Draft

Report on Carcinogens Background Document for

Talc
Asbestiform and Non-Asbestiform

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Prepared for the:
U.S. Department of Health and Human Services
Public Health Service
National Toxicology Program
Research Triangle Park, NC 27709

Prepared by:
Technology Planning and Management Corporation
Canterbury Hall, Suite 310
4815 Emperor Blvd
Durham, NC 27703
Contract Number N01-ES-85421

Criteria for Listing Agents, Substances or Mixtures in the Report on Carcinogens

U.S. Department of Health and Human Services
National Toxicology Program

Known to be Human Carcinogens:

There is sufficient evidence of carcinogenicity from studies in humans, which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer.

Reasonably Anticipated to be Human Carcinogens:

There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible but that alternative explanations such as chance, bias or confounding factors could not adequately be excluded; or

There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors: (1) in multiple species, or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site or type of tumor or age at onset; or

There is less than sufficient evidence of carcinogenicity in humans or laboratory animals, however; the agent, substance or mixture belongs to a well defined, structurally-related class of substances whose members are listed in a previous Report on Carcinogens as either a *known to be human carcinogen, or reasonably anticipated to be human carcinogen* or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

Summary Statement

Talc

Asbestiform and Non-Asbestiform

Result of NIEHS Report on Carcinogens Review Group (RG1) Review

Carcinogenesis

Talc containing asbestiform fibers is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from human epidemiological studies. This evidence indicates a moderate increase in lung cancer mortality among workers exposed to talc dust in talc mining and milling operations and in other industrial settings where talc is used. Studies of facilities where the talc was known to have contained asbestos or been of fibrous form give the strongest evidence of risk (IARC 1987, Lamm *et al.* 1988). These studies are supported by the prior listing of asbestos as a known human carcinogen in the Report on Carcinogens (1980). Talc not containing asbestiform fibers is *reasonably anticipated to be a human carcinogen* based on consistent evidence from human epidemiological studies, which showed an increase in ovarian cancer in women who use cosmetic talc in the genital area, and evidence of carcinogenicity from a study in experimental animals.

Talc containing asbestiform fibers has been associated with increases in lung cancer and mesotheliomas in persons employed in talc mining. Workers in facilities producing talcs containing tremolite, anthophyllite and serpentine asbestiform habits demonstrated increased lung and pleural cancers (Kleinfeld *et al*. 1974, Brown *et al.* 1979, Dement *et al.* 1980, Lamm *et al.* 1988). Evidence of increased lung cancer mortality and/or morbidity in cohort studies of workers exposed to fibrous and nonfibrous forms of talc in the ceramics industry (Thomas and Stewart 1987), and in miners exposed to talc not containing asbestiform fibers (Selevan *et al.* 1979, Wergeland *et al*. 1990) is consistent with other reports, but confounding due to exposure to silica dust or radon prevents a definitive interpretation of these findings.

The use of talc for perineal dusting and on sanitary napkins and diaphragms has been associated with ovarian cancer. Fourteen of 16 case control studies of human ovarian cancer provided evidence for an association with the use of talc (presumably cosmetic grade, but information on fibrous content is lacking). A recent large prospective cohort study did not demonstrate an overall increase in risk for ovarian cancer with talc use (Gertig *et al.* 2000). However, in this study talc use was significantly associated with one subtype of ovarian cancer, invasive serous ovarian cancer. Risk of this tumor type was also elevated in several case-control studies (Harlow *et al*. 1992, Chang and Risch 1997, Cook *et al.* 1997, Wong *et al*. 1999, and Cramer *et al*. 1999). There is conflicting evidence concerning transport of talc through the genital tract to the ovary (Hamilton *et al*. 1984). Several studies provided evidence that factors preventing translocation of talc to the ovary, such as tubal ligation or hysterectomy, reduce the risk associated with talc use (Harlow *et al.* 1992, Whittemore *et al*. 1988, Cramer *et al.* 1999). Risk of ovarian cancer associated with talc use is unlikely to be a consequence of confounding or other biases.

There are no adequate experimental animal studies to evaluate the carcinogenicity of talc with asbestiform fibers. There is sufficient evidence in animals of the carcinogenicity of asbestos given by various routes based on multiple studies demonstrating increases in lung tumors and mesotheliomas. In one adequate inhalation study, rats exposed to non-asbestiform talc developed tumors of the adrenal glands and lungs (NTP 1993).

Other Information Relating to Carcinogenesis or Possible Mechanisms of Carcinogenesis

There are few published reports assessing the genotoxicity of talc, with or without asbestiform fibers. In cultures of rat pleural mesothelial cells, incubations with three types of talc failed to induce sister chromatid exchange or unscheduled DNA synthesis, whereas these endpoints were induced by chrysotile and crocidolite asbestos (Endo-Capron *et al*. 1993). There is also evidence from some studies of positive genotoxic effects with various types of asbestos in assays of bacterial mutation, aneuploidy in Drosophila, and DNA breaks, adducts and unscheduled synthesis in mammalian cells in culture.

The lung tumor response in female rats exposed by inhalation to non asbestiform talc has been attributed to a non specific dust overload mechanism, and its relevance for human hazard identification has been questioned (Goodman 1995, Oberdoster 1995, Zazenski *et al.* 1995). However, estimates of clearance rates of talc from human lung are slower than from rats (Pickrell *et al*. 1989), and talc particles and talc "bodies" have been isolated from human bronchiolar lavage fluid many years after exposure to talc, raising the possibility of similar pathologic responses in rats and humans to inhaled talc.

Talc

Asbestiform and Non-Asbestiform

Result of NTP Executive Committee Interagency Working Group for the Report on Carcinogens (RG2) Review

Carcinogenesis

Exposure to talc containing asbestiform fibers is *reasonably anticipated to be a human carcinogen* based on findings of elevated lung cancer mortality in occupational groups exposed to talc containing asbestiform fibers. These findings indicate a moderate increase in lung cancer mortality among workers exposed to talc dust in talc mining and milling operations and in other industrial settings where talc is used. Studies of facilities where the talc was known to have contained asbestiform fibers give the strongest evidence of risk (IARC 1987, Lamm *et al.* 1988). Talc not containing asbestiform fibers is *reasonably anticipated to be a human carcinogen* based on consistent evidence from human epidemiological studies, which showed an increase in ovarian cancer in women who use cosmetic talc in the genital area, and evidence of carcinogenicity from a study in experimental animals.

