (i.e., tremolite) and/or crystalline silica as a contaminant in some deposits of this mineral.

Talc (CAS No. 14807-96-6) is made up of pulverized, foliated hydrous magnesium silicates from minerals with low crystalline silica content. Talc is a layered silicate, and both talc crystals and fragments are commonly platey and nonfibrous. Its color can be white, yellow, green, or gray depending on the number of impurities present. The chemical composition of talc is $3MgO \bullet 4SiO_2 \bullet H_2O$. Minerals commonly found in commercial talc include MgO, TiO_2, calcium silicate, iron oxide, carbonates, and aluminates. Talc is insoluble in water and exhibits varying resistance to acids, alkalies, and temperature. Approximately 1.25 million short tons (1.13 million metric tons) of talc were produced in the United States in 1989. In 1990, talc production increased slightly, and apparent consumption increased 7%. The largest end uses of talc are in ceramics and paint; only 5% is used in cosmetics.

Estimates of environmental release of talc are not available. The National Occupational Hazard Survey (NOHS, 1976) conducted by the National Institute for Occupational Safety and Health reports that 1,536,754 workers were potentially exposed to talc in 1972-74, whereas the Institute's National Occupational Exposure Survey (NOES, 1984) estimated that 18,872 workers, including 5,244 females, were potentially exposed to talc in the workplace in 1980.

Occupational exposure to talc dust has been measured at various mining and milling facilities. The talc deposits have been found to differ in mineral composition. Average dust exposure at a talc plant in Georgia prior to 1970 was reported to be 32 to 855 millions of particles per cubic foot (mppcf) (mine) and 17 to 1,672 mppcf (mill). The talc dust was reported to contain dolomite, tremolite, and little or no free silica. Talc dust from mining

and milling operations in St. Lawrence County, NY, was reported to contain tremolite and anthophyllite. The exposures ranged from 5 to 19 mppcf (mine) and from 7 to 36 mppcf (mill) after 1945. Airborne fiber levels (>5 μm in length, 65% anthophyllite and 7% tremolite) in the mine and mill gave mean exposures of 4.5 and 5.0 fibers >5 $\mu m/cm^3$, respectively. Mean concentrations of respirable dust in samples from three Vermont talc mines and mills ranged from 0.5 to 5.1 mg/m^3 (mines) to 0.5 to 2.9 mg/m^3 (mills). Analysis of the dust showed talc, magnesite, and free silica; tremolite was reported but not documented. Average talc dust exposure in Montana, Texas, and North Carolina was reported in 1979 as 1.2, 2.6, and 0.3 mg/m^3, respectively. No fibers were found in samples of Montana talc, fibrous tremolite and antigorite were reported in Texas talcs, and talcs from North Carolina contained acicular cleavage fragments with particle length to diameter ratios as high as 100:1, with some <0.1 μm in diameter. Talc exposures in mines and mills in Italy were reported after 1965 to be 0.8 to 3 mppcf and 2 to 8 mppcf, respectively; analysis showed tremolite and silica fibers. Total dust exposure in a secondary industry such as rubber production was reported in 1972 as 5.4 to 199 mg/m^3, with fiber exposures ranging from 4.7 to 19.2 fibers >5 $\mu m/cm^3$ (fibers reported as silica).

The American Conference of Governmental Industrial Hygienists has recommended an 8-h threshold limit value-time weighted average (TLV-TWA) of 2 mg/m^3 respirable dust for talc containing no asbestos fibers, whereas the Occupational Safety and Health Administration has recommended a total dust TWA of 20 mppcf.

Exposure to cosmetic grade talc, as used in cosmetic and health care products, is infrequent and of short duration. A simulated study, however, indicated that talc exposure for an infant and mother during a 10-s dusting was 0.243 mppcf, which decreased to 0.124 mppcf during the next 65 s. The average respirable dust concentration was reported to be 0.10 $mg/min/m^3$. In a study of routine application of talcum powder, the calculated TWA exposure separately for infants and adults indicated levels of 0.095 $mg/min/m^3$ and 1.729 $mg/min/m^3$, respectively.

Estimates of airborne concentrations in ambient air are not available. Talc is not expected to undergo chemical transformation when released into the environment. The following analytical procedures are used to identify and quantitate talc: collection in an impinger and counting by optical microscopy (used prior to 1970), phase-contrast optical

microscopy, analytical electron microscopy and selected-area electron diffraction, and X-ray diffraction.

Following single inhalation exposures, talc was retained in the lungs of exposed hamsters. Talc was cleared slowly because it has a biological half-life of 7 to 10 days. The talc content decreased to the detection levels found in control animals 4 mo after exposure. Pulmonary deposition of talc following repeated exposures was dose dependent. Pulmonary clearance was facilitated by mucociliary activity, and talc was eliminated in the feces via the gastrointestinal tract. Little, if any, talc was absorbed from the gastrointestinal tract of rats, guinea pigs, mice, and hamsters following oral intubation. Most of the material was eliminated in the feces within one to two days after dosing. No measurable transport of talc was reported following intravaginal instillation into cynomolgus monkeys. In rats, however, intrauterine or intravaginal instillation resulted in migration of talc particles into the ovaries.

No information was available on the acute toxicity of talc, although intratracheal instillation of talc in hamsters resulted in pulmonary toxicity as shown by biochemical and cellular changes. A study of talc-induced synovial inflammation after injection (0.25 mL) showed that the response in white rabbits was a local increase in temperature, hyperemia, and venous congestion that facilitated anabolic cellular activity and increased production of cartilage. Subchronic inhalation exposure (3 to 12 mo) in rats resulted in pulmonary fibrosis that increased in severity as the exposure period increased. Intratracheal administration of talc resulted in a typical granulomatous lesion consisting of dust-laden multinucleated foreign body giant cells, as well as some fibrosis with collagen formation in several animal species. In addition to the development of granulomas, intratracheal instillation of talc resulted in moderate tissue destruction in hamsters, and intraperitoneal administration has been shown to cause abdominal adhesions in rats and swine. Chronic exposure by the intratracheal route in hamsters resulted in dust-laden macrophage aggregation with the accumulation of interstitial cells and histiocytes with some accumulation of proteinaceous exudate within the alveoli. No fibrosis or granulomas were observed. Talc alone caused moderate tissue destruction, slight metaplasia in the tracheobronchial region, and moderate hyperplasia in the alveolar region. Intraperitoneal injection of talc in another study resulted in foreign-body granulomas with adhesions in rats after 12 weeks. The development of these granulomas has also been reported in swine. Talc implanted surgically into the peritoneal cavity of rats produced

extensive granulomatous peritonitis within two weeks that persisted until Week 13. Nodules appeared and remained 52 weeks after exposure.

Limited data suggest that talc is not carcinogenic following inhalation exposure or intratracheal instillation in rats and hamsters. Similarly, no evidence of carcinogenicity was noted following intrapleural, intraperitoneal, or oral administration in rats. The results of one study suggest that talc may act as a cocarcinogen following intratracheal administration in combination with benzo[*a*]pyrene once weekly for life, but the exact mechanism is not known.

Limited data suggest that talc does not induce gene mutations in *Salmonella* or *Saccharomyces* at 200 mg/cm^3, chromosomal aberrations in rat bone marrow cells, or dominant lethal mutations in the germinal cells of male rats; however, no details of these studies were presented. Natural or acid-purified talc (particle size 0.2 to 20 μm) exhibits weak cytotoxicity in rat peritoneal and alveolar macrophages. Talc particles within the respirable range were not cytotoxic to A549 alveolar human tumor cells or V79-4 Chinese hamster lung cells.

Teratogenicity and reproductive effects studies were not available.

Several cross-sectional morbidity studies of miners and millers from the New York, Montana, Texas, North Carolina, and Vermont mines indicate increased respiratory symptoms, higher prevalence of pleural thickening or calcification and pneumoconiosis, and decreased pulmonary function in workers exposed to talc containing various amounts of tremolite, anthophyllite, or silica fibers. These effects increased with age of workers, intensity of smoking, and duration of exposure. However, exposure to talc free of asbestiform fibers was associated with less pronounced effects. Increased incidences of ovarian cancer are reported in a case-control study of 215 white females regularly using talc as a dusting powder on the perineum or on sanitary napkins, or both, when compared with controls. However, the purity of talc used was unknown. Additionally, other studies show neither a strong nor a consistent association between genital talcum powder exposure and ovarian cancer. Similar to the findings described above, several mortality studies indicate an excess of respiratory cancer and nonmalignant respiratory disease (NMRD) among mining and milling workers. Also, the talc was contaminated with asbestos, silicates, carbonates, or radon. These studies had important limitations such as no smoking data and lack of

dose-response data. Consequently, a direct relationship with talc exposure alone cannot be established. One study that investigated the effects of worker exposure to very pure talc showed no increase in mortality from lung cancer. An increase was seen in NMRD; however, this was attributed to silica exposure.

The above findings indicate that the evidence for carcinogenicity of talc depends on the presence of other contaminants, such as asbestos or crystalline silica. For talc without asbestos contamination, the International Agency for Research on Cancer (IARC) has concluded that the available epidemiological and animal toxicity data are inadequate to demonstrate or refute the potential for carcinogenicity. The presence of asbestos in talc would cause the talc to be viewed as a human carcinogen. In the case of crystalline silica, the IARC views the human evidence as limited and the animal evidence as sufficient, which classifies crystalline silica as a probable human carcinogen.

The U.S. EPA has not previously evaluated the data for talc or crystalline silica and has not done so in this assessment. The IARC views on weight-of-evidence are useful as an interim measure in considering the hazard perspective. The U.S. EPA and the IARC view asbestos as a human carcinogen. The quantitative question arises as to how much crystalline silica or asbestos contamination makes a difference in terms of potential risk, and this dose-response issue has not been included in this assessment.

2. BACKGROUND INFORMATION

2.1 PHYSICAL AND CHEMICAL PROPERTIES

Talc (CAS No. 14807-96-6) is composed of pulverized, natural, foliated hydrous magnesium silicates originating from nonasbestiform minerals that are low in crystalline SiO_2 content (Davies et al., 1983). It commonly exists as thin, tabular crystals up to 1 cm wide. The crystals can be pale to dark green or greenish-gray, white, silvery-white, gray, or translucent. Talc has a density of 2.58 to 2.83 g/cm^3 (Roberts et al., 1974), has perfect cleavage, is insoluble in water, and depending upon its purity, exhibits varying resistance to acids, alkalies, and heat. Synonyms for talc include soapstone, steatite, and talcum (International Agency for Research on Cancer, 1987; General Electric, 1978).

The structure of talc is characterized by hexagonal sheet arrangements of SiO_4 tetrahydral groups linked in a common plane. Two such sheets are oriented so that the unshared apical oxygen atoms face each other. The sheets are bonded by magnesium atoms, which are coordinated by two oxygen and one hydroxyl group from each sheet. Talc crystals are made up of stacks of these double-sheet units held together by Van der Waal's forces. Platey crystals of talc slide past one another to produce the smoothness associated with talc (Davies et al., 1983). The chemical composition of talc is $3MgO \bullet 4SiO_2 \bullet H_2O$ (Johnson, 1991). When expressed in the standard oxide form, the ideal chemical composition is 31.7% MgO, 63.5% SiO_2, and 4.8% H_2O (Pooley and Rowlands, 1977).

Because talc is formed by the alteration or metamorphosis of rocks, it is found associated with many types of minerals. Minerals commonly found in commercial talc include MgO, TiO_2, calcium silicate, iron oxide (a color determinant), carbonates, pyrophyllite, and aluminates. Tremolite and/or anthophyllite asbestos are also found as contaminants of some talc deposits (National Research Council, 1984; Lockey, 1981; Rohl and Langer, 1974).

The mineral composition of talc mined in Montana, for example, is essentially talc with minor chlorite, dolomite, calcite, and quartz. In Texas, depending on the mining district, associated minerals include quartz, magnetite, chlorite, tremolite, and anthophyllite. In Vermont, magnesite, serpentine, chloride, and sulfides are associated with talc rock (Johnson,

1991). The mineral compositions of various talcs from the United States and other parts of the world have been listed by the International Agency for Research on Cancer (1987).

2.2 PRODUCTION AND INDUSTRIAL USES

Talc is derived by the alteration of mineral rocks, which sometimes include the amphibole and serpentine groups of asbestos, after their exposure to specific temperatures, pressures, and circulating liquid solutions or by the thermal metamorphism of silicon dolomites (Hildick-Smith, 1976). The abundance of talc and the facility with which it can be mined, combined with its many desirable functional properties, have made it an important industrial mineral. Large-scale U.S. production of ground talc products began about 1880. Talc is mined using hand tools, drilling, or blasting methods (Clifton, 1985).

Practices for refining talc ores vary greatly. Some operations initially sort the talc by hand according to color and physical characteristics (Clarke, 1979). The latest technology, however, employs flotation separation. Flotation techniques are especially prevalent in North America, Norway, and Finland (Roe and Olson, 1983; Sinha, 1982). The amount of crude talc and pyrophyllite ($AlSi_2O_5(OH)$) (a mineral that occurs commonly in talc deposits) produced in the United States in 1984 is shown in Table 2-1.

TABLE 2-1. U.S. PRODUCTION OF CRUDE TALC AND PYROPHYLLITE IN 1984 (thousand short tons)

State	Quantity
California	74
Georgia (talc)	15
North Carolina	87
Oregon (talc)	—[a]
Texas (talc)	283
Other[b]	711
Total	1,170

[a]Less than one-half unit.
[b]Includes Arkansas, Montana, New York, Vermont, Virginia, and Washington.

Source: Clifton (1985).

Recently, the U.S. Bureau of Mines reported that U.S. production of talc in 1989 was 1.25 million short tons (1.13 million metric tons). Actual sales of talc totaled 1.057 million short tons (0.96 million metric tons) in 1987 and 1.070 million short tons (0.97 million metric tons) in 1986 (Johnson, 1991). Approximately 23 talc-producing mines in 10 states were in operation in 1990; Montana, Texas, Vermont, and New York collectively produced 88% of the domestic yearly total. The largest domestic producers of talc are as follows: Cyprus Industrial Minerals Company; Dal Tile (Texas Talc Company); Gouverneur Talc Company; Pfizer, Inc., Minerals, Pigments, and Metals Division; Vermont Talc Company; and Windsor Minerals, Inc. (Johnson, 1991).

In 1990, talc production increased slightly and apparent consumption increased by 7%. Canada, Japan, and Mexico were the major importers of talc produced in the United States, whereas Australia and Canada supplied approximately 96% of the imported talc (Johnson, 1991).

Talc is one of the most versatile inorganic substances available to industries (Roe and Olson, 1983). Technical products of talc are dependent upon the mineral character of the refined ore and are sold in a multitude of grades, which have functional or physical characteristics especially suited for certain applications (International Agency for Research on Cancer, 1987). The end uses for ground talc and pyrophyllite are shown in Table 2-2. The largest portion of ground talc is used in ceramics (37%), followed by paint (19%), paper (10%), roofing (9%), other (9%), plastics (7%), cosmetics (5%), rubber (3%), and insecticides (1%) (Clifton, 1985).

2.3 SOURCES OF EMISSIONS

Talc-milling processes do not usually alter the mineral composition of the talc mixture, but rather produce a talc with different physical properties dependent on particle size. Emissions of talc are associated with mining, crushing, separating, bagging, loading, and end-use facilities. Because industrial talc is a mixture of various associated minerals, occupational exposure involves exposure to a mixture of mineral dusts (International Agency for Research on Cancer, 1987). Fiber intergrowths are often such that even extensive beneficiation may not yield a pure product. Thus, where fine-grained intergrowths of talc

TABLE 2-2. END USES FOR GROUND TALC AND PYROPHYLLITE (thousand short tons)

Use	Talc	Phyrophyllite	Quantity
Ceramics	358	29	387
Cosmetics[a]	44	—[b]	44
Insecticides	8	14	22
Paint	189	1	190
Paper	100	—	100
Plastics	67	1	68
Refractories	4	21	25
Roofing	86	6	92
Rubber	29	—	29
Other[c]	85	11	96
Total	970	83	1,053

[a]Incomplete data; some cosmetic talc is known to be included with "other."
[b]No data reported.
[c]Includes art sculpture, asphalt filler and coatings, crayons, floor tile, foundry facings, rice polishing, stucco, and uses not specified.

Source: Clifton (1985).

and tremolite occur, emissions of talc will probably contain residual tremolite fibers (Rohl et al., 1976).