Talc containing asbestiform fibers has been associated with increases in lung cancer and mesotheliomas in persons employed in talc mining. Workers in facilities producing talcs containing tremolite, anthophyllite and serpentine asbestiform habits demonstrated increased lung and pleural cancers (Kleinfeld *et al*. 1974, Brown *et al.* 1979, Dement *et al.* 1980, Lamm *et al.* 1988). Evidence of increased lung cancer mortality and/or morbidity in cohort studies of workers exposed to fibrous and nonfibrous forms of talc in the ceramics industry (Thomas and Stewart 1987), and in miners exposed to talc not containing asbestiform fibers (Selevan *et al.* 1979, Wergeland *et al*. 1990) is consistent with other reports, but confounding due to exposure to silica dust or radon prevents a definitive interpretation of these findings.

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There are no adequate experimental animal studies to evaluate the carcinogenicity of talc with asbestiform fibers. In one adequate inhalation study, rats exposed to non-asbestiform talc developed tumors of the adrenal glands and lungs (NTP 1993).

Other Information Relating to Carcinogenesis or Possible Mechanisms of Carcinogenesis

There are few published reports assessing the genotoxicity of talc, with or without asbestiform fibers. In cultures of rat pleural mesothelial cells, incubations with three types of talc failed to induce sister chromatid exchange or unscheduled DNA synthesis, whereas these endpoints were induced by chrysotile and crocidolite asbestos (Endo-Capron *et al*. 1993).

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1 Introduction

Talc is a hydrous mineral consisting of magnesium silicate ($3MgO.4SiO_2.H_2O$) and is generally identified as either containing asbestiform fibers (asbestiform talc) or not containing asbestiform fibers (non-asbestiform talc). Talc ore may contain several other minerals, including calcite, carbonates, dolomite, free silica, magnesite, tremolite, serpentines (including chrysotile), quartz, or micas. "Asbestiform talc" generally refers to talcs containing asbestiform tremolite/actinolite, athophyllite, or chrysotile. These are the predominant asbestiform mineral species found in talcs. Because talc products are sold in a multitude of grades that have physical or functional characteristics especially suited for particular applications, occupational and consumer exposures to talc are complex. The International Agency for Research on Cancer (IARC) reported in 1987 that there was sufficient evidence for the carcinogenicity of asbestiform talc in humans and classified it as *carcinogenic to humans* (Group 1) (IARC 1987a). The IARC also reported in 1987 that there was inadequate evidence for the carcinogenicity of non-asbestiform talc in humans or for the carcinogenicity of either form of talc in experimental animals. A number of human and experimental animal carcinogenicity studies of talc have been published since the IARC listing (NTP 1993, Wehner 1994, Shoham 1994, Harlow and Hartge 1995, Gross and Berg 1995, Whysner and Mohan 2000) that suggest an association between exposure to non-asbestiform talc (including cosmetic talc) and cancer risk in humans. Based on this evidence, both asbestiform and non-asbestiform talc were nominated for listing in the Report on Carcinogens (RoC) by the National Institute of Environmental Health Sciences (NIEHS)/National Toxicology Program (NTP) RoC Review Group (RG1).

1.1 Chemical identification

The term "talc," in the mineralogical sense, denotes a specific rock-forming mineral of the sheet silicate category. However, when talc is referenced in the commercial or industrial setting, it may represent a mixture of a variety of minerals (such as calcite, quartz, magnesite, serpentines, diopside, and fibrous and non-fibrous amphiboles) with chemical properties similar to those of mineral talc. Some talc deposits may contain talc which occurs in a fibrous habit. Also, fibrous talc and one or more of the asbestiform minerals may be found in the same ore depsits.

Talc is formed by geological metamorphosis and is therefore associated with many types of minerals. Table 1-1 lists some minerals commonly found in talcs.

Table 1-1. Minerals commonly found in talcs

Mineral Group	Phase	Formula CASRN	Properties
Carbonates	calcite	$CaCO_3$ 471-34-1	hygroscopic, used for generating carbon dioxide, dehydrohalogenating agent
	dolomite	$CaMg(CO_3)_2$ 7000-29-5	NA
	magnesite	$MgCO_3$ 13717-00-5, 546-93-0	solid
Amphiboles	tremolite[a]	$Ca_2Mg_5Si_8O_{22}(OH)_2$ 14567-73-8 (non-asbestiform)	NA
	anthophyllite[a]	$(FeMg)_7Si_8O_{22}(OH)_2$ 1332-21-4 (asbestiform)	fine, slender, flaxy fibers; resists fire and most solvents
Serpentine	antigorite	$Mg_3Si_2O_5(OH)_4$	NA
	chrysotile[b]	$Mg_3Si_2O_5(OH)_4$	NA
	lizardite[b]	$Mg_3Si_2O_5(OH)_4$	NA
Others	quartz	SiO_2 14808-60-7	solid
	mica, e.g., phlogopite	$K_2(Mg, Fe)_6Si_6Al_2O_{20}(OH)_4$ 12001-26-2	colorless, odorless flakes or sheets
	chlorite, e.g., penninite	$(Mg, Al, Fe)_{12}(SiAl)_8O_{20}(OH)_{16}$	NA
	pyrophyllite	$Al_4Si_8O_{20}(OH)_4$	NA

Source: IARC 1987a
NA: not available.
[a]Occurring as asbestiform and non-asbestiform varieties.
[b]Uncommon.

Talc ($Mg_3Si_4O_{10}[OH]_2$, mol wt 379.26, CASRN 14807-96-6) is a white to grayish-white, very fine crystalline powder (unctuous) consisting of natural hydrous magnesium silicate. Talc in its pure mineral form is composed of 63.5% SiO_2, 31.7% MgO, and 4.8% H_2O (NTP 1993). Most, if not all, talcs have a triclinic structure (IARC 1987a). Talc also is known by the following names:

hydrous magnesium silicate
fibrous non-tremolite talc
silica, talc, non-asbestos form
talc, non-asbestos form
talcum
steatite talc
talc (containing no asbestos)
talc (containing no asbestos fibers)
magnesium silicate talc
talc, non-asbestos form, silica

French chalk	steatite
mineral graphite	non-asbestiform talc
non-fibrous talc	talc

Its RTECS code is WW2700000. The chemistry of talc shows little variation, suggesting that only a limited substitution of ions might take place in the mineral lattice. Small amounts of aluminum and titanium may substitute for silicon to some extent. Iron, nickel, manganese, or chromium may also substitute for magnesium (IARC 1987a).

Cosmetic talc is powdered magnesium silicate. It contains at least 90% talc mineral and no detectable asbestos (Rohl *et al.* 1976). Cosmetic talcs (and talcs used as fillers in pharmaceuticals) are required to meet strict standards in order to assure the quality of the product. The major requirement is that 98% of the particles should be less than 200 mesh and that the talc should contain no gritty material. It should also contain less than 6% acid-soluble minerals, contain no amphiboles, and have a consistent color and mineralogical composition (Zazenski *et al.* 1995).

1.2 Physical-chemical properties

Pure talc is a translucent mineral and is mineralogically defined as hydrous magnesium silicate ($Mg_3(Si_2O_5)_2(OH)_2$). The crystal structure of talc is characterized by composite sheet arrangements lying parallel to a common plane. These sheets consist of three sublayers comprising a layer of edge-linked $MgO_4(OH)_2$ octahedra sandwiched between two identical layers of corner-linked SiO_4 tetrahedra. The apical oxygen atom positions of the tetrahedra layers are shared with one of the oxygen atom positions of the octahedra layer (Zazenski *et al.* 1995).

Talc is an odorless powder that has a pearly or greasy luster and a greasy feel. It has a high resistance to acids, alkalis, and heat, with a melting point of 800^{o}C. It readily adheres to skin. The physical and chemical properties of talc are listed in Table 1-2.

Table 1-2. Physical and chemical properties of talc

Property	Information	Reference
Molecular weight	379.26	Radian 1996
Color	white to grayish white	HSDB 1994, ChemFinder 2000
Odor	odorless	HSDB 1994, ChemFinder 2000
Physical state	very fine crystalline powder (unctuous) with a pearly or greasy luster and a greasy feel	HSDB 1994, ChemFinder 2000
Melting point (°C)	800	ChemFinder 2000
Mohs hardness	1–1.5	HSDB 1994
Specific gravity or density (at 20°C/4°C)	2.7–2.8	HSDB 1994

Property	Information	Reference
Vapor pressure (mm Hg at 20°C)	0	Radian 1996
Solubility:		
Water at 21°C	insoluble, < 0.1 g/100 mL	ChemFinder 2000, HSDB 1994
DMSO at 21°C	insoluble, < 0.1 g/100 mL	Radian 1996
95% Ethanol at 21°C	insoluble, < 0.1 g/100 mL	Radian 1996
Acetone at 21°C	insoluble, < 0.1 g/100 mL	Radian 1996
Cold acids	insoluble	HSDB 1994
Alkalis	insoluble	HSDB 1994

Because of the variety of ways in which the geological formation of talc is manifest, virtually every talc deposit is unique in both its chemistry and its morphology (Piniazkiewicz *et al.* 1994, cited in Zazenski *et al.* 1995). Talc may contain asbestiform fibers (tremolite, anthophyllite, and chrysotile) in total concentrations greater than the concentration of the talc mineral itself (Kleinfeld *et al.* 1973, 1974, Rohl and Langer 1974, all cited in IARC 1987a). Some minerals have different names depending on whether they are asbestiform or non-asbestiform (e.g., the non-asbestiform of chrysotile is antigorite) (Morgan 1990).

1.3 Asbestiform talc

Unlike many chemical substances that are discrete entities definable by a fixed chemical structure, asbestiform fibers comprise a group of materials that are not easily defined. They have a broad range of chemical compositions and crystal structures, sizes, shapes, and properties, and have been described with diverse terminology.

The term “crystal” refers to a solid with a highly ordered, periodic arrangement of atoms. The arrangement of atoms is called the crystal structure. “Crystallization habit” refers to the distinct natures and shapes of individual crystals or aggregations of several crystals. The crystallization habit of a mineral usually is identified by terms describing its appearance, such as equant (equidimensional), filiform (hairlike), and so on, according to the dominant geometric shape. The basic properties of minerals usually do not vary with different crystallization habits, but a noteworthy exception is the asbestiform habit.

“Asbestiform habit” refers to the unusual crystallization habit of a mineral in which the crystals are thin, hairlike fibers. Historically, the definition of the asbestiform habit was based primarily on appearance, and the properties were only implied. At present, the definition of asbestiform habit often is augmented to include a statement on the properties of asbestiform fibers: shape; enhanced strength, flexibility, and durability; diameter-dependent strength; and unique surfaces. The fibers of asbestos are good examples of the asbestiform habit.

Asbestiform describes a special type of fibrosity. “Fibrous” is a broad term that includes, for example, both asbestos and pseudomorphic fibrous quartz. Asbestos is composed of distinct fibers with unique properties, whereas most fibrous quartz breaks into odd-shaped fragments unrelated to its apparent fibrous appearance. The proper use of

mineralogical nomenclature for fibrous materials, particularly asbestos, and problems that have arisen from improper usage have been discussed in several reports (Campbell *et al*. 1977, Langer *et al*. 1979, Zoltai 1978). In particular, the term "asbestiform" has been used in a variety of ways in the past, sometimes applying only to asbestos or to fibers that look like asbestos.

"Acicular crystals" are crystals that are extremely long and thin and have a small diameter (an acicular crystal is a special type of prismatic crystal). However, small-diameter crystals with a high aspect ratio may be asbestiform if they are strong and flexible. Larger-diameter crystals, even if stronger and more flexible than the parent mineral, usually are described as "filiform" or hairlike. The limiting upper diameter of "whiskers" (synthetic crystals that share the properties of asbestiform fibers) usually is considered to be 15 μm; the same diameter may be used for the definition of asbestiform fibers.

"Fibrous" refers to (l) single crystals that resemble organic fibers such as hair or cotton and (2) large crystals or crystalline aggregates that look like they are composed of fibers (i.e., long, thin, needlelike elements) (Dana and Ford 1932). The apparent fibers do not need to be separable. If the fibers are separable and are strong and flexible, they are asbestiform. If they have the normal strength and brittleness of the mineral, they are acicular. If the apparent fibers are not separable, the specimen may be a single crystal or a multiple (polycrystalline) aggregate displaying a fibrous pattern (resulting, for example, from striation or pseudomorphic replacement of an initially fibrous mineral).

The term "mineral fibers" has traditionally referred to crystals whose appearance and properties resembled those of organic fibers, such as hair and cotton. In some recent literature, however, the term sometimes refers only to the appearance of the material, which can cause confusion about whether particular properties also are implied.

Although talcs can be virtually free of fibrous materials, they also have been reported to contain asbestos fibers in quantities sometimes constituting almost half the total product weight (Dement and Zumwalde 1979). Surveys published in the late 1960s and 1970s reported that talcum powders contained measurable amounts of chrysotile, tremolite, and anthophyllite fibers that may be of asbestiform nature (Rohl *et al.* 1976). However, the purity of cosmetic talc appears to have improved as a result of voluntary guidelines proposed by the cosmetic industry in 1976 (see Section 2).

Natural talc deposits and commercial talc products sometimes are found to contain serpentines (chrysotile, antigorite, and lizardite) and fibrous and non-fibrous amphiboles (Rohl *et al*. 1976). This form is also known as asbestiform talc, talc (containing asbestos), or talc containing asbestiform fibers. Its ACX number is X1005061-4 (ChemFinder 2000). Conflicting views have been expressed regarding the extent to which these fibrous constituents are asbestos. Table 1-3 summarizes information about the use of the term "asbestiform talc."