2.4 EXPOSURE

The greatest human exposure to talc dust is when it is used industrially or while it is mined or milled. Occupational, consumer, and industrial exposure levels are given in Table 2-3. Dreessen (1933) measured talc exposure for workers involved in mining and milling processes in a talc plant in Georgia. Average dust exposures for miners using jackhammer drills were 1,440 million particles per cubic foot (mppcf) and those for millers were 52 mppcf. The talc was reported to contain 45% tremolite and 45% talc, with little or

TABLE 2-3. AIRBORNE CONCENTRATIONS OF TALC DUST

	Concentrations (mg/m³)				
	Gross		Respirable		
Reference	Range of Averages	Range of Concentrations	Range of Averages	Range of Concentrations	Type of Exposure
Boundy et al. (1979); Wegman et al. (1982)			0.5-5.1		Occupational
Dement and Zumwalde (1979); Dement et al. (1980); Selevan et al. (1979a)	4.3-5.0	0.2-29.1	0.86	0.23-4.64	Occupational
Dreessen and Dalla Valle (1935); Dreessen (1933)		17-1,672[a]			Occupational
Fine et al. (1976)			0.47-3.55	0.28-5.73	Industrial
Gamble et al. (1982); Greife (1980)			0.14-1.56	0.07-2.54	Occupational
Hildick-Smith (1976)			0.1752[a]		Consumer
Hogue and Mallette (1949)			15-50[a]		Occupational
Kleinfeld et al. (1974, 1973, 1967, 1955); Messite et al. (1959)			69-1,227[b,c,d,e]		
Rubino et al. (1976)			12-798[f]		
			4-49[g]		
			0.8-8[h]		Occupational
Russell et al. (1979)			0.106-3.52[a]		Consumer
Dement and Shuler (1972)		5.4-199		0.9-7.8	Industrial

[a]In mppcf.
[b]In mppcf; pre-1945 (for both mining and milling operations).
[c]In mppcf; 1946-1965 (for both mining and milling operations).
[d]In mppcf; 1966-1969 (for both mining and milling operations).
[e]In mppcf; 1972 (for both mining and milling operations).
[f]In mppcf; to 1955.
[g]In mppcf; 1956-1965.
[h]In mppcf; 1966-1972.

no free silica. Average dust concentrations in the mine were reported to range from 32 to 855 mppcf (six samples), whereas average mill exposures ranged from 17 to 1,672 mppcf (14 samples). The dust was reported to contain 70% talc, 20 to 30% dolomite, 10%

tremolite, and occasional fragments of free silica. The dust morphology was described as "bladed crystals." Highest exposures were in the bagging operation (Dreessen and Dalla Valle, 1935).

Occupational exposures to talc dust in mining and milling operations in St. Lawrence County, NY, have been studied. Talc deposits in the state have been found to differ significantly in mineral composition. Siegal et al. (1943) reported that talc in that area contained tremolite, anthophyllite, and only traces of quartz, and described the particle morphology as straight, needlelike fibers with a maximum length of 15 μm. Kleinfeld et al. (1973) also reported the major fibrous components of these talcs to be tremolite and anthophyllite. The mineral composition of other bulk samples of talc in the area revealed that the samples contained 14 to 48% talc, 37 to 59% tremolite (fibrous and nonfibrous), 4.5 to 15% anthophyllite (fibrous and nonfibrous), and 0.25 to 26% free silica (Dement and Zumwalde, 1979; Dement et al., 1980).

Kleinfeld et al. (1974) studied fibrous talc exposures in a mining and milling operation in St. Lawrence County, NY, during the period from 1945 to 1972. Prior to dust control measures such as wet drilling, average exposures to mine dust ranged from 120 to 818 mppcf; after 1945, these were reduced to 5 to 19 mppcf. Exposures in mills prior to 1945 ranged from 69 to 278 mppcf; average exposures in 1972 ranged from 7 to 36 mppcf. In 1972, optical fiber counts revealed that exposures in mines were low (2 to 3 fibers >5 μm/cm^3), whereas exposures in mills were severalfold higher, ranging from 25 to 62 fibers/cm^3 (Kleinfeld et al., 1974).

Time-weighted average exposures to respirable dust ranged from 0.23 to 1.29 mg/m^3 and from 0.25 to 2.95 mg/m^3 for mining and milling operations, respectively, in upper New York State (Dement et al., 1980). Analysis of the airborne samples revealed that 65% of the fibers in the talc dust >5 μm were anthophyllite fibers and 7% were tremolite fibers. Airborne fiber levels gave mean exposures in the mine and mill of 4.5 and 5.0 fibers >5 μm/cm^3, respectively, with peak values as high as 29.1 fibers/cm^3 in the mill (Dement and Zumwalde, 1979; Dement et al., 1980).

Concentrations of respirable dust in mass samples from three Vermont talc mines and mills were surveyed in 1975 and 1976. Geometric mean exposures to respirable dust ranged from 0.5 to 5.1 mg/m^3 in the mines and from 0.5 to 2.9 mg/m^3 in the mills; however,

exposures in the mills were generally higher than those in the mines. Optical fiber counts of as much as 60 fibers/cm^3 were reported. Subsequent analyses of these samples by scanning electron microscopy demonstrated rolled talc and elongated talc particles. X-ray diffraction analyses showed that talc and magnesite were the major (20 to 100%) mineral components. Trace amounts of free silica were found in 15% of the samples (Boundy et al., 1979; Wegman et al., 1982). One closed mine was reported to contain tremolite microinclusions, but its fibrosity was not documented (Selevan et al., 1979a,b).

The results of a cross-sectional study of occupational exposures in U.S. talc mines and mills were reported by Gamble et al. (1982). Work histories and personal respirable dust samples were compiled for 299 miners and millers in Montana, Texas, and North Carolina. The average time worked was 7, 6, and 10 years; and the average talc dust exposure was 1.2, 2.6, and 0.3 mg/m^3 in Montana, Texas, and North Carolina, respectively. No fiber was found in any sample of Montana talc; fibrous tremolite and antigorite were reported in Texas talcs (0.5 to 3.0 μm in diameter, 4 to 30 μm in length); talcs from North Carolina contained acicular cleavage fragments with particle length to diameter ratios as high as 100:1, with some <0.1 μm in diameter (Greife, 1980; Gamble et al., 1982).

Analysis of 362 personal samples of respirable dust collected over a full shift by the Mine Safety and Health Administration from talc mines and mills in the United States showed the median dust exposure to be 1.20 mg/m^3; 90% of all exposures were <2.78 mg/m^3 (National Institute for Occupational Safety and Health, 1979).

Talc exposure in the Germanasca and Chisone Valleys (Piedmont), Italy, were reported by Rubino et al. (1976). Prior to 1955, talc dust exposures were approximately 442 mppcf (range, 151 to 798 mppcf) in the mines and 23 mppcf (range, 19 to 35 mppcf) in the mills. The free silica content was 6% (range, 1 to 14%) in the mines and 1% (range, <1 to 2%) in the mills. Between 1956 and 1965, the average exposures in the mines and mills were 21 mppcf (range, 4 to 49 mppcf) and 13 mppcf (range, 8 to 23 mppcf), respectively. As a result of dust control measures, the average exposures dropped to 1.05 mppcf (range, 0.8 to 3 mppcf) and 5 mppcf (range, 2 to 8 mppcf) in the mines and mills, respectively, after 1965. Sample analyses of these talcs showed that small amounts of tremolite and silica fibers were present. Fiber counts >5 μm in length were 0.01 fibers/cm^3 for both the mines and mills.

Limited information was available about exposures in secondary industries where talc was used or processed further. Dement and Shuler (1972) collected personal air samples in a rubber band production plant, where housekeeping, ventilation, and work practices were poor and in which talc was used as an antistick agent. Time-weighted average respirable dust concentrations were 2.5 to 7.8 mg/m^3 (average, 4.8 mg/m^3) for extruders, 5.3 to 6.1 mg/m^3 for vulcanizers, and 0.9 to 1.3 mg/m^3 for cutters. Total dust exposures were found to range from 5.4 to 199 mg/m^3. The talc was reported to contain 2 to 3% silica fibers. Fiber exposures ranged from 4.7 to 19.2 fibers >5 μm/cm^3.

Sahle et al. (1990) characterized airborne dust in a soft-paper mill. Elongated fragments of talc were identified on transmission electron microscopy (TEM) micrography, structurally by electron diffraction, and compositionally by energy-dispersive X-ray fluorescence spectroscopy (EDX) analysis.

Fine et al. (1976) measured respirable dust concentrations in two rubber-manufacturing plants where Vermont talc was used as an antistick agent. Eighteen of 21 samples analyzed for free silica contained less than 1% by weight. In 12 samples analyzed for fibers, all concentrations were less than 2 fibers >5 μm/cm^3.

Hogue and Mallette (1949) studied two groups of specially selected workers for an assessment of talc dust exposure in two rubber plants utilizing Vermont talc. Only those workers who were exposed to the longest and heaviest concentration of dust were used. The investigators found that tube machine operators had an average exposure of 20 mppcf; tube "bookers," 35 mppcf; tube cure men, 15 mppcf; and "line rollers," 50 mppcf. The analyzed talc was free from fibrous impurities.

The National Institute for Occupational Safety and Health conducted two workplace exposure surveys. The National Occupational Hazard Survey (NOHS) conducted from 1972 to 1974 estimated the number of workers potentially exposed to chemical agents in the workplace in 1970 (NOHS, 1976). These estimates were derived from observations of the actual use of the agent, the use of trade name products known to contain the agent, and the use of generic products suspected of containing the agent. The NOHS estimated that 1,536,754 people were exposed to talc, with 14% exposed to the actual product, 31% exposed to trade name products containing talc, and 56% exposed to generic products suspected of containing talc.

The National Occupational Exposure Survey (NOES), conducted from 1980 to 1983, estimated the number of workers potentially exposed to chemical agents in the workplace in 1980 (NOES, 1984). Unlike NOHS, the NOES estimates were based only on observations by the surveyor of the actual use of the agent. NOES estimated that 18,872 workers, including 5,244 females, were potentially exposed to talc.

The American Conference of Governmental Industrial Hygienists has recommended an 8-h threshold limit value-time weighted average (TLV-TWA) of 2 mg/m^3 respirable dust for talc containing no asbestos fibers (American Conference of Governmental Industrial Hygienists, 1991), whereas the Occupational Safety and Health Administration has recommended a total dust TWA of 20 mppcf of air (International Agency for Research on Cancer, 1987).

Exposure to cosmetic grade talc as used in cosmetic and health care products is infrequent and of short duration (Hildick-Smith, 1976). However, due to the reported cases of accidental aspiration of excessive amounts of talc by infants and children, a simulated study was conducted to determine the amount of talc to which an infant and mother are exposed. Analysis of the data indicated that during a 10-s dusting period, the total median dust concentration is 0.243 mppcf, which decreases to an average of 0.124 mppcf during the 65 s required for the dust to settle. An estimated median exposure per application was estimated at 0.1752 mppcf. A further study showed that the average respirable dust concentration was 0.10 $mg/min/m^3$ when dust samples were obtained during actual use of talc by mothers (Hildick-Smith, 1976).

Russell et al. (1979) later conducted a study on the routine application of talcum powder to infants and adults to determine the mass concentrations of potentially respirable particles. The tests were conducted on 44 adults exposed to talc over the whole body area and on 48 infants exposed to talc in the diaper area only. The total exposure time, the amount of powder used, and the average airborne talc concentration in the nasal region were measured. For infant exposures, the TWA ($\pm$ the standard deviation) was 0.095 ± 0.039 $mg/min/m^3$. For adult exposures, the TWA was 1.729 $mg/min/m^3$. For a more accurate estimate of exposure, these values were converted to weekly exposure measurements. The average values obtained were 0.055 and 0.20 $mg/h/m^3$ for infants and adults, respectively.

2.5 AMBIENT LEVELS

No information was found in the available literature concerning ambient levels of talc.

2.6 ENVIRONMENTAL FATE

Talc is not expected to undergo chemical transformation when released into the environment. Its refractory nature precludes the effects of melting/boiling point, solubility, vapor pressure, octanol/water partition coefficient, etc., on its transport. Terrestrial and fluvial transport processes affecting talc are not well characterized.

2.7 ANALYTICAL METHODS

Because talc is frequently contaminated with a number of other mineral phases, some known to be biologically active, an analytical protocol is often required that can distinguish among these phases. As with most industrial exposures, nearly all measurements of talc made prior to approximately 1970 were done by collecting particles in an impinger and counting them by optical microscopy (Dreessen, 1933; Dreessen and Dalla Valle, 1935; Siegal et al., 1943; Kleinfeld et al., 1955, 1967, 1973, 1974; Messite et al., 1959; Rubino et al., 1976; Hogue and Mallette, 1949). More recent studies, however, have used gravimetric analysis followed by optical and/or electron microscopy fiber counts (Dement and Zumwalde, 1979; Dement et al., 1980; Boundy et al., 1979; Greife, 1980; Gamble et al., 1982; Dement and Shuler, 1972; Fine et al., 1976).

Phase contrast optical microscopy is a conventional technique for the identification of minerals. A microscope equipped with bright-field illumination and polarized light optics may be used to analyze talc powders (Hamer et al., 1976; Rohl and Langer, 1979). There are, however, limitations to this technique such as a restrictive resolution allowing large numbers of small fibers to go undetected and indices of refraction that are difficult to measure (Rohl et al., 1976). Analytical electron microscopy and selected-area electron diffraction can be used to obtain morphological, structural, and chemical information on single particles of talc and associated minerals (Rohl et al., 1976).

Quantitative mineralogical analyses by X-ray diffraction of bulk samples are sensitive to 1 to 2% talc (Pooley and Rowlands, 1977). The application of X-ray diffraction analysis, both continuous and step-scan modes, for quantitative determination of contaminating minerals in talc has been described. This includes the selection of talc and the reference materials, the preparation of standard dilutions of fibers in talc to ensure sensitivity and reproducibility, the selection of characteristic X-ray reflections to be scanned, and instrumental technique. Tremolite, chrysotile, and anthophyllite impurities in talc can be determined at levels as low as 0 to 1.2% (Rohl and Langer, 1974; Rohl et al., 1976).

3. TOXICOLOGY

3.1 RETENTION AND BIODISPOSITION

This section provides a review of the information on retention of talc following inhalation, oral, and vaginal administration. In addition, data on the biodisposition and clearance of talc from the body are presented.

The pulmonary deposition, translocation, and clearance of inhaled talc (Johnson's Baby Powder®) in Syrian Golden hamsters were studied by Wehner et al. (1977a,b). A group of 44 10-week-old female hamsters was exposed by nose only to neutron-activated talc aerosols for 2 h. The mean aerosol concentrations during the two sampling periods (from 15 to 30 min and from 60 to 90 min during the 2-h exposure period) were 40 and 75 mg/m^3. After exposure, the urine and feces were collected. Groups of four animals were killed at various times, and the lungs, liver, kidneys, ovaries, and skinned carcass were collected and radioassayed by X-ray spectrometry. The counts were compared with those obtained from nine unexposed control hamsters. Considerable variations in pulmonary deposition among animals killed at the same period were attributable to variations in aerosol concentration at the different tier levels for animal exposure and to differences in individual breathing patterns. It was estimated that animals placed on tier levels 2 to 4 of the exposure chamber inhaled an average of 360 μg talc, whereas those on tier 1 inhaled an average of 570 μg. Nonetheless, the data indicated high talc levels in lung during the first 4 days after exposure, with mean total measurements ($\pm$ standard deviation) of 33.1 $\pm$ 31 μg and 21.0 $\pm$ 15.3 μg at 15 min and 4 days after exposure, respectively. Thereafter, talc content in the lungs dropped gradually; mean values (3.7 $\pm$ 1.4 μg) were similar to those found in controls (2.3 $\pm$ 0.4 μg) after 4 mo. The "biological" half-life of the talc based on measurements of radioactivity deposited in the lung was reported to be 7 to 10 days, and alveolar clearance was complete within approximately 4 mo after exposure.

No significant differences were observed among mean radioactivity levels found in the liver, kidneys, and ovaries of exposed and control animals (Wehner et al., 1977b). Radioactive residues in carcasses were highest 4 h after exposure (455 $\pm$ 338 μg) and decreased gradually to control levels (about 3.5 μg) by Day 8. This activity was attributed to

talc deposited on or about the nose and nares during exposure, as well as to talc passing through the gastrointestinal tract after mucociliary clearance. Fecal samples contained relatively high quantities of talc. The mean mass of talc excreted by 21 h after exposure was 106 ± 53 μg; by Day 4, this value had increased by 3.5-fold (350 ± 292 μg). The presence of talc in the feces was attributed to mucociliary clearance from the lungs, probably together with a fraction from licking the nose, lips, and so forth. Low levels of radioactivity found in the urine were attributed to ^{60}Co leached from the lungs or absorbed in the gastrointestinal tract.

Wehner et al. (1977c) exposed groups of 50 male and 50 female 4-week-old Syrian Golden hamsters to talc aerosol (baby powder) for 3, 30, or 150 min/day, 5 days/week for 30 days. In a second study, 50 hamsters/sex (7-weeks-old) were exposed for 30 or 150 min/day either until they died naturally or for a maximum of 300 days. Following exposures, the animals were observed for the remainder of their lifespans. The mean concentration of the respirable aerosol fraction was approximately 8 mg/m^3, and the mass mean aerodynamic diameter (MMAD) was 6 μm. The estimated alveolar deposition-per-exposure ranges were as follows: 0.04 to 0.06, 0.4 to 0.6, and 2 to 3 μg talc for the 3-, 30-, and 150-min exposures, respectively, in the 30-day study, and 0.86 to 1.15 and 4.3 to 5.8 μg talc for the 30- and 150-min exposures, respectively, in the 300-day study (Wehner et al., 1977b).