The biological activity of mineral fibers depends upon respirability as defined by the dimensions and density of the fibers, the dose, and the durability of the fibers in the

biological system. The aerodynamic diameter of fibers is largely determined by actual fiber diameter rather than fiber length. Generally, respirable dust includes those unit-density particles with a diameter of less than 7 μm according to the criteria of the British Medical Research Council or a diameter of less than 10 μm according to the criteria of the U.S. Atomic Energy Commission or the American Conference of Governmental Industrial Hygienists (ACGIH). Respirable fibers are generally considered to be airborne fibers having actual diameters smaller than approximately 3 to 4 μm. Fibers and dust particles satisfying these criteria are capable of reaching and being deposited in the nonciliated portion of the lung, where gas exchange takes place (Asbestos Institute 2000).

Table 1-3. Physical and chemical properties of some mineral silicate fibers

Chemical name CASRN	Synonyms	RTECS	Physical state	Reactivity
Asbestos fiber 1332-21-4	sodium hydroxide coated non-fibrous silicate; asbestos; anthophyllite; anthophyllite fibers; grunerite; tremolite fibers; asbestos (friable); asbestos; asbestos by TEM; ascarite (II) (R); grunerite fibers	CI6475000	fine, slender, flaxy fibers	resists fire and most solvents
Chrysotile 12001-29-5	asbestos (white); serpentine chrysotile; chrysotile asbestos; chrysotile fibers	NA	curled sheet silicate, spiraled as a helix around a central capillary	NA
Anthophyllite 17068-78-9	asbestos, all forms; anthophyllite asbestos	NA	orthorhombic magnesium-iron amphibole with possible aluminum substitution	NA
Actinolite 13768-00-8	actinolite asbestos	NA	NA	NA
Amosite 12172-73-5	asbestos (brown); amosite asbestos; asbestos, grunerite	NA	an exploited variety of grunerite that tends to occur with more iron than magnesium, and manganese substitution may occur	NA
Crocidolite 12001-28-4	asbestos (blue); crocidolite; crocidolite fibers; crocidolite asbestos	NA	an exploited form of rock-forming amphibole mineral riebeckite	NA
Tremolite 14567-73-8	tremolite asbestos	NA	NA	NA

Source: IARC 1977, ChemFinder 2000
NA: not available.

2 Human Exposure

2.1 Use

Talc is an extremely versatile inorganic substance with many uses in industry. The largest commercial use of talc is in industrial applications such as rubber, paint, plastics, paper, ceramics, and construction materials. The largest portion of ground talc is used in ceramics (U.S. EPA 1992). Talc has also used extensively in the rubber industry as many synthetic rubbers inlcude ground talc as fillers in compound formulations (IARC 1987a). Table 2-1 summarizes direct consumer applications of talc. End uses for ground talc are shown in Table 2-2.

2.1.1 Ceramics

In the United States, about 35% of all native or imported talc is used in ceramics. Talc is used for its color, fast firing, and low shrinkage properties. It is used in floor and wall tiles, china, glazes, electrical porcelains, sanitary ware, kiln furniture, and pottery. Ceramic insulators contain up to 80% talc. Some china contains up to 15% talc by weight, and some pottery contains up to 40% talc (IARC 1987a, U.S. EPA 1992).

2.1.2 Paint

Around 20% of all talc used in the United States is used as a pigment extender and filler in paints. Fineness of grade and color are important functional characteristics of talc used in paints (IARC 1987a, U.S. EPA 1992).

2.1.3 Plastics and building materials

The plastics, rubber, and roofing industries use around 20% of all talc used in the United States. Talc is used in plastics (7%) as a stabilizer, reinforcer, and filler; it can be used at a content of up to 70% w/w. In roofing materials (9%), talc is added to asphalt at a content of 10% to 35% in composite shingling materials, where it imparts stability and weather resistance. Around 3% of the talc quarried in the United States is used in the rubber industry (IARC 1987a, U.S. EPA 1992).

2.1.4 Paper

About 10% of all talc used in the United States is used in paper coatings and fillings. This is the fastest growing use of talc in the United States (IARC 1987a, U.S. EPA 1992).

2.1.5 Pharmaceutical and over-the-counter tablets

Talc is used for various processes in the tableting of pharmaceutical and over-the-counter products. Talc can be used as a glidant, in quantities ranging from 0.5% to 2.0% by weight of tablet. It helps as a processing aid (flow agent) for other active and inactive ingredients. Talc also is used as a lubricant, in quantities ranging from 1.0% to 2.0% by weight of tablet. It is used to ensure that tablets released from the die wall in the tablet press remain smooth and do not crack. Talc is used as a dusting agent to prevent tablets from sticking to various surfaces. It is used as a coating aid, in quantities ranging from 1.0% to 5.0% by weight of the formulation. Talc is added to ensure that the coating or

film will stay without showing cracks and ridges. Talc also can brighten the pigments or colorants used in the coating (Zazenski *et al.* 1995).

2.1.6 Confectionery food products

In the United States, about 3% of all talc is used in the production of chewing gum and selected hard candy. Talc is used as a detackifying agent as well as a filler and general stabilizer. Candies can contain up to 33% talc by volume when it is used as a filler (Zazenski *et al.* 1995).

2.1.7 Cosmetic applications

Talc has many characteristics that make it ideal for use in the cosmetic industry. It is one of the softest minerals known that can yield and bend without fracturing. Because sheets of talc are held together by relatively weak Van der Waals forces, talc platelets slide upon one another, resulting in lubricity. The platelet structure of talc allows it to lie over skin, covering blemishes while minimizing cover thickness. Talc is used in several types of cosmetic formulations. Solid-matrix formulations include antiperspirants, lipstick, and concealing makeup. Semi-solid-matrix formulations include blushes, eyeshadows, pressed finishing powders, and base powders. Liquid-matrix formulations include cream and liquid makeups, moisturizing creams, and lotions. Loose-matrix products include foot, body, and baby powders, where talc is used to carry fragrances (Zazenski *et al.* 1995). Current databases indicate that about 2,000 products containing talc, in some 45 different cosmetic product categories, were voluntarily registered with the U.S. Food and Drug Administration (FDA). Categories of cosmetic products that contain talc include baby products (baby lotions, oils, powders, and creams), generic powders, blushers, face powders and foundations, men's talcum products, and foot powders (Gilbertson 1995).

Table 2-1. Direct consumer applications of talc

Application	Estimated percentage of total use
Loose powders	71
Pressed powders (eye and face makeup)	18
Pharmaceutical tableting	5
Chewing gum and other food applications	3
Antiperspirants	3

Source: Zazenski *et al.* 1995

Table 2-2. End uses for ground talc in the United States

Use	Amount of talc used (thousand short tons)	Percentage of all talc used
Ceramics	358	37
Cosmetics[a]	44	5
Insecticides	8	1
Paint	189	19
Paper	100	10
Plastics	67	7
Refractories	4	< 1
Roofing	86	9
Rubber	29	3
Other[b]	85	9
Total	**970**	**~100**

Source: Clifton 1985, cited in U.S. EPA 1992
[a]Incomplete data; some cosmetic talc is known to be included with "other."
[b]Includes art sculpture, asphalt filler and coatings, crayons, floor tile, foundry facings, rice polishing, stucco, and uses not specified.

2.2 Production

Talc is derived by alteration of mineral rocks after exposure to specific temperatures, pressures, and circulating liquid solutions or by the thermal metamorphism of silicon dolomites. Large-scale talc production in the United States started in 1880. Talc is mined by means of hand tools, drilling, and blasting (U.S. EPA 1992).

In 1985, U.S. talc production was reported to be 1.21 million short tons (1.09 million metric tons) (HSDB 1994). In 1989, U.S. production of talc was reported by the U.S. Bureau of Mines to be 1.25 million short tons (1.13 million metric tons). Production levels in 1990 increased by 7%. Approximately 23 talc-producing mines in 10 states were operating in 1990. More than 88% of the domestic yield of talc was produced in Montana, Texas, Vermont, and New York (U.S. EPA 1992).

2.3 Analysis

Before 1970, nearly all measurements of talc exposures were made by collecting particles in an impinger and counting them by optical microscopy. For determination of fiber exposures, samples are collected on a different type of filter than is typically used for mass sampling. Determination of fiber concentrations is done by counting of fibers using phase contrast microscopy. Transmission electron microscopy can be used for fiber identification and to observe fibers too small to be seen using phase contrast microscopy.

Analysis of bulk samples for mineral content is normally done using polarizing light microscopy, X-ray diffraction, and transmission electron microscopy. X-ray diffraction of bulk samples is sensitive to talc at concentrations of 1% to 2%, and the detection limit is

0.4 μg/cm^2. Tremolite, chrysotile, and anthophyllite impurities in talc can be detected at concentrations as low as ≤ 1.2% (U.S. EPA 1992).

The National Institute for Occupational Safety and Health (NIOSH) method 7601 describes how to determine the amount of crystalline silica in respirable or total dust, settled dust, and in biological samples by visible absorption spectrophotometry. No accuracy of overall precision was determined for this method (NIOSH 1994).

NIOSH also describes methods (NIOSH methods 7400, 7402, and 9000) to determine asbestos content in various samples. Method 7400 is used to determine an index of airborne fibers by phase contrast light microscopy (PCM). This method is used to estimate asbestos concentrations, though PCM does not differentiate between asbestos and other fibers. PCM is usually used in conjunction with electron microscopy (method 7402). Transmission electron microscopy is used to determine asbestos fibers in the optically visible ranges and is intended to complement the results obtained by PCM. The quantitative working ranges for these 2 methods is 0.04-0.5 fiber/cm^3 for a 1,000 L air sample. Method 9000 is used to determine the percent chrysotile asbestos in bulk samples by X-ray powder diffraction (NIOSH 1994). Transmission electron microscopy and energy dispersive X-ray spectroscopy can be used to analyze talc concentrations in lungs (HSDB 1989).

2.4 Environmental occurrence

Talc is a mineral product with widely varying compositions from one deposit to another and even within the same deposit. No information about ambient levels of talc was found in the published literature.

2.5 Environmental fate

Talc is not expected to undergo chemical transformations when released into the environment. Environmental fate and transport processes affecting talc are not well characterized (U.S. EPA 1992).

2.6 Environmental exposure

Environmental exposure to talc usually is due to consumer use of products that contain talc. Talc may also migrate to food from packaging materials (HSDB 1989). Exposure to talc in cosmetic and health care products is infrequent and of minimal duration. Studies were done to determine talc exposure levels in infants and adults because of reported cases of accidental aspiration of excess talc. During a 10-second dusting period, children were exposed to 0.243 million particles per cubic foot (mppcf) (~32.4 μg/m^3, approximate conversion NIOSH 2000). During the 65 seconds required for the dust to settle, the average exposure was 0.124 mppcf (~16.5 μg/m^3, approximate conversion NIOSH 2000). The median exposure per application was estimated at 0.1752 mppcf (~23.4 μg/m^3, approximate conversion NIOSH 2000) (U.S. EPA 1992).

Another study was conducted to determine talc exposure of 48 infants and 44 adults during routine application of talcum powder. The time-weighted average (TWA) for infant exposure was 0.095 mg/m^3 per minute. For adult exposures, the TWA was

1.729 mg/m^3 per minute. The average weekly exposure measurements were calculated to be 0.055 mg/m^3 per hour for infants and 0.20 mg/m^3 per hour for adults (U.S. EPA 1992).

2.7 Occupational exposure

The greatest exposure to talc dust is when it is used industrially or while it is being mined or milled. In 1933, miners using jackhammer drills in a Georgia talc plant were exposed to talc at concentrations of 1,440 mppcf, and millers at the same plant were exposed to talc at 52 mppcf. Occupational exposure to fibrous talc was evaluated in a New York mine from 1945 to 1972. Average exposures to mine dust ranged from 120 to 818 mppcf. After 1945, when dust-control measures such as wet drilling were implemented, exposure was reduced to 5 to 19 mppcf. Exposure in the mills before 1945 ranged from 69 to 278 mppcf. In 1972, average exposures ranged from 7 to 36 mppcf. Occupational exposure to talc in this mine, as in others that were studied, was much higher in the mills than in the mines (U.S. EPA 1992, IARC 1987a).

A cross-sectional study of occupational exposures in U.S. talc mines and mills was conducted in 1982. Work histories and personal respirable dust samples were obtained for 299 miners and millers in Montana, Texas, and North Carolina. The average talc dust exposures were 1.2, 2.6, and 0.3 mg/m^3, respectively, and the average times worked were 7, 6, and 10 years (U.S. EPA 1992).

The Mine Safety and Health Administration analyzed 362 personal samples of respirable dust collected from talc mines and mills in the United States. The median exposure to respirable dust was 1.20 mg/m^3, with 90% of all exposures < 2.78 mg/m^3 (U.S. EPA 1992).