Hanson et al. (1985) developed a method to determine the lung burden of talc in rats and mice after repeated inhalation exposure to talc aerosols. This method was based on the analysis of acid-insoluble magnesium (Mg) content in the lungs by atomic absorption spectrometry. Magnesium was selected because it accounts for 19.2% of the composition of talc, and most of the endogenous Mg present in the lung can be removed by dilute acids. Whole-body exposures of 36 Fischer 344 (F-344) rats (sexes combined) and 27 $B6C3F_1$ mice (sexes combined) were performed 6 h/day, 5 days/week for a total of 20 exposures. The mean lung burdens in rats were 77, 187, and 806 μg talc/g lung tissue at exposure levels of 2.3, 4.3, and 17 mg talc/m^3, respectively. In mice, mean lung burdens were 114, 325, and 1,150 μg talc/g lung tissue at exposure levels of 2.2, 6.3, and 20.6 mg talc/m^3, respectively. The higher contents of talc in mouse lungs, as compared to rats, were related to a difference in initial deposition probably due to a greater minute volume respiration in mice.

Pickrell et al. (1989) studied the relationship between the inhalation exposure concentration of talc and the resulting lung burdens and histologic lesions using groups of 20 F-344/control rats and 20 $B6C3F_1$ mice (10 male and 10 female) exposed to one of three concentrations of asbestos-free talc for 6 h/day, 5 days/week for 4 weeks. The mean exposure concentrations for rats were 0, 2.3, 4.3, and 17 mg talc/m^3. Lung burdens in rats averaged 0, 0.07, 0.17, and 0.72 mg talc/g lung after the 20-day inhalation exposure; thus, the amount retained in the lung per unit of exposure concentration increased with increasing concentration. Similar results were obtained for mice. Lung burdens for this study were used to project lung burdens that would result from longer exposure of rodents and humans. A model simulating chronic talc inhalation exposure of rats and mice predicted lung burdens of 2 to 3 mg talc/g lung (wet wt.) if the animals were exposed to 17 mg talc/m^3 for 2 years, and deposition and clearance of talc were unchanged by continued exposure. The model projected lung burdens that were significantly smaller than lung burdens that resulted from experimental exposures to talc of 10.8 mg/m^3 (Wagner et al., 1977). It is possible that the model did not account for changes in alveolar lung clearance which exhibit progressive inhibition starting at lung burdens $\geq$1 mg/gm lung. Humans exposed to aerosols of respirable talc are projected to accumulate much higher lung burdens than would occur in rodents exposed to the same aerosol, because humans have a higher estimated deposition fraction and slower estimated clearance of the deposited talc dust. Equilibrium lung burdens of $\geq$2 mg talc/g lung were predicted for human exposures at or near 2 mg talc/m^3.

In two studies with humans (Churg, 1983; Churg and Warnock, 1980), talc constituted approximately 16.0% of the nonasbestos fibers recovered from the lungs of 20 individuals with no history of occupational dust exposure. All subjects (11 men and 9 women) were selected from a general autopsy service. All were 40 years of age or older at the time of death. The average number of nonasbestos fibers was $106 \times 10^3 \pm 87 \times 10^3$ fibers/g wet lung, with no significant differences noted between men (96×10^3 fibers/g) and women (115×10^3 fibers/g). Similarly, no significant differences were noted between the 15 smokers (93×10^3 fibers/g) and 5 nonsmokers (140×10^3 fibers/g). A total of 13 different mineral groups other than asbestos were identified, of which apatite, gypsum, talc, silica, and attapulgite accounted for more than half the fibers. Silica was found in the lungs of all 20 subjects and talc in 19 of 20. About 86% of all fibers (71% for talc) were

shorter than 5 μm, and most had aspect ratios less than 15. In addition, the mean number of nonasbestos fibers was similar to the number of asbestos fibers (102×10^3/g wet lung) found in these subjects, with chrysotile accounting for more than 80% of the asbestos fibers (Churg, 1983; Churg and Warnock, 1980).

Several studies have been conducted to determine the metabolism of talc powder following oral administration (Phillips et al., 1978; Wehner et al., 1977a). Little, if any, is absorbed from the gastrointestinal tract following oral intubation of rats, guinea pigs, mice, and hamsters; most of the material is eliminated in the feces within 1 or 2 days after dosing. These studies will not be discussed further.

Wehner et al. (1986) examined the migration of talc from the vagina in monkeys. Six female exbreeder cynomolgus monkeys each received 30 intravaginal talc applications, consisting of 125-mg neutron-activated powder per application, over a 45-day period. Doses were equivalent to 29 to 52 mg talc/kg/day, depending on the animal's body weight. Six untreated females served as controls. Animals were between 4 and 12 years of age and weighed between 2.4 and 4.35 kg. The radioisotopes ^{46}Sc, ^{60}Co, ^{59}Fe, and ^{51}Cr were used as tracers for the administered talc. Two days after the final application, abdominal lavage fluid, ovaries, oviducts, uterus, and vagina with cervix were collected for X-ray analysis. Only the vagina with cervix samples from dosed animals contained talc tracers. The authors concluded that despite repeated applications to the fornix of cynomolgus monkeys, no measurable quantities (i.e., greater than 0.5 g) of talc translocated to the uterus or beyond.

In contrast, Henderson et al. (1986) reported that talc particles introduced into the uterus and vagina of the rat migrated to the ovaries. Eight female exbreeder (age 7.5 mo) Sprague-Dawley rats each received an intravaginal dose of 250 μL of a talc-saline suspension (100 mg talc/cm^3). Four of the rats received additional uterine instillations on Days 6 and 15, and two of these rats were treated again on Days 22 and 30. Ovaries were removed from all animals at the time of sacrifice (Days 56, 20, and 49, respectively). In a separate experiment, six Sprague-Dawley exbreeders were given 250 μL of the same talc suspension, and an additional six rats received the saline vehicle only. Two animals from each of these groups were sacrificed at 24, 49, and 96 h after treatment; ovaries were removed as before. Talc particles were recovered from the ovaries of all animals given intrauterine doses of the

test material and from the two rats that were killed 96 h after intravaginal instillation. No talc was found in the ovaries of the other treated or untreated animals.

In summary, the pulmonary deposition of talc following repeated exposure is dose dependent. Following single inhalation exposures, alveolar clearance is slow, with a biological half-life of 7 to 10 days. Talc is cleared by mucociliary action from the lungs and eliminated in the feces via the gastrointestinal tract. Results of studies that investigated the migration of talc from the vagina are equivocal.

3.2 ACUTE TOXICITY

There was no information in the available literature on the acute toxicity of talc. However, intratracheal instillation of talc has been shown to result in pulmonary toxicity in hamsters (Beck et al., 1987). Groups of six hamsters (sex and strain not specified) were given single intratracheal injections of talc (mean diameter, 0.8 μm) suspended in 0.9% saline containing 13.3 g/cm^3 rabbit surface active material (SAM) at concentrations of 0.15, 0.75, or 3.75 mg/100 g body weight. Controls received saline plus SAM. The pulmonary responses were quantified by measuring biochemical and cellular indicators of injury in the bronchoalveolar lavage (BAL) fluid. One day after talc instillation, elevated enzyme levels, pulmonary edema, and increased cell numbers in the BAL fluid (red blood cells, macrophages, and polymorphonuclear leukocytes) were noted. Persistent elevation of enzyme levels and inhibition of phagocytosis were also noted in a group of four hamsters receiving 3.75 mg/100 g body weight which were killed 1, 4, 7, and 14 days after administration.

The biochemical response of rabbit cartilage tissue to talc-induced synovitis was investigated by Gershuni et al. (1981). In this study, approximately 0.25 cm^3 of a talc-saline suspension was injected into the right hip of 30 immature (age 1 mo) New Zealand White rabbits (sex and weight not specified). Left hips and saline-injected animals served as controls. Groups of rabbits were sacrificed 1, 2, 3, and 4 weeks after injection. Sections of cartilage were removed, and levels of water, hexuronic acid, hexosamine, and collagen were measured. Cartilage thickness was measured directly on corresponding hemisections from left and right femoral heads. Significant ($0.05 < p < 0.005$) swelling of the medial joint space of the right hip was apparent in treated animals at all sacrifice intervals. Water content

was significantly ($p < 0.05$) increased at Weeks 1 and 2; hexuronic acid and hexosamine content were decreased ($p < 0.05$), but only at the end of the first week. Collagen content was not affected. The 15% increase in cartilage thickness (compared with control cartilage thickness) could not be attributed solely to the 3% increase in hydration. The authors concluded that the talc-induced synovial inflammation caused a local increase in temperature, hyperemia, and venous congestion that, in turn, facilitated anabolic cellular activity and increased production of cartilage.

3.3 SUBCHRONIC AND CHRONIC TOXICITY AND CARCINOGENICITY

This section provides a review of the data on the systemic toxicity and carcinogenicity of talc given by various routes of administration.

3.3.1 Inhalation Exposure

Wagner et al. (1977) exposed groups of male and female Wistar rats to a dust cloud containing 10.8 mg/m^3 talc (mean respirable concentration) for 3 mo (24/sex), 6 mo (12/sex), or 12 mo (12/sex). Equal numbers of rats remained unexposed as cage controls or were exposed to 10.8 mg/m^3 chrysotile asbestos as positive controls. Exposure was for 7.5 h/day, 5 days/week. The test material (Italian 00000 grade) contained approximately 92% talc, 3% chlorite, 1% carbonate minerals, and 0.5 to 1.0% quartz by weight. The remaining 3.0 to 3.5% was not defined. Particle size ranged up to 70 μm but averaged 25 μm; 40% of the talc cloud was respirable, and only 2% was fibrous. An unspecified number of rats from each group was sacrificed at 10 days and 1 year after the end of each exposure period, and the remaining rats were observed for life.

The severity of fibrosis produced was similar for the talc- and asbestos-exposed groups, ranging from minimal to slight. Evidence of progression in severity was seen as the exposure length increased and after the exposure was discontinued in animals exposed for 6 and 12 mo. The severity of fibrosis was graded on a 7-point scale (1: nil, 2: minimal, 4: slight, 8: severe). The average scores were 2.2, 2.7, and 3.4, respectively, at the end of the 3-, 6-, and 12-mo exposure periods for talc, and 2.4, 3.4, and 4.6 by 1 year. Scores for

controls ranged from 1.3 to 1.9. One of 48 rats exposed to talc developed a pulmonary adenoma, and 7 of 48 asbestos-exposed rats developed pulmonary tumors. No pulmonary tumors were noted in 48 control rats. These results suggest that exposure levels were near the maximum tolerated dose (MTD); however, an inadequate number of animals was used.

Pickrell et al. (1989) report a study discussed in Section 3.1 indicating that for various talc exposures, no clinical signs in rats or mice were seen prior to sacrifice at the end of the 20-day exposure. Also, histologic alterations in lung tissue consisted of only a modest, diffuse increase of talc-containing free macrophages within alveolar spaces in both rat and mouse groups exposed to the highest level of talc (17 to 20.4 mg talc/m^3) for 20 days.

3.3.2 Intratracheal Administration

Trautwein and Helmboldt (1967) studied the pulmonary effects of talc after intratracheal instillation into chinchillas. Groups of male and female chinchillas received intratracheal instillations of 2 mL of a 2% suspension of talcum powder (purified $Mg_3Si_4O_{11}H_2O$; particle size not specified) in saline. Controls were treated similarly to test animals and received 2 mL of saline per injection. The study consisted of three experiments. In the first, 14 chinchillas received injections on study Days 1, 20, 50, 70, and 90, and were killed 11 months after the last injection. A second group of 24 animals received a single intratracheal injection; two animals were killed 24, 48, 72, and 120 h and 1, 2, 3, 4, 6, 17, and 28 weeks, postdose. The last group of 18 animals received 11 weekly intratracheal injections for 10 weeks, and chinchillas were killed 1, 2, and 3.5 mo after the last injection.

Several animals died during the study from the acute effects of talc exposure. All of these animals exhibited some form of pneumonia caused by talc accumulation in the lungs. Two animals from the first experiment died 3 days after the initial injection from acute suppurative pneumonia. Five animals died from the third experiment: two from proliferative and exudative pneumonia after 12 and 21 days (these animals received two and three injections, respectively), and three from extensive granulomatous pneumonia between 41 and 46 days after the initial talc injection. Results indicated that talc caused exudative pneumonia that developed into proliferative, granulomatous pneumonia. The granulomas consisted of multinucleated foreign body giant cells that surrounded or engulfed the talc particles. Several stages of transformation were noted in alveolar lining cells located only in areas of talc

deposition or in close proximity to granulomas. Initially, swelling of alveolar epithelial cells was noted. This was followed by hyperplasia and progressed to epithelialization. Finally, columnar cells appeared, lining the affected alveoli and imparting an "adenomatous appearance." No fibrosis was noted in talc-injected or control animals. Furthermore, single or multiple injections resulted in the same tissue reactions.

Stenback and Rowland (1978) treated two groups of 24 male and 24 female hamsters with 18 intratracheal instillations, once weekly, of talc (3 mg) or talc plus benzo[*a*]pyrene (B[*a*]P) (3 mg talc + 3 mg B[*a*]P); controls received saline only or were untreated. The repeated instillation of talc plus B[*a*]P produced papillomas, squamous cell carcinomas, and undifferentiated tumors of the larynx, trachea, and lungs. Talc alone produced only minor respiratory disorders. In some cases, pulmonary congestion and interstitial fibrosis was noted; however, there was no granuloma formation or signs of neoplastic transformation.

In a subsequent chronic study by Stenback et al. (1986), groups of 48 Syrian hamsters received weekly intratracheal instillations of 3 mg talc alone or in combination with 3 mg B[*a*]P in saline for life. The talc sample consisted of 64 to 66% SiO_2 and 34 to 36% MgO, and 54% of the talc granules had a particle size of < 10 μm. Dust-laden macrophage aggregation and accumulation of interstitial cells and histiocytes were noted in hamsters exposed to talc alone. There were also increases in fibrillary material (elastic fibers) surrounding alveolar and interstitial spaces, and some accumulation of proteinaceous exudate within the alveoli. However, no fibrosis or granulomas were observed in talc-exposed hamsters. Talc alone caused moderate tissue destruction, slight metaplasia, and no dysplasia in the tracheobronchial zone; moderate hyperplasia was seen in the alveolar zone. Talc plus B[*a*]P resulted in moderate destruction, moderate metaplasia, and severe dysplasia in the tracheobronchial zone, and severe hyperplasia and dysplasia in the alveolar zone. Talc alone did not induce tumors in hamsters but, when given in combination with B[*a*]P, was found to be an effective cocarcinogen, inducing an increased incidence of tumors in both the upper and lower respiratory tract when compared to talc or B[*a*]P alone. There was a high incidence of peripheral (alveolar) lung tumors, and adenocarcinomas were the predominant tumor type.

3.3.3 Intraperitoneal Administration

In a study by Styles and Wilson (1973) that was designed to compare the in vitro cytotoxicity with in vivo fibrogenesis of several synthetic and mineral fibers, a single intraperitoneal injection of 50 mg/kg talc into Wistar rats (sex not specified) resulted in the development of a granulomatous reaction that consisted of the aggregation of foreign body giant cells containing talc particles 1 mo after administration. The lesions were still evident 3 mo after injection, but no fibrosis was evident. In this study, talc was found to have low in vitro cytotoxicity, resulting in the death of less than 2% of peritoneal macrophages following phagocytosis.

Kaiser et al. (1982) reported the development of foreign body granulomas, with adhesions, in male and female Wistar rats 12 weeks after intraperitoneal injection of talcum (dose and composition not specified). The development of foreign body granulomas has also been reported in swine (Migaki and Garner, 1969). The lesions found in the inguinal canal of four castrated male swine consisted of talc-containing epithelioid and giant cells, lymphocytes, and fibrous tissue. The pigs were thought to have been exposed to talc during castration, but the exposure period was not reported.

The tissue response to talc was also studied in rats by Pelling and Evans (1986). Talc (50 mg) was implanted surgically into the peritoneal cavity of 60 male Sprague-Dawley rats. Sham-operated rats served as controls. Animals were killed 2, 4, 8, 13, 26, and 52 weeks after implantation and examined. Talc produced extensive granulomatous peritonitis within 2 weeks that persisted until Week 13. Numerous focal lesions described as discrete pale nodules were observed in all animals receiving talc (100% incidence). These nodules were still apparent 52 weeks after exposure. Both control and talc-exposed animals developed adhesions. The animals receiving talc, however, had a significantly increased incidence ($p < 0.001$) of adhesions over the entire time period when compared with control rats. Histologically, the lesions consisted of granulomas containing dust-laden macrophages and dust-laden multinucleated giant cells with some collagen formation.