NIOSH estimated that 1,536,754 people were exposed to talc according to the National Occupational Hazard Survey, conducted from 1972 to 1974. Only 14% of the workers were exposed to the talc product itself, while 31% were exposed to trade-name products containing talc, and 56% were exposed to generic products suspected of containing talc. According to the National Occupational Exposure Survey, conducted from 1980 to 1983, 18,872 workers, including 5,244 females, were potentially exposed to talc (U.S. EPA 1992). Occupational exposure levels are given in Table 2-3.

Table 2-3. Occupational airborne concentrations of talc dust

Reference	Concentrations (µg/m3)			
	Gross		Respirable	
	Range of averages	Range of concentrations	Range of averages	Range of concentrations
Boundy *et al.* 1979, Wegman *et al.* 1982	–	–	0.5–5.1	–
Dement and Zumwalde 1979, Dement *et al.* 1980, Selevan *et al.* 1979	4.3–5.0	0.2–29.1	0.86	0.23–4.64
Fine *et al.* 1976	–	–	0.47–3.55	0.28–5.73
Gamble *et al.* 1982, Greife 1980	–	–	0.14–1.56	0.07–2.54
Dement and Shuler 1972	–	5.4–199	–	0.9–7.8
	Concentrations (mppcf)			
Dreessen and Dalla Valle 1935, Dreessen 1933	–	17–1,672	–	–
Hogue and Mallette 1949	–	–	15–50	–
Kleinfeld *et al.* 1974, 1973, 1967, 1955, Messite *et al.* 1959	–	–	69–1,227[a] (pre-1945–1969)	–
Rubino *et al.* 1976	–	–	12–798 (to 1955) 4–49 (1956–1965) 0.8–8 (1966–1972)	–

Source: U.S. EPA 1992
[a]For both mining and milling operations.

2.8 Biological indices of exposure

No information about biological indices of exposure was found in the published literature.

2.9 Regulations

The U.S. Environmental Protection Agency (EPA) regulates talc under the Federal Insecticide, Fungicide, and Rodenticide Act, stating that talc and soapstone are exempt from requirement of a tolerance when they are used as a solid diluent or carrier in pesticides. The U.S. EPA also sets effluent limitations in the talc, steatite, soapstone, and pyrophyllite industries.

The FDA regulates talc, stating that it is generally recognized as safe for use in color additives in foods, drugs, and cosmetics and in paper, paper products, cotton, and cotton fabrics that come in contact with food. The FDA also states that talc is present in over-the-counter (OTC) astringent drug products, but that based on evidence currently available, the data are inadequate to establish general recognition of talc's safety and effectiveness in astringent drug products. Talc also is identified as a constituent in nystatin topical powder and nystatin–neomycin sulfate–gramicidin topical powder, both antifungal antibiotic drugs. The FDA states that companies shall voluntarily file cosmetic product ingredient and cosmetic raw material composition statements. However, because reporting is not mandatory, the FDA does not know exactly how many products on the market contain talc. The FDA does maintain a Voluntary Registration Program for cosmetics, in which companies can report their finished products and qualitative disclosures of ingredient composition.

The FDA, under the federal Food, Drug, and Cosmetic (FD&C) Act, has established Current Good Manufacturing Practices (CGMPs) for food, drugs, and medical devices. Talc facilities engaged in the manufacture of Food Chemical Codex (FCC), the United States Pharmacopeia (USP), and Cosmetic, Toiletry, and Fragrances Association (CTFA) grade talc products are subject to the FD&C Act and are prohibited from introducing adulterated articles into interstate commerce. Talc facilities engaged in the production of FCC- and USP-grade talc products must comply with the FDA's CGMPs for manufacturing, processing, packing, or holding of food and drugs, respectively. Under the voluntary guidelines initiated in 1976, the CFTA stated that all cosmetic talc should contain at least 90% platy talc that is free of detectable amounts of fibrous minerals, including asbestos (Harlow and Hartge 1995, Gilbertson 1995, Zazenski *et al.* 1995).

The Occupational Safety and Health Administration's (OSHA's) current permissible exposure level (PEL) for non-asbestiform talc is ~3 mg/m^3 (20 mppcf) measured as respirable dust. The current ACGIH threshold limit value (TLV) TWA limit is 2 mg/m^3 (15 mppcf), which also is the proposed OSHA limit. The OSHA standard for asbestiform talc is 0.1 fiber/cm^3 of air as an 8-hour TWA. Excursions in worker exposure levels may exceed three times the TLV-TWA for no more than 30 minutes during the workday.

EPA regulations for talc are summarized in Table 2-4, FDA regulations in Table 2-5, and OSHA regulations in Table 2-6.

Table 2-4. EPA regulations

Regulatory action	Effect of regulation and other comments
40 CFR 180.1001—SUBPART D—Exemptions From Tolerances. Promulgated: 36 FR 22540, 11/25/71.	Residues of talc and soapstone are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops or to raw agricultural commodities after harvest when used as a solid diluent or carrier.
40 CFR 436—PART 436—MINERAL MINING AND PROCESSING POINT SOURCE CATEGORY. Promulgated: 60 FR 35796, 07/11/95.	This part contains effluent limitations guidelines representing the degree of effluent reduction attainable by the application of the best practicable control technology currently available for the talc, steatite, soapstone and pyrophyllite subcategory.

Source: The regulations in this table have been updated through the 1999 Code of Federal Regulations 40 CFR, 1 July 1999.

Table 2-5. FDA regulations

Regulatory action	Effect of regulation and other comments
21 CFR 73—PART 73—LISTING OF COLOR ADDITIVES EXEMPT FROM CERTIFICATION. Promulgated: 42 FR 15643, 03/22/77. U.S. Codes: 21 U.S.C. 321, 341, 342, 343, 348, 351, 352, 355, 361, 362, 371, 379e.	Talc may be safely used in amounts consistent with good manufacturing practice to color drugs generally. The label of the color additive and of any mixtures prepared therefrom intended solely or in part for coloring purposes shall conform to the requirements of 21 CFR 70.25.
21 CFR 82—PART 82—LISTING OF CERTIFIED PROVISIONALLY LISTED COLORS AND SPECIFICATIONS. Promulgated: 42 FR 15669, 03/22/77. U.S. Codes: 21 U.S.C. 371, 379e, 379e.	A batch of a straight color listed in this subpart may be certified, in accordance with the provisions of the regulations in this part, for use in food, drugs, and cosmetics, if such batch conforms to the requirements of 21 CFR 82.5 and to the specifications in this subpart set forth for such color. Talc may be used in the formation of lakes for food, drugs, and cosmetics provided the basic color is stated in the labeling.
21 CFR 110—PART 110—CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PACKING, OR HOLDING HUMAN FOOD. Promulgated: 51 FR 24475, 06/19/86. U.S. Codes: 21 U.S.C. 342, 371, 374; 42 U.S.C. 264.	The criteria and definitions in this part shall apply in determining whether a food is adulterated (1) in that the food has been manufactured under such conditions that it is unfit for food or (2) in that the food has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health.
21 CFR 176—PART 176—INDIRECT FOOD ADDITIVES: PAPER AND PAPERBOARD COMPONENTS. Promulgated: 42 FR 14554, 03/15/77. U.S. Codes: 21 U.S.C. 321, 342, 346, 348, 379e.	Talc may be safely used without extractives limitations as a component of the uncoated or coated food-contact surface of paper and paperboard in contact with aqueous or fatty food.
21 CFR 178.3010—SUBPART D—Certain Adjuvants and Production Aids. Promulgated: 58 FR 64895, 12/10/93.	Color additives and their lakes listed for direct use in foods, under the provisions of the color additive regulations in parts 73, 74, 81, and 82 of this chapter, like talc, may also be used as colorants for food-contact polymers.

Regulatory action	Effect of regulation and other comments
21 CFR 182—PART 182—SUBSTANCES GENERALLY RECOGNIZED AS SAFE. Promulgated: 42 FR 14640, 03/15/77. U.S. Codes: 21 U.S.C. 321, 342, 348, 371.	Talc is generally recognized as safe for its intended use as a substance migrating to food from paper and paperboard products and as a substance migrating to food from cotton and cotton fabrics used in dry food packaging.
21 CFR 210—PART 210—CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS; GENERAL. Promulgated: 43 FR 45076, 09/29/78. U.S. Codes: 21 U.S.C. 321, 351, 352, 355, 356, 357, 360b, 371, 374.	The regulations set forth in this part contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess. The failure to comply with any regulation set forth in this part in the manufacture, processing, packing, or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) of the act, and such drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action.
21 CFR 310—PART 310—NEW DRUGS. Promulgated: 55 FR 46919, 11/07/90. U.S. Codes: 21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b-360f, 360j, 361(a), 371, 374, 375, 379e; 42 U.S.C. 216, 241, 242(a), 262, 263b-263n.	Talc is present in OTC drug products in astringent drug products. However, based on evidence currently available, there are inadequate data to establish general recognition of the safety and effectiveness of talc in astringent drug products.
21 CFR 449—PART 449—ANTIFUNGAL ANTIBIOTIC DRUGS. Promulgated: 39 FR 19134, 05/30/74. U.S. Codes: 21 U.S.C. 357.	Talc is identified as a constituent in the following types of antifungal antibiotic drugs: Nystatin topical powder and nystatin–neomycin sulfate–gramicidin topical powder.
21 CFR 720—PART 720—VOLUNTARY FILING OF COSMETIC PRODUCT INGREDIENT AND COSMETIC RAW MATERIAL COMPOSITION STATEMENTS. Promulgated: 39 FR 10060, 04/15/74. U.S. Codes: 21 U.S.C. 321, 331, 361, 362, 371, 374.	Information concerning certain powders (dusting and talcum) is required to be provided by manufacturers to any that inquire. Manufacturers must provide ingredient information (and, when requested, ingredient samples) to a licensed physician, and provide poison control centers with ingredient information and/or adequate diagnostic and therapeutic procedures to permit rapid evaluation and treatment of accidental ingestion or other accidental use of the cosmetic product, and various other information.

Source: The regulations in this table have been updated through the 1999 Code of Federal Regulations 21 CFR, 1 April 1999.

Table 2-6. OSHA regulations

Regulatory action	Effect of regulation and other comments
29 CFR 1910.155—SUBPART L—Fire Protection. Promulgated: 62 FR 111, 06/96. U.S. Codes: 29 U.S.C. 653, 655, 657.	Dry talc has been specifically approved as a "universal agent" for use on a variety of combustible metal fires if necessary.
29 CFR 1910.1000—SUBPART Z—Toxic and Hazardous Substances. Promulgated: 40 FR 23072, 05/28/75. U.S. Codes: 5 U.S.C. 553, 29 U.S.C. 653, 655, 655(a), 657, and 40 U.S.C. 333.	Talc, soapstone, and mica has a PEL of 20 mppcf (3 mg/m^3) measured as respirable dust. Asbestiform talc and tremolite has a PEL of 0.1 $fiber/cm^3$, with an excursion level (30 minutes) of 1 $fiber/cm^3$.
29 CFR 1915.1000—SUBPART Z—Toxic and Hazardous Substances. Promulgated: 58 FR 35514, 07/01/93.	Exposure to talc, soapstone, and mica should be limited to 20 mppcf (3 mg/m^3) measured as respirable dust in shipyards. Asbestiform talc and tremolite has a PEL of 0.1 $fiber/cm^3$, with an excursion level (30 minutes) of 1 $fiber/cm^3$.
29 CFR 1926.50—SUBPART D—Occupational Health and Environmental Controls. Promulgated: 62 FR 1619, 01/10/97. U.S. Codes: 29 U.S.C. 653, 655, 657 and 40 U.S.C. 333. Gases, vapors, fumes, dusts, and mists.	Exposure of employees to inhalation, ingestion, skin absorption, or contact with any material or substance at a concentration above those specified in the "Threshold Limit Values of Airborne Contaminants for 1970" of the American Conference of Governmental Industrial Hygienists shall be avoided. The limit for non-asbestiform talc and soapstone is 20 mppcf.

Source: The regulations in this table have been updated through the 1999 Code of Federal Regulations 29 CFR, 1 July 1999.

3 Human Cancer Studies

The carcinogenicity of talc was evaluated by the IARC in 1987 (IARC 1987a, Appendix A). The IARC panel judged that the evidence accumulated at that time was sufficient to classify talc containing asbestiform fibers as *carcinogenic to humans* (Group 1), but that talc that does not contain asbestiform fibers was *not classifiable as to its carcinogenicity to humans* (Group 3), because evidence for carcinogenicity was inadequate. The IARC evaluation was based primarily on epidemiologic studies of mortality among talc miners and millers, but included one case-control study that examined the risk of ovarian cancer among women who used perineal talcum powders.

A significant number of new reports relevant to the carcinogenicity of talc have been published since the IARC review, with seven new historical cohort studies and three new case-control studies evaluating exposure to talc in occupational settings and 15 new case-control studies and 1 prospective cohort study considering the risk of ovarian cancer among users of talcum powder. This latter group of studies also has been the subject of several reviews and meta-analyses (Wehner 1994, Shoham 1994, Harlow and Hartge 1995, Gross and Berg 1995, Whysner and Mohan 2000).

This section summarizes the current epidemiological evidence on the carcinogenicity of talc, with attention to the evidence for different effects of talc with and without asbestiform fibers.