No tumors were found after four intraperitoneal injections of 25 mg in 40 female Wistar rats (Pott et al., 1974) or after a single intraperitoneal injection of 20 mg talc in 24 Swiss mice (Oezesmi et al., 1985) when these animals were observed for life.

3.3.4 Other Administration

Single intrapleural administration of 40 mg of talc to Osborne-Mendel rats (Stanton et al., 1981) or 20 mg of talc to Wistar rats (Wagner et al., 1977) did not result in tumor induction after lifetime observation.

Ingestion of talc (100 mg/rat/day) for 101 days resulted in the development of leimyosarcoma of the stomach in 1/32 Wistar rats observed for life (Wagner et al., 1977). No controls developed tumors.

Hamilton et al. (1984) injected talc (10 mg) intrabursally on the surface of ovaries of rats; the animals were observed for 18 mo. No tumors were found.

3.3.5 Summary

In summary, talc exposure generally results in a typical granulomatous lesion consisting of dust-laden multinucleated foreign body giant cells, as well as some fibrosis with collagen formation in several animal species. In addition to the development of granulomas, intratracheal instillation of talc results in moderate tissue destruction in hamsters, and intraperitoneal administration has been shown to cause abdominal adhesions in rats and swine.

Talc is not carcinogenic following inhalation exposure or intraperitoneal, intrapleural, or intrabursal administration to rats, hamsters, and mice. However, these studies are not fully adequate to evaluate the carcinogenic potential of talc. Oral administration of talc did result in a leimyosarcoma of the stomach in 1/32 rats. Evidence from two studies suggests that talc may be an effective co-carcinogen when administered intratracheally with B[*a*]P. A summary of the carcinogenicity studies with talc appears in Table 3-1.

3.4 DEVELOPMENTAL AND REPRODUCTIVE TOXICITY

No information on the developmental or reproductive toxicity of talc was found in the available literature.

TABLE 3-1. SUMMARY OF CARCINOGENICITY STUDIES ON TALC

Route	Species/Strain	Dosage/Duration	Particle Size	Comments	Reference
Inhalation	Rat, Wistar	10.8 mg/m^3 7.5 h/day, 5 days/week, 6 or 12 mo	Mean: 25 μm	No tumors	Wagner et al. (1977)
Inhalation	Hamster, Syrian	8 mg/m^3 2.5 h/day, 5 days/week, 300 days	Mean: 6 μm	No tumors	Wehner et al. (1977a,b)
Intratracheal	Hamster, Syrian	3 mg, weekly for life	Particle size: <10 μm	No tumors	Stenback et al. (1986)
Intrapleural	Rat/F, Osborne-Mendel	40 mg, 1× injection	Log fibers/mg ≤0.25x >8 μm	No tumors	Stanton et al. (1981)
Intrapleural	Rat, Wistar	20 mg, 1× injection	Mean: 25 μm	No tumors	Wagner et al. (1977)
Intraperitoneal	Rat/F, Wistar	25 mg, 4× injection	Size not characterized	2.5% tumor incidence	Pott et al. (1974)
Ingestion	Rat, Wistar	100 mg/rat/day for 101 days	Mean: 25 μm	1/32 developed stomach tumor	Wagner et al. (1977)

3.5 MUTAGENICITY AND CYTOTOXITY

The mutagenicity of talc has been studied in gene mutation assays involving *Salmonella* or *Saccharomyces*, in addition to chromosomal aberration in rat bone marrow cells and dominant lethal mutation assays. This section also reviews the cytotoxicity data from in vitro assays, intratracheal instillation of talc, monolayer cultures of tracheal epithelial cells, suspensions of sheep erythrocytes, and preparations of phospholipid-cholesterol vesicles.

Lord (1978) reported that Litton Bionetics, Inc., evaluated talc for mutagenicity in 1973. There were no increases in gene mutation in *Salmonella* or *Saccharomyces* at 200 mg/cm^3, and no increase was reported for chromosomal aberrations in rat bone marrow cells or for dominant lethal mutation in the germinal cells of male rats exposed to 30, 300, or 3,000 mg/kg. Study details were not available.

In vitro cytotoxicity assays conducted with natural or acid-purified talc (diameter from 0.2 to 20 μm) indicate low-level cytotoxic activity in peritoneal and alveolar macrophages from Wistar rats (Styles and Wilson, 1973), which corresponded to the minimal toxicity exhibited by talc in vivo. It is noteworthy that within 1 h of exposure, approximately 50% of the treated macrophages contained talc particles. Other investigators have reported that talc particles (50 μg/mL) within a respirable range were not cytotoxic to V79-4 or A549 cells (Chamberlain and Brown, 1978).

In contrast, intratracheal instillations of asbestos- and quartz-free Vermont talc (0.15, 0.75, or 3.75 mg/100 g body weight; median aerodynamic diameter 7.5 μm, calculated using known relationships) produced a dose-related cytotoxic effect in hamsters, as evidenced by elevated lactate dehydrogenase, β-N-acetylglucosaminidase, and peroxidase levels in BAL (Beck et al., 1987). Cellular damage was also indicated at 1-day postexposure by significantly increased BAL albumin levels in high-dose animals when compared with controls.

The effects of silica and talc on cellular and artificial membranes were examined using three test systems: monolayer cultures of tracheal epithelial cells, suspensions of sheep erythrocytes (sRBCs), and preparations of phospholipid-cholesterol vesicles (Woodworth et al., 1982). Each mineral preparation was at least 99% pure, and approximately 60 to 70% of the talc or silica fibers were 3.0 μm or smaller. Particles were suspended in veronal-buffered 0.95% sodium chloride and added to the test systems at concentrations ranging from

0.003 to 20.0 mg/cm^3. Activity was monitored via radiolabeled sodium chromate (specific activity of ^{51}Cr, 200 to 500 Ci/g). At the end of a 24-h incubation period, both minerals were cytotoxic to the tracheal epithelial cells. Phagocytosis of talc and silica particles was evident within 4 h, and cells containing talc or silica demonstrated retraction of lamellipodial extensions, surface blebbing, and morphological changes. Release of ^{51}Cr by tracheal epithelial cells was higher for cells exposed to 0.1 mg/cm^3 silica (20%) and talc (35%) than for nonexposed cells. As talc and silica concentrations increased from 1 to 20 mg/cm^3, percent hemolysis of sRBC increased steadily from approximately 5 to 90% following a 60-min incubation period. Membrane distortion and sRBC ghosts were observed. Percent spontaneous leakage of [^{51}Cr]chromate from liposomes and liposomes exposed to 10 mg silica particles/cm^3 was approximately 4 to 6%; following a 1-h exposure to 10 mg talc/cm^3, chromate release rose to about 20%, suggesting an increased permeability of the liposomes.

In conclusion, limited evidence suggests that there is no mutagenicity from talc in *Salmonella* or *Saccharomyces*, no chromosomal aberrations in rat bone marrow cells and no dominant lethal mutation in germinal cells of male rats. Low-level cytotoxicity was reported in rat alveolar macrophages but not in V79-4 or A549 cells. Intratracheal instillation of talc produced a dose-related cytotoxic effect. Cytotoxicity was also observed in cultures of tracheal epithelial cells, sRBCs, and phospholipid-cholesterol vesicles.

3.6 EFFECTS ON HUMANS

3.6.1 Cross-Sectional Studies, Clinical Evaluations, and Case Reports

The health effects of talc in humans, studied in cross-sectional studies, clinical evaluations, and case reports, are reviewed in this section with reference to the consequence resulting from pulmonary, dermal, intrapleural, surgical, intravenous administration, and ingestion.

3.6.1.1 Respiratory Effects

In general, most silicates such as talc were considered harmless until Dreessen and Dalla Valle (1935) studied the health effects of exposure to talc at two mining milling operations in Murray County, GA. Analysis of the talc deposits showed them to consist of talc as fibrous

splinters, fibrous aggregates, and foliated masses (70%), dolomite as broken rhombs (20 to 30%), and tremolite in two samples as bladed crystals (10%). No quartz was found except for occasional fragments. Physical examinations were performed on 66 talc workers; 33 mill workers were exposed to ≥300 million particles per cubic foot (mppcf), 13 miners were exposed to an average of 135 mppcf, and 20 additional workers were exposed to an average of 17 mppcf. Twenty-nine workers (44%) had worked less than 5 years, 18 (27%) worked 5 to 9 years, 13 (20%) worked 10 to 14 years, and 6 (9%) worked 15 years or more. Sixteen of the 33 mill workers in the higher dust groups were diagnosed as having pneumoconiosis: eight were classified as Stage I, five were Stage II, and three were Stage III. Five persons in this group were diagnosed as having pneumoconiosis plus tuberculosis. The miners showed no evidence of advanced pneumoconiosis, although 6 out of 13 men were Stage I. Workers in the lowest exposure category were negative for pneumoconiosis.

In a study designed to investigate the health effects associated with exposure to pure talc, Hogue and Mallette (1949) examined two groups of workers from two rubber plants: One group was composed of 20 men exposed to talc alone (21 ± 10 mppcf) for periods ranging from 10 to 36 years, whereas the second group consisted of 20 men with a major exposure to whiting and minor exposure to pyrophyllite and talc (58 ± 24 mppcf) ranging from 10 to 25 years. Physical examinations and chest roetgenograms of men from the group exposed to talc alone were normal. Workers in the second group were also normal, with the exception of one man with Stage III pneumoconiosis who had the highest dust exposure of the two groups (150 mppcf) and a previous occupational history of 5 years in mining. The study suggested that exposure to talc alone does not produce pathological changes in the lungs.

Negri et al. (1989) noted an increased relative risk (RR) for pleural cancer in a northern Italian cohort of rubber workers. The authors considered a possible link to fibers containing talc in tire manufacturing and storage, but also considered possible asbestos exposure related to prior work experience or to the mechanical maintenance job category that had the highest RR by job category. The data do not allow any conclusions.

Fine et al. (1976) conducted pulmonary function tests, performed chest X rays, and sent respiratory questionnaires to 80 talc workers and 189 controls (nonexposed rubber workers) from three rubber tire manufacturing plants. There were no important differences between

the exposed and control groups with regard to age, cigarette smoking, past occupational exposure, and socioeconomic and ethnic factors. Environmental sampling indicated that exposure for the majority of jobs was under 1 mg/m^3. The maximum lifetime exposure was estimated to be below 60 mppcf-years, and the average lifetime exposure was estimated as less than 20 mppcf-years. The talc was characterized by a low content of silica and fiber (18 in 21 samples contained less than 1% free silica). The 12 samples counted for fibers showed less than 2 asbestos fibers/cm^3. None of the workers had severe dyspnea or talc pneumoconiosis; however, the talc workers had a significantly ($p \leq 0.05$) greater prevalence of productive cough and positive criteria for chronic obstructive lung disease than control workers. Workers with greater than 10 years of exposure had impaired ventilatory function. The forced expiratory volume in 1 s ($FEV_{1.0}$) was significantly decreased ($p \leq 0.02$). Multiple regression analysis of $FEV_{1.0}$ in talc workers suggested that for each year of exposure, a talc worker suffers a 26 cm^3 loss of $FEV_{1.0}$ in excess of that related to age and cigarette smoking.

The results of a study of 93 New York miners and millers exposed to talc containing tremolite and anthophyllite fibers indicated increased respiratory symptoms, abnormalities detected by X-ray examinations, and decreased pulmonary function when compared with a population of potash miners (Gamble et al., 1979). Among the talc workers, higher respiratory symptom rates were found for those who had worked for less than 15 years than for those with 15 years or more of employment. However, most of the workers with symptoms were either smokers or ex-smokers. Mean pulmonary function values ($FEV_{1.0}$, forced vital capacity, and maximum respiratory flow at 50 and 75% of VC) of talc workers were significantly decreased in comparison to those of the potash workers. These decreases remained after controlling for age, height, smoking, and number of years of employment. An association was found between decreased pulmonary function and fiber and particulate exposure and the number of years worked. The prevalence of pleural calcification and pneumoconiosis in talc workers with 15 or more years of employment was higher than in potash miners. The greatest difference between the two groups was the increased prevalence of pleural thickening in talc workers. Among the talc workers, pleural thickening occurred in 1.6% of workers with less than 15 years of employment and in 31% of those with more than

15 years employment. Corresponding values for potash miners were 0.5% and 4.0%, respectively.

Fitzgerald et al. (1991) conducted a case history study of radiographic chest abnormalities in a talc-mining region of upstate New York. Chest X rays taken between April 1, 1982, and March 31, 1983, for 4,280 male and 5,160 female residents (age 40 and above) of St. Lawrence or Jefferson Counties were examined. The prevalence rate of confirmed pleural changes and/or parenchymal fibrosis was 3.8% (i.e., 355 of 9,442 patients). Men were 12 times more likely to exhibit parenchymal abnormalities and 5 times more likely to show pleural changes than were women. Of the 355 patients whose radiographs were confirmed positive by the beta-reader, 306 (or their next-of-kin) were interviewed. Occupational distribution of the cases was compared to that for men in both counties according to the 1960 U.S. Census. Two-thirds of the cases were at least age 60, and 86.5% were men; approximately 70% had smoked cigarettes at some time during their lives. Sixty percent reported occupational exposure to asbestiform minerals for at least 1 year. More than one-third of the cases had worked in talc mining and milling industries, and one-quarter had been employed in construction trades. In contrast, the U.S. Census indicated that only 2.4% of men in these counties engaged in such employment in 1960. The results also suggest no evidence of widespread radiographic abnormalities resulting from ambient dust exposure.

A cross-sectional study of 299 workers from Montana, Texas, and North Carolina, who were exposed to talc containing low levels of silica and tremolite and antigorite fibers, was conducted by Gamble et al. (1982). The mean age of the study population was 40, and the mean duration of exposure to talc dust was less than 10 years. The average concentration of airborne dust ranged from 0.28 to 2.64 mg/m^3. Respiratory symptoms did not show any consistent association with years worked or cumulative exposure. There were no significant increases in pneumoconiosis among the study group or significant reductions in lung function. An increased prevalence in bilateral pleural thickening was found in some exposed workers. The prevalence was related to age and smoking habits and was greater (23%) in those employees working 10 years or more when compared with those working less than 10 years (2.5%). Moreover, workers with bilateral pleural thickening had higher average and

cumulative exposures than those with no pleural thickening. All pulmonary function values of these affected workers were reduced when compared with those of unaffected workers.

Evidence of fibrosis in workers exposed to talc containing minimal amounts of crystalline silica and asbestiform minerals was reported in a pulmonary pathology study by Vallyathan and Craighead (1981). Pulmonary tissue from seven deceased Vermont talc workers exhibited various degrees of pulmonary fibrosis. The severity of the fibrosis increased with duration of employment and concentration of heavy mineral deposits in fibrotic lesions of the lung. X-ray crystallographic studies of lung digestates revealed that the predominant mineral in the lungs was talc.

A study of 202 talc (purity not specified) workers in India showed a significant increase ($p < 0.001$) in respiratory symptoms among the workers when compared to 101 matched control subjects of the same socioeconomic status but not engaged in any dusty trade (Bachani and Agarwal, 1985; Bachani, 1984). Exposure levels were not reported. Signs and symptoms included pain and burning of the nose and throat, increased phlegm production, difficulty in breathing, and chest pain. Clinical examinations revealed a higher number of workers with nasal and pharyngeal mucosal congestion and scattered rhonchi. Over 13% of the workers and 9% of the controls had clinical evidence of chronic airflow limitation (CAL). The prevalence of CAL was related to age and smoking history. A positive correlation was found between the prevalence of CAL and duration of exposure to talc dust. In addition, the presence of eosinophils in sputum samples of 13 of 38 workers and none in the control subjects suggested that talc exposure may induce an allergic-type pathology.

Changes in ventilatory functions in response to industrial grade talc dust exposure (no levels given) were investigated in 202 workers (Damodar et al., 1983). Smoking habits were graded by duration in years times frequency per day. Forced vital capacity, $FEV_{1.0}$, and FEV% were measured. All indices decreased with increasing age, intensity of smoking, and duration of exposure. A significant decrease in pulmonary function was found for workers who smoked compared with control subjects who smoked. No significant difference was found between workers and control subjects who did not smoke. The authors postulated a complementary effect of smoking on talc-induced changes in lung function.

A cross-sectional study of the respiratory function of 116 Vermont miners and millers of talc ore, free from asbestos and silica, was performed by Wegman et al. (1982). Exposure

levels were found to be below 3.0 mg/m^3 respirable dust with a geometric mean exposure of 1.8 mg/m^3 respirable dust. In addition, a 1-year followup evaluation of pulmonary function was performed on 103 workers. A significant reduction in pulmonary function was found in workers who smoked. After adjusting for smoking, the effect of exposure to talc was not statistically significant, although there was evidence of an exposure-related effect in workers with an annual dust exposure of 1.5 mg/m^3. Effects on pulmonary function in nonsmokers were not associated with exposure. Talc exposure was also associated with small, rounded, and irregular opacities seen on chest X rays. An annual loss in pulmonary function occurred in the workers at a rate greater than expected. However, the loss did not correlate with exposure to talc dust.

A microscopic analysis of the lung and lymph node dust samples from 12 deceased Austrian workers occupationally exposed to talc dust revealed a slightly increased concentration of real fibers and elongated particles in comparison to normal individuals (Friedrichs, 1987). The ratio of length to diameter was inconsistent throughout the diameter range examined and was not comparable to that found in asbestos workers with mesothelioma. It was concluded that the carcinogenic potential of the fibers was not very high, because neither of the two factors postulated to be important in assessing the carcinogenic hazard of a fiber (i.e., increased numbers of very fine fibers <0.01 m in diameter and high numbers of fibers in the Stanton range) appeared to be related to the disease state.

Talc is considered to be hazardous when inhaled in large quantities. The hazard is acute in cases of accidental inhalation and chronic in cases of industrial exposure or prolonged use of commercial products. However, since talc is not always a uniform substance, the association between talc exposure and adverse health effects may be related in some instances to the presence of contaminating minerals such as asbestos and silica. Most reports describing acute and chronic effects of talc exposure include little characterization of the talc involved.

Infants and small children have died from cardiorespiratory arrest, pulmonary edema, and pneumonia within hours after inhaling talcum powder (Cotton and Davidson, 1985; Motomatsu et al., 1979; Gould and Barnardo, 1972; Anonymous, 1969). The powder dries the mucous membranes of the bronchioles, thus disrupting pulmonary clearance and clogging

the small airways. Victims usually display dyspnea, tachypnea, tachycardia, cyanosis, and fever. Bronchopulmonary lavage is not effective, since talc is insoluble in water. Gould and Barnardo (1972) described the case of a 7-year-old girl who survived a massive aspiration of powdered talc and later developed bronchiectasis of the left lung.

Hollinger (1990) states that if talc is taken in via the airway, it acts as a pulmonary irritant producing acute symptoms, typically including cough, dyspnea, sneezing, vomiting, and cyanosis. Inhalation of talc can lead to complete obstruction of the small airways, resulting in respiratory distress syndrome. Hollinger (1990) states that in view of the questionable efficacy of talc and its potential for producing pulmonary toxicity, there are no compelling indications for use of talc-based topical powders for infants. A more desirable alternative would be the substitution of appropriate creams and lotions.

Lund and Feldt-Rasmussen (1969) described the case of a child who survived a massive aspiration of talc but only after exhibiting cyanosis, tachypnea with intercostal retractions, and tachycardia. There was fine crepitation over the lungs, and X rays revealed signs of bronchitis and peribronchitis with atelectases. Clinical treatment provided a gradual regression back to normal.

In addition to the effects of a massive acute inhalation, cases of talc pneumoconiosis or chronic sarcoidosis characterized by foreign body granulomas and interstitial fibrosis have been reported as a result of chronic use of cosmetic talcum powder (Tukiainen et al., 1984; Wells et al., 1979). Signs and symptoms included dyspnea, productive cough, and weakness. Abnormal chest radiographs and decreased pulmonary function were also observed.

Increased respiratory symptoms, higher prevalence of pleural thickening or calcification and pneumoconiosis, and decreased pulmonary function have been reported in workers exposed to talc containing various amounts of tremolite, anthophyllite, or silica fibers. The extent of these effects increased with age of workers, intensity of smoking, and duration of exposure. These effects were less pronounced with exposure to talc free of asbestiform fibers. In cases of accidental inhalation of large quantities of talc, victims usually display dyspnea, tachypnea, tachycardia, cyanosis, and fever. Signs of bronchitis and peribronchitis with atelectases are noted. Chronic use of cosmetic talcum powder can result in talc pneumoconiosis or chronic sarcoidosis with foreign body granulomas and interstitial fibrosis.

3.6.1.2 Effects From Dermal Application

An analogy between asbestos-induced mesotheliomas and talc-induced ovarian cancers was originally based upon the close relationship between talc and asbestos. Additional supporting evidence for this analogy is derived from the similarity in origin and histology between mesotheliomas and ovarian cancers (Longo and Young, 1979).

In a case-control study of 215 white females with epithelial ovarian cancers and 215 controls from the general population, 92 in 215 (42.8%) cancer cases regularly used talc either as a dusting powder on the perineum or on sanitary napkins compared with 61 in 215 (28.4%) of controls (Cramer et al., 1982). The relative risk adjusted for parity and menopausal state was 1.92 ($p < 0.003$). A total of 32 in 215 (14.9%) of cancer cases regularly used talc both on the perineum and on sanitary napkins compared with 13 in 215 (6.0%) of the controls. Women with both exposures, therefore, had the greatest adjusted relative risk of 3.28 ($p < 0.001$).

An extraction-replication technique (Griffiths et al., 1973; Henderson, 1972; Henderson et al., 1973; Henderson and Griffiths, 1975) was used to examine tissue from patients with ovarian tumors. No asbestos particles were found in any of the tissues studied (Henderson et al., 1971). Particles of talc were identified in approximately 75% (10 in 13) of the ovarian tumors. Talc particles were found localized deep within the tumor tissue; some were as small as 1,000 Å in size, but they were generally within a range from 1,000 Å to 2 μm.

In a letter to the editor, Hartge et al. (1983) refuted the association between talc use and ovarian cancer. The data collected were part of a case-control interview study of epithelial ovarian cancer conducted on 197 women with pathologically confirmed primary epithelial ovarian cancer from 1974 to 1977. The control population consisted of 197 women treated at the same hospital for conditions other than gynecologic, psychiatric, or malignant diseases or pregnancy. Questions about talc were added to the questionnaire after the study began so that 135 cases and 171 controls were questioned about talc exposure. No increase was found in the relative risk to women who used talc as a body powder or on diaphragms. A reliable estimate of relative risk in women who used talc specifically on sanitary napkins, underwear, or the genital area was not possible, however, because of the small numbers of women involved.

Harlow and Weiss (1989) report a case control study of borderline ovarian tumors and the influence of perineal exposure to talc. Borderline ovarian tumors differ from epithelial malignant ovarian tumors described in the other studies in that borderline tumors are lesions of low malignant potential that are usually noninvasive. The authors interviewed 116 female residents of western Washington state with serous and mucinous borderline ovarian tumors diagnosed between 1980 and 1985 and questioned them on their use of hygienic powders. A sample of 158 control women from the same counties was identified through random digit dialing. These women were interviewed as well. The authors reported 18 RR calculations with number of subjects for cases in the subset analysis ranging from 4 to 49 of the total 116 cases. Neither the perineal application of baby powder (RR of 0.8 with 95% confidence interval [CI] at 0.4 to 1.9; 18 cases, 31 controls) nor talc (RR of 1.0 with 95% CI of 0.4 to 2.4; 13 cases, 19 controls) was associated with appreciably altered risk of borderline ovarian tumors. Women who used deodorizing powder alone or in combination with other talc-containing powder had RR at 2.8 (95% CI of 1.1 to 11.7; 14 cases, 7 controls). The authors suggest caution in interpreting the results of the study, because the elevated risk among women who specifically used deodorizing powders could have been due to chance or applicable only to borderline, not malignant, ovarian tumors. Additionally, they note that the risk of ovarian tumors in women who apply deodorizing powder to the perineum may not relate to talc per se, but rather to asbestos contamination or a substance or substances used specifically for deodorization.

Whittemore et al. (1988) reported a study on exposure to talcum powder and epithelial ovarian cancer in 188 women in the San Francisco Bay area diagnosed in 1983-1985 and in 539 control women. To investigate the roles of blood-borne environmental exposures on ovarian cancer risk, they assessed lifetime consumption of coffee, tobacco, and alcohol in these women. Ninety-seven (52%) of the cancer patients habitually used talcum powder on the perineum, compared with 247 (46%) of the controls. Adjusted for parity, the RR equals 1.4, $p = 0.06$. There were no statistically significant trends with increasing frequency or duration of talc use. Thus, the results of this study show neither a strong nor a consistent association between genital talcum powder exposure and ovarian cancer. While these data do not exonerate talc as an ovarian carcinogen, neither do they provide strong evidence to

implicate it. Further epidemiologic studies are needed to clarify the role of talc as a carcinogen, cocarcinogen, or promoter of epithelial ovarian carcinogenesis.

Granulomas of the skin postulated to be caused by entrance of talc through the skin at sites of draining or incised furuncles were reported by Tye et al. (1966).

3.6.1.3 Effects From Intrapleural Instillation

Adverse systemic effects, including dyspnea followed by acute respiratory failure and bilateral pleural effusion with interstitial infiltrates, was reported in a patient a few hours after talc pleurodesis (Bouchama et al., 1984). The patient improved with corticosteroid therapy.

A total of 210 cases of patients who had undergone pleurodesis with iodized talc or kaolin 14 to 40 years previously were traced, and the numbers of deaths from all causes and cancer of the lung and pleura were compared with a control death rate derived from age- and year-specific tables from England and Wales (Research Committee of the British Thoracic Association and the Medical Research Council Pneumoconiosis Unit, 1979). No increase was found in the incidence of lung cancer in these patients, and no cases of mesothelioma were reported.

3.6.1.4 Effects From Surgical Introduction

Inadvertent introduction of talc into the body has been shown to produce granulomas. A granuloma that completely obstructed the ureter of a 53-year-old woman was attributed to the introduction of talc as a glove powder 20 years previously during a hysterectomy operation (Joannides, 1978). However, the granuloma may also have been produced by either starch granules or Lycopodium spores. Sahi et al. (1967) reported that granuloma formation on the bowel and peritoneum was believed to be the result of talcum powder use during a previous surgical intervention. Fienberg (1937) reported two cases of granuloma formation caused by talc introduced during surgical procedures.

3.6.1.5 Effects From Intravenous Administration

Intravenous abuse of stimulant drugs intended for oral administration can lead to the embolization of insoluble tablet fillers such as talc to the pulmonary vasculature. The

vasculature acts as a filter in most cases, thereby restricting talc-induced pathologic lesions to the lungs. Blockage of pulmonary perfusion by the passage of intravenously injected talc particles can result in pulmonary hypertension with the formation of arterio-venous shunts. The venous blood can then bypass the lungs and enter the arterial system, lodging particles in various organs such as the eye. The resulting peripheral retinal neovascularization has been noted after injection of talc emboli (Lederer and Sabates, 1982). Particles smaller than 7 mm can travel to the retina via the pulmonary capillary bed. Bilateral intraretinal talc emboli were reported in 23 patients by Tse and Ober (1980). A case of talc retinopathy that included vitreous hemorrhage and retinal detachment was reported by Bluth and Hanscom (1981). In this case the effects of talc particle injection resulted in blindness.

Granulomatous lesions found in lungs, liver, spleen, bone marrow, and systemic lymph nodes as a result of systemic talc embolization were reported by Mariani-Costantini et al. (1982). Larger talc crystals (10 to 17 μm) remained localized in the lungs; small crystals (2 to 10 μm) spread systemically. No crystals were found in numerous sections of the central nervous system, and only a few were present in the myocardium, retina, optic nerve, and kidneys. The talc particles were present in urine, demonstrating that they may have been able to pass through the glomerular capillary bed. Self-induced pulmonary granulomatosis was described by Waller et al. (1980). Cases of intravenous talc granulomatosis (Tao et al., 1984), liver talc granulomas (Molos et al., 1987), and systemic talc granulomatosis (Lewis et al., 1985) have been reported in association with intravenous drug abuse.

Kehrer (1990) comments that talc has not been shown to produce any toxic effects when ingested orally. As a result, the use of talc in various tablet formulations is not considered hazardous for the ingestion route. However, Hollinger (1990) notes that during drug abuse oral medication containing talc may be crushed, solubilized, and injected intravenously. The terminal pulmonary arterioles and capillaries serve as a sieve for the talc crystals. Granulomas develop in the arteries, and vascular endothelial proliferation and secondary thrombosis may lead to pulmonary hypertension and cor pulmonale.

3.6.2 Retrospective and Prospective Studies

Several studies have been conducted to identify potential relationships between exposure to talc and nonmalignant respiratory disease (NMRD). However, except in one study,

workers were simultaneously exposed to talc containing asbestos (i.e., tremolite), silicates, carbonates, or radon.

Kleinfeld et al. (1967) conducted a proportionate mortality study of 220 talc miners and millers employed between 1940 and 1965 who had achieved at least 15 years of exposure to talc dust. In addition to talc, exposure also included tremolite and anthophyllite (asbestiform and nonasbestiform fibers), carbonate dusts, and a small amount of free silica. Data for this cohort concerning employment and health histories as well as deaths were obtained from a number of sources, including plant records, death certificates (when available), private physician records, state health department files, hospital records, and autopsy records (procured for 35 of 91 deaths). The degree of completeness for disease ascertainment of the study population and the criteria for classifications of morbidity and mortality were not specified. The reference population used for calculating expected mortality was U.S. white males for the year 1957, which was the median year of death for the 91 total deaths occurring out of 220 workers. An analysis of the 91 deaths by cause yielded a significant increase in the proportional mortality of the total observed deaths from cancer of the lung and pleura (11 observed, 3.2 expected, proportionate mortality ratio [PMR] = 344, $p < 0.01$). When the cohort was analyzed by age group (<40, 40 to 59, 60 to 79, >80 years), a significant increase in cancer of the lung and pleura occurred in the subgroup 60 to 79 years old (17 observed, 3.9 expected, PMR = 436, $p < 0.01$). The authors expressed concern that this finding was at variance with the results from asbestos workers who had a similar duration of exposure during a similar period. Increased respiratory cancer incidence was found in both the 40 to 59 and 60 to 79 age groups of asbestos workers. A possibility exists that the discrepancy in these findings could be due to a greater carcinogenic potential and/or greater exposure levels in the case of asbestos workers. However, since the power to detect a carcinogenic risk in the 40 to 59 age group of talc workers was inadequate (21%), no definite conclusions could be drawn. An analysis of individuals with carcinoma of the lung or pleura, by duration of exposure, found that all these individuals were initially exposed prior to the institution of wet drilling (a period of heavy exposure before 1945), with an average duration of exposure of 14.6 years. Environmental dust exposure concentrations before 1945 ranged from 120 to 818 mppcf for mines and 69 to 1,227 mppcf for mills, and concentrations between 1946 and 1965 ranged from 5 to 9 mppcf for mines and 25 to 73 mppcf for mills.

No direct relationship was observed, however, between the duration of exposure before wet drilling and the occurrence of pulmonary carcinoma.

Of the 91 total deaths, 28 were attributed to pneumoconiosis or complications or both. Nineteen of the 28 were due to cor pulmonale, which was reported as a major cause of death among talc workers. Because of the absence of adequate data, the role of smoking in the causation of pulmonary carcinoma could not be ascertained in this study.

Findings from an update of this previous study through 1969 further supported the increased incidence of cancer of the lungs and pleura (Kleinfeld et al., 1974). The criteria for inclusion in the cohort remained the same for the followup study. The total number of workers studied was 260, and the analysis used was a comparison of observed proportional mortality rates from specific causes with expected rates. Expected mortality for the total group represented the proportion of deaths among white men in the United States due to specific causes in 1955 (median year of death among the total 108 deaths). For each of the 5-year periods, median years 1942, 1947, 1952, 1957, and 1962 were selected. Data for the cohort were obtained from the same sources as those in the previous study. The total number of deaths out of 260 workers was 108, and an analysis of these deaths by cause yielded results consistent with the previous study; there was a significant increase in proportional mortality from respiratory cancer in the 60 to 79 age group (16.6 observed, 3.6 expected, PMR = 461, $p < 0.05$).

Insufficient power to detect an increase in other age groups was still a confounding problem in this analysis. An analysis of carcinoma of the lung and pleura as related to six 5-year periods (1940-44, 1945-49, 1950-59, 1960-64, and 1965-69) revealed significant increases in the observed proportional mortality for respiratory cancer for three periods: 1945-49 (observed = 11.7, expected = 3.1, PMR = 377, $p < 0.05$); 1950-54 (12.5 observed, 4.3 expected, PMR = 291, $p < 0.01$); and 1955-59 (observed = 20.0, expected = 5.7, PMR = 351, $p < 0.05$). Investigators found no differences in mortality for respiratory cancer occurring after 1960 and no correlation between respiratory cancer deaths and age or years of exposure. Ten of the 13 deaths from respiratory tract cancer occurred in the period between 15 and 24 years of exposure to talc dust. However, a prolonged exposure of more than 25 years did not produce any additional risk. Although they remained major causes of death, deaths attributable to pneumoconisis and its complications decreased by more

than 50% in the last 5-year period studied (decrease from nine to four deaths). A firm conclusion of an elevated lung cancer risk is difficult to make for this study because of the lack of a dose-response relationship and the lack of smoking information.

The only mortality study conducted with very pure talc was reported by Rubino et al. (1976). The cohort consisted of 1,514 talc miners and 478 talc millers, who began work in the years between 1921 and 1950, and who had been employed for at least 1 year in talc operations of the Germanasca and Chisone Valleys in Italy. Because millers were exposed to very pure talc, while miners' exposures included a certain amount of inhalable silica particles, miners and millers were analyzed separately. Data for each worker were obtained from payrolls and records of a mining company of Pinerolo. Age-matched control subjects were chosen from the population of the town of Alba, which represented similar ethnic, social, and economic conditions. Followup for the study cohort was 88.9% complete for miners and 91.6% complete for millers. The cause of death was obtained from death certificates for exposed and control persons and was coded according to the 8th Revision of the International Classification of Deaths (ICD). For both internal and external controls, an age-adjusted modified life-table technique was used to compute expected deaths. The age intervals used were <30, 30 to 50, 51 to 70, and >70, and the latency periods were 1 to 10, 11 to 20, 21 to 30, 31 to 40, 41 to 50, and >50.

Cumulative exposure was computed by multiplying dust level for a period by number of years exposed and summing the resulting values for each period. Three exposure levels were then classified for miners (Exposure Level 1 = 566 to 1,699; Exposure Level 2 = 1,700 to 5,665; Exposure Level 3 = 5,666 to 12,750) and millers (Exposure Level 1 = 25 to 141; Exposure Level 2 = 142 to 424; Exposure Level 3 = 425 to 906). Analysis of mortality data indicated a significantly lower mortality for talc miners and millers than expected (miners = 704 observed, 791.2 expected, SMR = 89, $p < 0.01$; millers = 227 observed, 258.4 expected, SMR = 88, $p < 0.01$). When the overall mortality was subdivided by cause of deaths, deaths from all NMRD in miners were significantly higher than in controls (140 observed, 101.8 expected, SMR = 138, $p < 0.01$). Among malignant diseases, deaths from lung cancer were significantly lower than in controls (9 observed, 19.7 expected, SMR = 46, $p < 0.01$). An analysis of cause of death by exposure levels in miners showed a trend of increasing deaths with increasing exposure from NMRD (Exposure Level 1 =

26 observed, 36.9 expected, SMR = 70, $p < 0.05$; Exposure Level 2 = 38 observed, 36.3 expected, SMR = 105, not significant, Power = 85.8%; Exposure Level 3 = 76 observed, 67.1 expected, SMR = 113, $p < 0.05$). No clear trends, by exposure level, were observed for deaths from any other cause in miners or millers. When mortality by cause of death was analyzed by latency, the only significant increase found was for NMRD after 20 to 40 years of latency (76 observed, 54.4 expected, SMR = 140, $p < 0.01$); and after >40 years of latency (36 observed, 23.9 expected, SMR = 151, $p < 0.01$). No significant increase in observed deaths by latency was found for millers.

The choice of the control population was discussed by the authors as a confounding factor that could contribute to the observed differences. It was not possible to verify the appropriateness of this reference group. In addition, smoking data were unavailable; therefore, it was assumed that the control and exposed groups were similar in this respect. An internal comparison of groups of workers by increasing dose and latency period produced a pattern of excess mortality for respiratory causes of death in miners. This trend, plus the different incidence of silicosis in miners (62 observed, 30.9 expected, SMR = 201, $p < 0.01$), led the authors to conclude that the increased risk of death from NMRD was due to silica rather than talc. The lack of increased risk from any cause of death in talc-exposed millers led the authors to conclude that no evidence from the study supported the role of pure talc in carcinogenesis. It should be noted, however, that the power to detect lung cancer in the study population of millers was inadequate.

Brown et al. (1979) conducted a mortality study involving 398 white males initially employed some time between January 1, 1947, and December 31, 1959, at a talc mine and mill in upper New York State (Gouverneur region). Vital status for cohort members as of June 30, 1975, was determined through government records including the Social Security Agency, state vital statistics offices, and the state motor vehicle registration office. Death certificates were obtained and causes of death were interpreted by a qualified nosologist and converted to the 7th Revision of the ICD. A modified life-table technique was used to obtain person-years at risk of dying by 5-year time periods, 5-year age groups, duration of employment, and number of years since initial employment. The reference population used was U.S. white males. Vital status was determined for 96% of the exposed cohort.

No significant difference in overall mortality was observed. However, a significantly higher mortality from all malignant neoplasms was detected (19 observed, 10.6 expected, SMR = 180, $p < 0.01$). This was ascribed, in part, to the significant increase in deaths due to bronchogenic cancer (9 observed, 3.3 expected, SMR = 270, $p < 0.05$). In addition, investigators found an increase in deaths from NMRD, excluding influenza, pneumonia, bronchitis, and acute upper respiratory infection (5 observed, 1.3 expected, SMR = 380, $p < 0.05$). An analysis of the association between bronchogenic cancer and latency revealed a significant increase in the interval 20 to 28 years since onset of employment (6 observed, 1.3 expected, SMR = 460, $p < 0.01$).

The study of mortality patterns in workers exposed to talc from the Gouvernour mining area demonstrated an excess in mortality from both NMRD and bronchogenic cancer. This study had the confounding variables of smoking and exposure to asbestiform tremolite and anthophyllite. The authors postulated that the exposure to asbestiform tremolite and anthophyllite may have been responsible for the results observed. Another problem with the study cohort was the relatively short duration of employment for many of the workers: 50% were employed less than 1 year, and less than 25% were employed more than 10 years. Of the 10 deaths from bronchogenic cancer, 4 occurred in workers employed less than 1 year. Only two of these four were known to have been previously exposed to talc containing asbestiform minerals.

Stille and Tabershaw (1982) conducted a mortality study of 655 white male workers employed between January 1, 1948, and December 31, 1977, at one talc mine and mill (TMX) in upper New York State. Exposure data were not included. Due to small numbers and lack of talc exposure, women were excluded from analysis. The cohort was followed until December 12, 1978. Data on the workers were retrieved from employment records. Vital status was unknown for 36 members (5.5%) of the cohort. Death certificates were obtained and coded according to the 8th Revision of the ICD by a trained nosologist. Expected values were based on the U.S. white male population by means of a modified life-table method.

The mortality analysis of the cohort revealed no significant increases in deaths from all causes, from cancer of the respiratory tract and lung, from NMRD, or from other causes of death. The cohort was divided into workers with a prior work history before TMX

employment and workers with no known prior work experience. Investigators found no significant difference in mortality rates for all disease categories in workers without prior employment. However, workers with prior work histories did show significant increases in deaths attributable to a number of causes including respiratory cancer (9 observed, 4 expected, SMR = 228, $p < 0.05$) and NMRD (9 observed, 2.9 expected, SMR = 307, $p < 0.01$). The authors postulated that the observed mortality cancer was from exposures that occurred in the workers' previous jobs.

An analysis of the dose-response relationship of the lung cancer cases observed in the entire cohort and cumulative dose as measured by years of exposure resulted in an inverse dose-response relationship. Investigators found a clustering of 9 out of 12 cases within the first 5 years of employment at TMX. In addition, a calculation of the average latency time for lung cancer among TMX workers was 19.9 years. The authors cited the lack of a dose-response relationship and the short latency period as evidence that the prior occupational exposures and not exposures at TMX may have been responsible for subsequent cancers.

Confounding variables in the study included the small cohort size and inclusion of short-term (<1 year) employees. Although the U.S. white male population was used as a reference group, the authors pointed out that the New York State cancer death rate is substantially higher (199.24 compared to 174.04). Lack of data concerning smoking histories and incomplete work histories were also limitations of this study.

Reger and Morgan (1990) discuss the implication of an updated data and analysis of the original cohort of talc workers from upstate New York. Eight more years of followup were added plus an exposure by latency analysis, and a nested case-control study to account for possible confounding by smoking and other occupational exposures. When the data were stratified by smoking, the odds ratio decreased with tenure and the trend analysis was significant. The analysis showed a strong association between lung cancer and cigarette smoking. These results were considered to provide an argument against a causal relation between lung cancer and exposure to nonasbestiform tremolite.

Selevan et al. (1979b) conducted a mortality study of 392 white male talc workers who had been radiographed as part of the Vermont Health Department annual surveys. The workers were employed by five companies in the Vermont talc industry for at least 1 year between January 1, 1940, and December 31, 1969. Followup was begun from the initial

radiographic examination, when 1 year of employment was achieved, or January 1, 1940, whichever was later, and was continued through December 31, 1975. Vital status ascertainment was performed through government records including those from the Social Security Administration, state vital statistics offices, and state motor vehicle registration files. Vital status was unknown for 1% (4 of 392 workers) of the cohort. Death certificates were obtained, and causes of death were classified by a qualified nosologist and converted to the 7th Revision of the ICD. A modified life-table technique was used to obtain person-years of observation by 5-year time periods, 5-year age groups, 5-year exposure groups, and 5-year latency groups. The study cohort was divided into two groups: milling (225 workers) and mining (163 workers). A minimum of 1 year of employment in the work area was required for inclusion; 47 workers (12% of the total population) qualified for inclusion in both groups. United States rates were used for calculation of expected values. In addition, Vermont rates were used for comparison in the cases of NMRD and respiratory cancer deaths, since Vermont rates are higher for these causes. An analysis of exposure revealed that both airborne dust and bulk samples of talc from the mines and mills were similar in composition: No asbestos was detected; free silica was below 0.25% for nearly all samples; and the minerals magnesite, chlorite, and dolomite were present in significant quantities. Although no cumulative exposures could be calculated, it was not uncommon for past levels to exceed the OSHA and Mine Safety and Health Administration standard of 20 mppcf. Miners, but not millers, may also have been exposed to serpentine rock and radon.

The mortality analysis of the total cohort showed that the only significant excess occurred from NMRD (excluding influenza and pneumonia) (11 observed, 1.79 expected, SMR = 615, $p < 0.01$), particularly among millers (7 observed, 0.89 expected, SMR = 787, $p < 0.01$). A significant increase in respiratory cancer mortality was observed only among miners (5 observed, 1.15 expected, SMR = 435, $p < 0.05$). These two significant excesses were maintained when expected numbers of deaths from the Vermont population were used (NMRD, 1.33 expected, $p < 0.01$; respiratory cancer, 1.22 expected, $p < 0.05$). To confirm that the excess of NMRD deaths in millers was from talc exposure, chest radiographs for 8 of the 11 men who died from this disease were examined for pneumoconiosis. Of the eight radiographs, six (75%) had indications of pneumoconiosis. When 2 of the 11 workers with prior dust exposure were included, five of the six (83.3%)

radiographs were read as having pneumoconiosis. Qualitative radiograph readings by the Vermont Health Department provided information on three deaths with missing radiographs; all three had evidence of pneumoconiosis, which provided a total of 9 of 11 deaths with readings consistent with pneumoconiosis. This supported the association between talc exposure and NMRD.

The authors stated that the possibility of a selection bias was small because workers who were missed by the radiographic surveys were mostly short-term workers. An examination of NMRD mortality by latency resulted in a pattern of significant excess after 15 years (2 observed, 0.31 expected, SMR = 645, $p < 0.05$), and after 30 years (5 observed, 0.41 expected, SMR = 1,220, $p < 0.01$), but not before 15 years. This suggested that no selection bias toward less healthy workers existed. No data were available on the smoking histories of workers. In addition, the small cohort size resulted in a lack of adequate power to detect increased risk in many of the disease categories.

Thomas and Stewart (1987) and Thomas (1990) conducted a mortality study of 2,055 white males employed for at least 1 year between January 1, 1939, and January 1, 1966, at three plants of a ceramic plumbing fixture company. More than 60% of the cohort was employed for 10 or more years. Nonwhite males and females were excluded from the cohort because their group was small. Vital status was determined from company, Social Security Administration, credit bureau, and department of motor vehicle records. As of January 1, 1981, 1,394 (67.8%) of the 2,055 cohort members were alive; 578 (28.1%) had died; and 83 (4.0%) were lost to followup. Death certificates were obtained for all but 1.7% of the decedents and coded by a qualified nosologist using the 8th Revision of the ICD. Expected numbers of deaths were calculated using rates for U.S. white males rather than local mortality rates. Because exposure data for talc dust were unavailable, exposure classifications were based on the potential exposure to silica dust (none, low, or high). All jobs involving talc exposure had high silica exposure and were further classified into no talc, nonfibrous talc, and fibrous talc exposures; no talc was the lowest exposure, and fibrous talc was the highest exposure. No information on smoking patterns was known for this cohort.

The mortality analysis showed a significant increase in deaths from lung cancer (52 observed, 36.3 expected, SMR = 143) and NMRD (64 observed, 37.0 expected, SMR = 173, $p < 0.05$). The increase in NMRD deaths was mainly from respiratory disease

other than pneumonia or emphysema, which included 23 deaths nosologically classified as pneumoconiosis from silica and silicates (41 observed, 14.1 expected, SMR = 290, $p < 0.05$). An analysis of lung cancer and NMRD by year of hire showed a significant increase in lung cancer among workers hired between 1940 and 1949 (22 observed, 11.4 expected, SMR = 193, $p < 0.05$) and a significant increase in NMRD among workers hired before 1940 (55 observed, 24.5 expected, SMR = 224, $p < 0.05$). Analysis of mortality by exposure category for lung cancer and NMRD revealed a significant excess only in workers in the high silica exposure category (44 observed, 24.3 expected, SMR = 181, $p < 0.05$), particularly among those exposed to nonfibrous talc (21 observed, 8.3 expected, SMR = 254, $p < 0.05$). In addition, a significant increase in NMRD was found among those exposed to high silica with no talc exposure (36 observed, 13.7 expected, SMR = 264, $p < 0.05$) and to nonfibrous talc (16 observed, 7.3 expected, SMR = 220, $p < 0.05$). An analysis by duration of exposure and years since first silica exposure revealed an increase in NMRD mortality by duration of exposure (15 to 29 years: 21 observed, 12.1 expected, SMR = 173, $p < 0.05$; 30+ years: 36 observed, 12.8 expected, SMR = 281, $p < 0.05$); and years since first exposure (50 observed, 22.0 expected, SMR = 227, $p < 0.05$). Lung cancer mortality did not increase with duration of exposure, but there was an increase in years since first exposure (30+ years: 32 observed, 20.6 expected, SMR = 156, $p < 0.05$). The analysis by duration of exposure and years since first exposure to nonfibrous talc, revealed an increased mortality from lung cancer with duration of exposure (5 to 14 years: 11 observed, 4.0 expected, SMR = 276, $p < 0.05$; and 15+ years: 8 observed, 2.2 expected, SMR = 364, $p < 0.05$) and with years since first exposure (5 to 14 years: 8 observed, 2.9 expected, SMR = 281, $p < 0.05$; and 15+ years: 13 observed, 4.7 expected, SMR = 275, $p < 0.05$). Mortality from NMRD was not affected by duration or time since first exposure to nonfibrous talc.

The excess NMRD was elevated among workers with exposure to high levels of silica, regardless of nonfibrous talc exposure. This risk decreased over time, suggesting a reduction in silica exposure. Risk of NMRD was also unaffected by duration or time since first exposure to nonfibrous talc. The authors concluded an association between silica dust rather than talc exposure with this disease. The excess in lung cancer found in this study, however, occurred primarily in workers exposed to both nonfibrous talc and silica. Risk of lung cancer

occurred only among those hired after 1940 and increased with increasing duration of exposure to nonfibrous talc but not with duration of silica exposure. This suggested that exposure to nonfibrous talc was related to lung cancer risk. However, the confounding problem of simultaneous silica exposure prevented any conclusions as to their respective roles in the disease. The possibility that silica acts as a co-factor or promoting agent cannot be ruled out.

In Norway, Wergeland et al. (1990) studied cancer incidence and cause-specific mortality in a male cohort of 94 talc miners and 295 talc millers exposed to nonasbestiform talc with low quartz content. All employees from the mine in the years 1944-1972 with at least 1 year of employment in talc-exposed jobs and all employees from the mill in the years 1935-1972 with at least 2 years of employment in talc-exposed jobs were included. Information about the miners was gathered from company payrolls, lists of union membership, and the central registry of silica-exposed workers of the National Board of Occupational Safety and Health. Information about smoking habits was available for 63 of the 94 miners.. No information was available on smoking habits of the millers. Information on date and main cause of death was obtained from the death certificate registry of the Central Bureau of Statistics. Information on cancer cases was provided by the Cancer Registry. Dust exposure was determined by samples collected in 1980-1982 and varied greatly by job category. Air samples were analyzed for fiber concentration, which varied from less than 0.2 up to 0.9 fibers/mL and consisted of tremolite, antophyllite, and talc particles.

No excess risk was found compared with national age-specific incidence, SMR of 75, with 117 observed deaths and 155.2 expected. Six cases of lung cancer occured versus 6.49 expected. Three deaths were due to NMRD against 10.9 expected. Both the healthy population and survivor population effect may be factors here. The mortality from NMRD may increase with further follow-up time, as any impact of "healthy worker" selection becomes less prominent. The probability of detecting an increased mortality from NMRD ($\alpha = 0.05$, one-sided) is 83% for a true RR of 2.0 and 100% for RR = 3.0, assuming a Poisson distribution.

In both groups the numbers are too small to form inference on particular cancer types. The International Agency for Research on Cancer (1987) found sufficient evidence for

carcinogenicity of crystalline silica to experimental animals and limited evidence for carcinogenicity to humans. They found inadequate evidence for carcinogenicity of talc to either experimental animals or humans. The result of this low quartz content talc exposure is compatible. The possibility of detecting an increased lung cancer incidence during the follow-up period in this study ($\alpha = 0.05$, one-sided) assuming a Poisson distribution is 65% for a true RR = 2.0 and 97% for RR = 3.0. This study does not show an association between lung cancer morbidity or respiratory disease mortality and exposure to nonasbestiform talc with low quartz content in the one mine and one mill studied. Further follow-up time is needed, however, to lessen any impact of "healthy worker" selection.

The American Thoracic Society (Weill et al., 1990) review examines the carcinogenicity of talc and tremolite and concludes that the talc studies do not convincingly demonstrate an increased cancer risk reliably attributed to talc exposure and further do not support a role for tremolite as a lung carcinogen in talc mining whether the tremolite is an asbestiform or not. However, the authors do state further that, from all studies considering tremolite "fibers", they have been demonstrated in both humans and animals to cause health effects identical to those produced by other forms of asbestos.

3.7 QUALITATIVE AND QUANTITATIVE EVALUATION OF TOXICOLOGICAL EFFECTS ASSOCIATED WITH EXPOSURE TO TALC

This section summaries and evaluates noncarcinogenic effects and carcinogenic effects.

3.7.1 Noncarcinogenic Effects

Data from animal studies indicate that talc exposure generally results in a granulomatous lesion consisting of dust-laden multinucleated foreign body giant cells, as well as some fibrosis with collagen formation. Systemic effects in humans after inhalation exposure include increased respiratory symptoms, higher prevalence of pleural thickening or calcification and pneumoconiosis, and decreased pulmonary function. These effects were more pronounced in those exposed to talc containing asbestiform fibers than to pure talc.

Humans chronically exposed to talc exhibit pneumoconiosis or chronic sarcoidosis with foreign body granulomas and interstitial fibrosis.

A review of the chronic toxicity data of talc in animals by the International Agency for Research on Cancer (1987) indicated the appearance of foreign body giant-cell granulomas, fibrosis, and chronic inflammatory changes eventually leading to emphysema. Toxic effects in humans after inhalation include pneumoconiosis, restrictive or obstructive breathing disorders, and decreased vital capacity. There was an association between the severity of the pneumoconiosis and the presence of asbestiform fibers.

The following three studies were considered for the development of a no-observed-adverse-effect level (NOAEL) and a lowest-observed-adverse-effect level (LOAEL): two inhalation studies in animals and one epidemiological study. However, the data were limited, and a NOAEL or LOAEL cannot be determined. In the study by Wehner et al. (1977a,b), Syrian Golden hamsters were exposed to 8 mg/m^3 (respirable fraction) cosmetic talc for 30 or 150 min/day, 5 days/week for 300 days; the animals were observed until death. The estimated alveolar deposition/exposure range was 0.86 to 1.15 and 4.3 to 5.8 μg talc for the 30- and 150-min exposures, respectively; the exposure concentration for continuous exposure would be 0.12 and 0.6 $mg/m^3/day$, respectively. No effects were seen on body weight, clinical signs, or microscopic pathology. These levels represent a rather low exposure and help confirm that the NOAEL is greater than 8 mg/m^3 (i.e., 0.6 $mg/m^3/day$).

Wagner et al. (1977) exposed Wistar rats to talc from northern Italy at 10.8 mg/m^3 for 7.5 h/day, 5 days/week for 3, 6, or 12 mo. The talc did not contain asbestos minerals of either the tremolite or chrysotile varieties. The exposure concentration for continuous exposure would be 2.4 $mg/m^3/day$. The lung burdens at the end of the 3-, 6-, and 12-mo exposure periods were 2.5, 4.7, and 12.2 mg talc/rat. The severity of fibrosis was minimal to slight, and there was a progression in severity as the exposure length increased, as well as after the exposure had been discontinued. These levels represent a rather high exposure and help confirm that a NOAEL is lower than 10.8 mg/m^3 (i.e., 2.4 $mg/m^3/day$).

In the epidemiological study conducted by Rubino et al. (1976) data were collected for workers in talc mines and mills in the Germanasca and Chisone Valleys (Piedmont) in Italy. The talc in the mines was described as pure; no amphibole or chrysotile was detected. Some tremolite microinclusions were detected; however, no other fibrous mineral was reported.

Environmental data were available for the mines and mills since 1948. Prior to 1950, exposures were reported to be approximately 800 mppcf in the mines and 25 mppcf in the mills. Exposures in both areas were reduced to less than 10 mppcf after 1965. Other than some rather crude estimates that could be devised for human exposure from the data presented, quantification of the human exposure to talc was not possible.

3.7.2 Carcinogenic Effects

Talc was not shown to be carcinogenic following inhalation exposure or intratracheal instillation to rats and hamsters. No evidence of carcinogenicity was noted following intrapleural, intraperitoneal, or oral administration in rats. However, these studies are inadequate to evaluate the carcinogenic potential of talc. Several mortality studies on mining and milling workers involving exposure to talc contaminated with asbestiform fibers indicated an excess of respiratory cancer and NMRD. However, these studies had important limitations such as lack of smoking data and lack of dose-response data. Recent updates seem to indicate that the talc studies do not convincingly demonstrate an increased lung cancer risk reliably attributable to exposure and as such do not support a role for tremolite as a lung carcinogen in talc mining whether the tremolite was asbestiform or not. A study of worker exposure to very pure talc showed no increase in mortality from lung cancer.

Consequently, the weight of evidence from human health effects and animal toxicity data are inadequate to characterize the carcinogenic potential of talc.

The evidence for carcinogenicity of talc has several aspects depending upon the nature of the contamination with other mineral substances. Of particular note is contamination with asbestos and crystalline silica.

The presence of asbestos in talc would cause the contaminated talc to be viewed as a human carcinogen from a weight-of-evidence perspective. In the case of crystalline silica, the International Agency for Research on Cancer (1987) views the human evidence for crystalline silica as limited and the animal evidence as sufficient, which places crystalline silica in IARC's "probable" human carcinogen classification. By inference, then, talc with crystalline silica would be viewed as inheriting the carcinogenic hazard potential of the crystalline silica.

In the case of talc without asbestos contamination, the International Agency for Research on Cancer (1987) found the available human and animal evidence to be inadequate to demonstrate or refute the potential for carcinogenicity. Some animal studies are nonpositive, but it is not clear that these are adequate to properly evaluate talc's carcinogenicity with and without the low content of crystalline silica.

The U.S. EPA has not previously evaluated the talc or the crystalline silica data and has not done so in this assessment. The International Agency for Research on Cancer views on weight-of-evidence are useful as an interim measure in considering the hazard perspective. The U.S. EPA and the International Agency for Research on Cancer view asbestos as a human carcinogen. The quantitative question arises as to how much crystalline silica or asbestos contamination makes a difference in terms of potential risk, and this dose-response issue has not been included in this assessment.

In a similiar evaluation, the American Thoracic Society (Weill et al., 1990) discusses the health effects of tremolite and reviews studies of talc health effects. With regard to tremolite asbestos, the American Thoracic Society (Weill et al., 1990) concludes the following after a review of other tremolite studies beyond those of contaminated talc:

1. Unquestioned health effects of tremolite asbestos have been demonstrated in both humans and animals. These effects are identical to those produced by other forms of asbestos.
2. There may be important physicochemical distinctions between asbestosform and nonasbestosform tremolite dust particles. However, there appears to be considerable controversy in applying these mineralogic definitions to specific samples of minerals, particularly individual particles viewed microscopically after collection by air sampling or found in human lungs or when used experimentally.
3. At present, the prudent public health policy course is to regard appropriately sized tremolite "fibers", in sufficient exposure dose (concentration and duration), as capable of producing the recognized asbestos-related diseases, and they should be regulated accordingly.

Several rebuttals have since been published for tremolite and its presence in talc addressing physicochemical distinctions: OSHA's analytical procedures and definitions, results of animal studies, etc. (Reger and Morgan, 1991, 1990; Case, 1991; Langer et al., 1991). However, this information is beyond the present scope of this document.

4. REFERENCES

American Conference of Governmental Industrial Hygienists. (1991) 1991-1992 Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists; p. 34.

Anonymous. (1969) Accidental inhalation of talcum powder. Br. Med. J. 4: 5-6.

Bachani, D. (1984) Chronic airflow limitation in talc industry: role of age, smoking habits and dust exposure. Indian J. Chest Dis. Allied Sci. 26: 220-224.

Bachani, D.; Agarwal, D. (1985) Impact of talc dust on the respiratory system of working population. J. Indian Med. Assoc. 83: 41-43.

Beck, B. D.; Feldman, H. A.; Brain, J. D.; Smith, T. J.; Hallock, M.; Gerson, B. (1987) The pulmonary toxicity of talc and granite dust as estimated from an in vivo hamster bioassay. Toxicol. Appl. Pharmacol. 87: 222-234.

Bluth, L. L.; Hanscom, T. A. (1981) Retinal detachment and vitreous hemorrhage due to talc emboli. JAMA J. Am. Med. Assoc. 246: 980-981.

Bouchama, A.; Chastre, J.; Gaudichet, A.; Soler, P.; Gibert, C. (1984) Acute pneumonitis with bilateral pleural effusion after talc pleurodesis. Chest 86: 795-797.

Boundy, M. G.; Gold, K.; Martin, K. P., Jr.; Burgess, W. A.; Dement, J. M. (1979) Occupational exposures to non-asbestiform talc in Vermont. In: Lemen, R.; Dement, J. M., eds. Dusts and disease: proceedings of the conference on occupational exposures to fibrous and particulate dust and their extension into the environment; 1977; Washington, DC. Park Forest South, IL: Pathotox Publishers, Inc.; pp. 365-378.

Brown, D. P.; Dement, J. M.; Wagoner, J. K. (1979) Mortality patterns among miners and millers occupationally exposed to asbestiform talc. In: Lemen, R.; Dement, J. M., eds. Dusts and disease: proceedings of the conference on occupational exposures to fibrous and particulate dust and their extension into the environment; 1977; Washington, DC. Park Forest South, IL: Pathotox Publishers, Inc.; pp. 317-324.

Case, B. W. (1991) On talc, tremolite, and tergiversation ter-gi-ver-sate: 2: to use subterfuges. Br. J. Ind. Med. 48: 357-358.

Chamberlain, M.; Brown, R. C. (1978) The cytotoxic effects of asbestos and other mineral dust in tissue culture cell lines. Br. J. Exp. Pathol. 59: 183-189.

Churg, A. (1983) Nonasbestos pulmonary mineral fibers in the general population. Environ. Res. 31: 189-200.

Churg, A.; Warnock, M. L. (1980) Asbestos fibers in the general population. Am. Rev. Respir. Dis. 122: 669-678.

Clarke, G. M. (1979) Talc: destiny in diversity. Ind. Miner. (London) 144: 23-59.

Clifton, R. A. (1985) Talc and pyrophyllite. In: Mineral facts and problems 1985. Washington, DC: U.S. Bureau of Mines, U.S. Department of the Interior; pp. 799-810. (Bulletin 675).

Cotton, W. H.; Davidson, P. J. (1985) Aspiration of baby powder. N. Engl. J. Med. 313: 1662.

Cramer, D. W.; Welch, W. R.; Scully, R. E.; Wojciechowski, C. A. (1982) Ovarian cancer and talc: a case-control study. Cancer (Philadelphia) 50: 372-376.

Damodar; Agrawal, D.; Sharma, P. N. (1983) Changes in ventilatory capacities due to exposure to talc dust. Indian J. Chest Dis. Allied Sci. 25: 21-24.

Davies, R.; Skidmore, J. W.; Griffiths, D. M.; Moncrieff, C. B. (1983) Cytotoxicity of talc for macrophages in vitro. Food Chem. Toxicol. 21: 201-207.

Dement, J.; Shuler, P. (1972) Talc dust and industrial hygiene survey, Plymouth Rubber Company, Canton, MA. Cincinnati, OH: National Institute for Occupational Safety and Health; report no. IWS-036.11A.

Dement, J. M.; Zumwalde, R. D. (1979) Occupational exposures to talcs containing asbestiform minerals. In: Lemen, R.; Dement, J. M., eds. Dusts and disease: proceedings of the conference on occupational exposures to fibrous and particulate dust and their extension into the environment; 1977; Washington, DC. Park Forest South, IL: Pathotox Publishers, Inc.; pp. 287-305.

Dement, J. M.; Zumwalde, R. D.; Gamble, J. F.; Fellner, W.; DeMeo, M. J.; Brown, D. P.; Wagoner, J. K. (1980) Occupational exposure to talc containing asbestos. Cincinnati, OH: National Institute for Occupational Safety and Health; DHEW NIOSH publication no. 80-115.

Dreessen, W. C. (1933) Effects of certain silicate dusts on the lungs. J. Ind. Hyg. 15: 66-78.

Dreessen, W. C.; Dalla Valle, J. M. (1935) The effects of exposure to dust in two Georgia talc mills and mines. Public Health Rep. 50: 131-143.

Fienberg, R. (1937) Talcum powder granuloma. Arch. Pathol. 24: 36-42.

Fine, L. J.; Peters, J. M.; Burgess, W. A.; Di Berardinis, L. J. (1976) Studies of respiratory morbidity in rubber workers: Part IV. respiratory morbidity in talc workers. Arch. Environ. Health 31: 195-200.

Fitzgerald, E. F.; Stark, A. D.; Vianna, N.; Hwang, S.-A. (1991) Exposure to asbestiform minerals and radiographic chest abnormalities in a talc mining region of upstate New York. Arch. Environ. Health 46: 151-154.

Friedrichs, K. H. (1987) Electron microscopic analyses of dust from the lungs and the lymph nodes of talc-mine employees. Am. Ind. Hyg. Assoc. J. 48: 626-633.

Gamble, J. F.; Fellner, W.; Dimeo, M. J. (1979) An epidemiologic study of a group of talc workers. Am. Rev. Respir. Dis. 119: 741-753.

Gamble, J.; Greife, A.; Hancock, J. (1982) An epidemiological-industrial hygiene study of talc workers. In: Walton, W. H., ed. Inhaled particles V: proceedings of an international symposium; September 1980; Cardiff, Wales, United Kingdom. Ann. Occup. Hyg. 26: 841-859.

General Electric. (1978) Fibrous glass (silicate base). Schenectady, NY: Materials Information Services; material safety data sheet no. 46.

Gershuni, D. H.; Amiel, D.; Gonsalves, M.; Akeson, W. H. (1981) The biochemical response of rabbit articular cartilage matrix to an induced talcum synovitis. Acta Orthop. Scand. 52: 599-603.

Gould, S. R.; Barnardo, D. E. (1972) Respiratory distress after talc inhalation. Br. J. Dis. Chest 66: 230-233.

Greife, A. (1980) Preliminary findings of an epidemiologic study of talc workers (industrial hygiene portion). In: Kraybill, H. F.; Blackwood, I. C.; Freas, N. B., eds. Proceedings of the 1st NCI/EPA/NIOSH collaborative workshop: progress on joint environmental and occupational cancer studies. Morgantown, WV: National Institute for Occupational Safety and Health; pp. 229-240.

Griffiths, K.; Chandler, J. A.; Henderson, W. J.; Joslin, C. A. F. (1973) Ovarian cancer: some new analytical approaches. Postgrad. Med. J. 49: 69-72.

Hamer, D. H.; Rolle, F. R.; Schelz, J. P. (1976) Characterization of talc and associated minerals. Am. Ind. Hyg. Assoc. J. 37: 296-304.

Hamilton, T. C.; Fox, H.; Buckley, C. H.; Henderson, W. J.; Griffiths, K. (1984) Effects of talc on the rat ovary. Br. J. Exp. Pathol. 65: 101-106.

Hanson, R. L.; Benson, J. M.; Henderson, T. R.; Carpenter, R. L.; Pickrell, J. A.; Brown, S. C. (1985) Method for determining the lung burden of talc in rats and mice after inhalation exposure to talc aerosols. J. Appl. Toxicol. 5: 283-287.

Harlow, B. L.; Weiss, N. S. (1989) A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc. Am. J. Epidemiol. 130: 390-394.

Hartge, P.; Hoover, R.; Lesher, L. P.; McGowan, L. (1983) Talc and ovarian cancer. JAMA J. Am. Med. Assoc. 250: 1844.

Henderson, W. J. (1972) The use of analytical electron microscopy in the study of foreign and naturally occurring minerals in biological tissues. Micron 3: 131-133.

Henderson, W. J.; Griffiths, K. (1975) Identification of particles in ovarian tissue. In: Brush, M. G.; Taylor, R. W., eds. Gynaecological malignancy: clinical and experimental studies. Baltimore, MD: Williams & Wilkins Company; pp. 225-240.

Henderson, W. J.; Joslin, C. A. F.; Turnbull, A. C.; Griffiths, K. (1971) Talc and carcinoma of the ovary and cervix. J. Obstet. Gynaecol. Br. Commonw. 78: 266-272.

Henderson, W. J.; Chandler, J. A.; Blundell, G.; Griffiths, C.; Davies, J. (1973) The application of analytical electron microscopy to the study of diseased biological tissue. J. Microsc. (Oxford) 99: 183-192.

Henderson, W. J.; Hamilton, T. C.; Baylis, M. S.; Pierrepoint, C. G.; Griffiths, K. (1986) The demonstration of the migration of talc from the vagina and posterior uterus to the ovary in the rat. Environ. Res. 40: 247-250.

Hildick-Smith, G. Y. (1976) The biology of talc. Br. J. Ind. Med. 33: 217-229.

Hogue, W. L., Jr.; Mallette, F. S. (1949) A study of workers exposed to talc and other dusting compounds in the rubber industry. J. Ind. Hyg. Toxicol. 31: 359-364.

Hollinger, M. A. (1990) Pulmonary toxicity of inhaled and intravenous talc. Toxicol. Lett. 52: 121-127.

International Agency for Research on Cancer. (1987) Talc. In: IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans: v. 42, silica and some silicates. Lyon, France: World Health Organization; pp. 185-224.

Joannides, J. I. (1978) Talc granuloma of the ureter: a case report. Br. J. Surg. 65: 883-885.

Johnson, R. L. (1991) Talc. Am. Ceramic Soc. Bull. 70: 886-887.

Kaiser, W.; Otten, G.; Koehnlein, H.-E.; Kitzinger, H. (1982) Unspezifische Gewebsreaktionen durch Handschuh-Puder [Unspecific reactions of web excited by surgical glove powder]. Fortschr. Med. 25: 1213-1216.

Kehrer, J. P. (1990) "Pulmonary toxicity of inhaled and intravenous talc" by M. A. Hollinger. Toxicol. Lett. 52: 117-119.

Kleinfeld, M.; Messite, J.; Tabershaw, I. R. (1955) Talc pneumoconiosis. AMA Arch. Ind. Health 12: 66-72.

Kleinfeld, M.; Messite, J.; Kooyman, O.; Zaki, M. H. (1967) Mortality among talc miners and millers in New York state. Arch. Environ. Health 14: 663-667.

Kleinfeld, M.; Messite, J.; Langer, A. M. (1973) A study of workers exposed to asbestiform minerals in commercial talc manufacture. Environ. Res. 6: 132-143.

Kleinfeld, M.; Messite, J.; Zaki, M. H. (1974) Mortality experiences among talc workers: a follow-up study. J. Occup. Med. 16: 345-349.

Langer, A. M.; Nolan, R. P.; Addison, J. (1991) On talc, tremolite, and tergiversation. Br. J. Ind. Med. 48: 359-360.

Lederer, C. M., Jr.; Sabates, F. N. (1982) Ocular findings in the intravenous drug abuser. Ann. Ophthalmol. 14: 436-438.

Lewis, J. H.; Sundeen, J. T.; Simon, G. L.; Schulof, R. S.; Wand, G. S.; Gelfand, R. L.; Miller, H.; Garrett, C. T.; Jannotta, F. S.; Orenstein, J. M. (1985) Disseminated talc granulomatosis: an unusual finding in a patient with acquired immunodeficiency syndrome and fatal cytomegalovirus infection. Arch. Pathol. Lab. Med. 109: 147-150.

Lockey, J. E. (1981) Nonasbestos fibrous minerals. Clin. Chest Med. 2: 203-218.

Longo, D. L.; Young, R. C. (1979) Cosmetic talc and ovarian cancer. Lancet (8138): 349-351.

Lord, G. H. (1978) The biological effects of talc in the experimental animal: a literature review. Food Cosmet. Toxicol. 16: 51-57.

Lund, J. S.; Feldt-Rasmussen, M. (1969) Accidental aspiration of talc. Acta Poediat. Scand. 58: 295-296.

Mariani-Costantini, R.; Jannotta, F. S.; Johnson, F. B. (1982) Systemic visceral talc granulomatosis associated with miliary tuberculosis in a drug addict. Am. J. Clin. Pathol. 78: 785-789.

Messite, J.; Reddin, G.; Kleinfeld, M. (1959) Pulmonary talcosis, a clinical and environmental study. AMA Arch. Ind. Health 20: 408-413.

Migaki, G.; Garner, F. M. (1969) Talc-induced granulomas in swine. J. Am. Vet. Med. Assoc. 155: 1595-1596.

Molos, M. A.; Litton, N.; Schubert, T. T. (1987) Talc liver. J. Clin. Gastroenterol. 9: 198-203.

Motomatsu, K.; Adachi, H.; Uno, T. (1979) Two infant deaths after inhaling baby powder. Chest 75: 448-450.

National Institute for Occupational Safety and Health. (1979) Mining surveillance: potentially toxic occupational exposures. Morgantown, WV: National Institute for Occupational Safety and Health.

National Research Council. (1984) Asbestiform fibers: nonoccupational health risks. Washington, DC: National Academy Press.

Negri, E.; Piolatto, G.; Pira, E.; Decarli, A.; Kaldor, J.; La Vecchia, C. (1989) Cancer mortality in a northern Italian cohort of rubber workers. Br. J. Ind. Med. 46: 624-628.

NOES, National Occupational Exposure Survey (1980-1983) [data base]. (1984) Cincinnati, OH: U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health. Disc; ASCII.

NOHS, National Occupational Hazard Survey (1972-1974) [data base]. (1976) Cincinnati, OH: U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health. Disc; ASCII.

Oezesmi, M.; Patiroglu, T. E.; Hillerdal, G.; Oezesmi, C. (1985) Peritoneal mesothelioma and malignant lymphoma in mice caused by fibrous zeolite. Br. J. Ind. Med. 42: 746-749.

Pelling, D.; Evans, J. G. (1986) Long-term peritoneal tissue response in rats to mould-release agents and lubricant powder used on surgeons' gloves. Food Chem. Toxicol. 24: 425-430.

Phillips, J. C.; Young, P. J.; Hardy, K.; Gangolli, S. D. (1978) Studies on the absorption and disposition of ^{3}H-labelled talc in the rat, mouse, guinea-pig and rabbit. Food Cosmet. Toxicol. 16: 161-163.

Pickrell, J. A.; Snipes, M. B.; Benson, J. M.; Hanson, R. L.; Jones, R. K.; Carpenter, R. L.; Thompson, J. J.; Hobbs, C. H.; Brown, S. C. (1989) Talc deposition and effects after 20 days of repeated inhalation exposure of rats and mice to talc. Environ. Res. 49: 233-245.

Pooley, F. D.; Rowlands, N. (1977) Chemical and physical properties of British talc powders. In: Walton, W. H.; McGovern, B., eds. Inhaled particles IV (in two parts): proceedings of an international symposium, part 2; September 1975; Edinburgh, United Kingdom. Oxford, United Kingdom: Pergamon Press; pp. 639-646.

Pott, F.; Huth, F.; Friedrichs, K. H. (1974) Tumorigenic effect of fibrous dusts in experimental animals. Environ. Health Perspect. 9: 313-315.

Reger, R.; Morgan, W. K. C. (1990) On talc, tremolite, and tergiversation. Br. J. Ind. Med. 47: 505-507.

Reger, R.; Morgan, W. K. C. (1991) Author's reply. Br. J. Ind. Med. 48: 358-359.

Research Committee of the British Thoracic Association and the Medical Research Council Pneumoconiosis Unit. (1979) A survey of the long-term effects of talc and kaolin pleurodesis. Br. J. Dis. Chest 73: 285-288.

Roberts, W. L.; Rapp, G. R., Jr.; Weber, J. (1974) Encyclopedia of minerals. New York, NY: Van Nostrand Reinhold; p. 601.

Roe, L. A.; Olson, R. H. (1983) Talc. In: LeFond, S. J., ed. Industrial minerals and rocks (nonmetallics other than fuels): v. 2. 5th ed. New York, NY: Society of Mining Engineers of the American Institute of Mining, Metallurgical, and Petroleum Engineers, Inc.; pp. 1275-1301.

Rohl, A. N.; Langer, A. M. (1974) Identification and quantitation of asbestos in talc. Environ. Health Perspect. 9: 95-109.

Rohl, A. N.; Langer, A. M. (1979) Fibrous mineral content of consumer talc-containing products. In: Lemen, R.; Dement, J. M., eds. Dusts and disease: proceedings of the conference on occupational exposures to fibrous and particulate dust and their extension into the environment; 1977; Washington, DC. Park Forest South, IL: Pathotox Publishers, Inc.; pp. 393-403.

Rohl, A. N.; Langer, A. M.; Selikoff, I. J.; Tordini, A.; Klimentidis, R.; Bowes, D. R.; Skinner, D. L. (1976) Consumer talcums and powders: mineral and chemical characterization. J. Toxicol. Environ. Health 2: 255-284.

Rubino, G. F.; Scansetti, G.; Piolatto, G.; Romano, C. A. (1976) Mortality study of talc miners and millers. J. Occup. Med. 18: 186-193.

Russell, R. S.; Merz, R. D.; Sherman, W. T.; Sivertson, J. N. (1979) The determination of respirable particles in talcum powder. Food Cosmet. Toxicol. 17: 117-122.

Sahi, R. P.; Kapoor, V. K.; Seth, S. K.; Yadav, R. V. S. (1967) Talcum granuloma. J. Indian Med. Assoc. 48: 550-551.

Sahle, W.; Sallsten, G.; Thoren, K. (1990) Characterization of airborne dust in a soft paper mill. Ann. Occup. Hyg. 34: 55-75.

Selevan, S. G.; Dement, J. M.; Wagoner, J. K.; Froines, J. R. (1979a) Mortality patterns among miners and millers of non-asbestiform talc: preliminary report. In: Lemen, R.; Dement, J. M., eds. Dusts and disease: proceedings of the conference on occupational exposures to fibrous and particulate dust and their extension into the environment; 1977; Washington, DC. Park Forest South, IL: Pathotox Publishers, Inc.; pp. 379-388.

Selevan, S. G.; Dement, J. M.; Wagoner, J. K.; Froines, J. R. (1979b) Mortality patterns among miners and millers of non-asbestiform talc: preliminary report. J. Environ. Pathol. Toxicol. 2: 273-284.

Siegal, W.; Smith, A. R.; Greenburg, L. (1943) The dust hazard in tremolite talc mining including roentgenological findings in talc workers. AJR Am. J. Roentgenol. 1: 11-29.

Sinha, R. K. (1982) Industrial minerals. New Delhi, India: Oxford and IBH Publishing; pp. 418-429.

Stanton, M. F.; Layard, M.; Tegeris, A.; Miller, E.; May, M.; Morgan, E.; Smith, A. (1981) Relation of particle dimension to carcinogenicity in amphibole asbestoses and other fibrous minerals. JNCI J. Natl. Cancer Inst. 67: 965-975.

Stenback, F.; Rowland, J. (1978) Role of talc and benzo(a)pyrene in respiratory tumor formation: an experimental study. Scand. J. Respir. Dis. 59: 130-140.

Stenback, F.; Wasenius, V.-M.; Rowland, J. (1986) Alveolar and interstitial changes in silicate-associated lung tumors in Syrian hamsters. Cancer Res. Monogr. 2: 199-213.

Stille, W. T.; Tabershaw, I. R. (1982) The mortality experience of upstate New York talc workers. J. Occup. Med. 24: 480-484.

Styles, J. A.; Wilson, J. (1973) Comparison between in vitro toxicity of polymer and mineral dusts and their fibrogenicity. Ann. Occup. Hyg. 16: 241-250.

Tao, L.-C.; Morgan, R. C.; Donat, E. E. (1984) Cytologic diagnosis of intravenous talc granulomatosis by fine needle aspiration biopsy: a case report. Acta Cytol. 28: 737-739.

Thomas, T. L. (1990) Lung cancer mortality among pottery workers in the United States. In: Simonato, L.; Fletcher, A. C.; Saracci, R.; Thomas, T. L., eds. Occupational exposure to silica and cancer risk. Lyon, France: International Agency for Research on Cancer; pp. 75-81. (IARC scientific publications no. 97).

Thomas, T. L.; Stewart, P. A. (1987) Mortality from lung cancer and respiratory disease among pottery workers exposed to silica and talc. Am. J. Epidemiol. 125: 35-43.

Trautwein, G.; Helmboldt, C. F. (1967) Experimental pulmonary talcum granuloma and epithelial hyperplasia in the chinchilla. Pathol. Vet. 4: 254-267.

Tse, D. T.; Ober, R. R. (1980) Talc retinopathy. Am. J. Ophthalmol. 90: 624-640.

Tukiainen, P.; Nickels, J.; Taskinen, E.; Nyberg, M. (1984) Pulmonary granulomatous reaction: talc pneumoconiosis or chronic sarcoidosis? Br. J. Ind. Med. 41: 84-87.

Tye, M. J.; Hashimoto, K.; Fox, F. (1966) Talc granulomas of the skin. JAMA J. Am. Med. Assoc. 198: 120-122.

Vallyathan, N. V.; Craighead, J. E. (1981) Pulmonary pathology in workers exposed to nonasbestiform talc. Hum. Pathol. 12: 28-35.

Wagner, J. C.; Berry, G.; Cooke, T. J.; Hill, R. J.; Pooley, F. D.; Skidmore, J. W. (1977) Animal experiments with talc. In: Walton, W. H.; McGovern, B., eds. Inhaled particles IV (in two parts): proceedings of an international symposium, part 2; September 1975; Edinburgh, United Kingdom. Oxford, United Kingdom: Pergamon Press; pp. 647-654.

Waller, B. F.; Brownlee, W. J.; Roberts, W. C. (1980) Structure-function correlations in cardiovascular and pulmonary diseases (CPC). Self-induced pulmonary granulomatosis: a consequence of intravenous injection of drugs intended for oral use. Chest 78: 90-94.

Wegman, D. H.; Peters, J. M.; Boundy, M. G.; Smith, T. J. (1982) Evaluation of respiratory effects in miners and millers exposed to talc free of asbestos and silica. Br. J. Ind. Med. 39: 233-238.

Wehner, A. P.; Tanner, T. M.; Buschbom, R. L. (1977a) Absorption of ingested talc by hamsters. Food Cosmet. Toxicol. 15: 453-455.

Wehner, A. P.; Wilkerson, C. L.; Cannon, W. C.; Buschbom, R. L.; Tanner, T. M. (1977b) Pulmonary deposition, translocation and clearance of inhaled neutron-activated talc in hamsters. Food Cosmet. Toxicol. 15: 213-224.

Wehner, A. P.; Zwicker, G. M.; Cannon, W. C.; Watson, C. R.; Carlton, W. W. (1977c) Inhalation of talc baby powder by hamsters. Food Cosmet. Toxicol. 15: 121-129.

Wehner, A. P.; Weller, R. E.; Lepel, E. A. (1986) On talc translocation from the vagina to the oviducts and beyond. Food Chem. Toxicol. 24: 329-338.

Weill, H.; Abraham, J. L.; Balmes, J. R.; Case, B.; Churg, A. M.; Hughes, J.; Schenker, M.; Sebastien, P. (1990) Health effects of tremolite. Am. Rev. Respir. Dis. 142: 1453-1458.

Wells, I. P.; Dubbins, P. A.; Whimster, W. F. (1979) Pulmonary disease caused by the inhalation of cosmetic talcum powder. Br. J. Radiol. 52: 586-588.

Wergeland, E.; Andersen, A.; Baerheim, A. (1990) Morbidity and mortality in talc-exposed workers. Am. J. Ind. Med. 17: 505-513.

Whittemore, A. S.; Wu, M. L.; Paffenbarger, R. S., Jr.; Sarles, D. L.; Kampert, J. B.; Grosser, S.; Jung, D. L.; Ballon, S.; Hendrickson, M. (1988) Personal and environmental characteristics related to epithelial ovarian cancer: II. exposures to talcum powder, tobacco, alcohol, and coffee. Am. J. Epidemiol. 128: 1228-1240.

Woodworth, C. D.; Mossman, B. T.; Craighead, J. E. (1982) Comparative effects of fibrous and nonfibrous minerals on cells and liposomes. Environ. Res. 27: 190-205.

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