3.1 Occupational exposure to talc

3.1.1 Previous evaluations by the IARC

The conclusions of the IARC's 1987 evaluation of the carcinogenicity of talc were based principally upon studies of four cohorts of talc miners and millers in the United States and Italy. The first studies considered mortality among a cohort of talc miners and millers in New York State and were published by Kleinfeld *et al.* (1967, 1974). The IARC report is based on the 1974 study, which included 260 men employed in 1940 who had accumulated at least 15 years of exposure by 1969. Exposures were to talc dust containing tremolite and anthophyllite. Proportionate mortality from lung and pleural cancer was 12%, versus 3.7% expected based on 1955 mortality for U.S. white males. One peritoneal mesothelioma also was reported. The IARC Working Group noted that no further data were available on exposure or other risk factors, including smoking.

NIOSH conducted a study of another group of 398 white male talc miners and millers in upstate New York (Brown *et al.* 1979, Dement *et al.* 1980). These men were employed from 1947 to 1959, and their vital status was ascertained as of 1975. Exposures to talc and other mineral dusts were assessed in detail and summarized in the exposure section of the IARC report (IARC 1987a). Workers in the facilities studied by NIOSH were exposed to dusts containing tremolite, anthophyllite, and serpentine in addition to talc. Some of these minerals had asbestiform characteristics. Statistically significant increases in mortality, reported as standardized mortality ratios (SMRs), were observed for all cancer (SMR 1.8), respiratory cancer (SMR 2.9), and bronchogenic cancer (SMR 2.7).

The investigators described tremolite and anthophyllite as the most likely etiologic agents. No data on smoking were available.

Stille and Tabershaw (1982) reported on an expanded investigation of the same talc mine and mill studied by NIOSH. Their study included 655 workers employed at any time between 1948 and 1977, with vital status determined through 1978. SMRs were 1.2 for all cancer and 1.6 for lung cancer. Further analyses stratified workers according to previous employment history and found no excess of lung cancer among workers who had been employed exclusively at the study facility. The IARC Working Group noted the lack of analysis by exposure as a methodological concern with this study, in addition to possible selection bias and small numbers.

Selevan *et al.* (1979) studied mortality among 392 talc workers who had participated in a radiography screening program. These workers, all white males, had worked in the Vermont talc industry for at least one year between 1940 and 1969. Samples of Vermont talc contained no detectable asbestos and low levels of crystalline silica. Excess mortality was observed for respiratory cancer among talc miners (SMR 4.3), but not among millers. However, millers, but not miners, had an excess of deaths from pneumoconiosis. The authors noted that miners were exposed to radon daughters in addition to talc dusts. The IARC Working Group noted several methodological concerns about this study, including inconsistent use of referent rates for respiratory diseases versus other causes of death, lack of analysis of mortality by latency, and lack of information on smoking.

Mortality among 1,992 workers employed for at least one year in Italian talc mines and mills between 1921 and 1950 was described by Rubino *et al.* (1976). The talc from Italian mines was described as largely free from fibrous material. Mortality from total cancer and lung cancer was lower than expected, whereas mortality from silicosis and silico-tuberculosis was increased.

Two other occupational studies, from France (Leophonte *et al.* 1983) and the U.S.S.R. (Katsnelson and Mokronosova 1979), were described in the IARC report but given little weight because of methodological concerns and limited availability of information.

3.1.2 Current epidemiologic studies

Ten studies of workers exposed to talc have been published since the IARC review in 1987. Most are based on historical cohorts and are methodologically similar to the studies previously evaluated by the IARC. Recent studies of workers in the talc industry are supplemented by studies conducted in other industries where talc was used in addition to other agents.

3.1.2.1 Cohort studies

Current occupational cohort studies of workers exposed to talc are summarized in Table 3-1. Only two of these studies were based in industrial settings where talc was the primary exposure.

Lamm *et al.* (1988) reported on a reanalysis of data from the cohort studied previously by NIOSH (Dement *et al.* 1980) and Stille and Tabershaw (1982). The SMR for lung cancer

was 2.4 (95% CI 1.2 to 4.2) among all workers. Additional analyses considered mortality among subcohorts defined by duration of employment (< 1 year or > 1 year) and estimated potential for exposure to pulmonary carcinogens in previous jobs. The lung cancer SMR was 3.2 among workers employed < 1 year and 1.9 among those employed > 1 year, but the numbers of deaths and person-years in each category were small. Because most workers had held previous jobs with potential exposure, the influence of prior exposure could not be meaningfully evaluated. Methodological concerns with this analysis include the lack of any analysis by exposure level or latency, small numbers, and the noncomparability of SMRs from different subcohorts.

A second cohort study of talc workers was reported by Wergeland *et al.* (1990), who investigated mortality and cancer incidence among 389 men employed in talc mines and mills in Norway between 1953 and 1987. According to the authors, the Norwegian mines produced non-asbestiform talc. There was no excess mortality from total cancer or excess morbidity from lung cancer in the cohort as a whole or among millers, but talc miners experienced a modest increase in lung cancer incidence, with a standardized incidence ratio (SIR) of 1.6. The SIR was on the order of 2 to 3 for workers employed for more than five years, but the numbers were small, and the risk estimates were unstable. The authors noted exposure to radon daughters in the mines as a potential explanation for the excess of lung cancer among miners but not millers. The interpretation of this study is limited by small size and the absence of quantitative information about exposure levels.

Thomas and Stewart (1987) reported the results of a study of mortality among 2,055 white male workers producing ceramic plumbing fixtures in the United States. Talc was used as a release agent for dusting molds, and both fibrous and nonfibrous forms were known to have been present. Lung cancer mortality was higher than expected for workers exposed to both forms of talc, but all workers exposed to talc also were exposed to silica dust. As a result, the effects of talc independent of silica cannot be evaluated from these data.

Other studies have examined cancer in the rubber and paper industries, where workers in some departments were potentially exposed to talc (seeTable 3-1). Studies of rubber workers in Germany and China suggest excess lung and stomach cancer in production areas where talc was used, but no measurements of the level of talc or its mineralogical content are available (Straif *et al.* 1999, Zhang *et al.* 1989). Rubber workers may also be exposed to a number of carcinogenic agents. The authors of the German and Chinese studies noted that workers in departments where talc was present also were exposed to solvents, asbestos, and carbon black.

The results of studies of women employed in the paper and printing industries (Langseth and Andersen 1999, Bulbulyan *et al.* 1999) are inconsistent, but suggestive of increased risk of cancer (esophageal, stomach, bladder, ovarian, and lung) in departments where workers were potentially exposed to paper dust, which often contains talc. As in the rubber industry studies, a number of other agents were present, and the talc exposures were not well characterized.

3.1.2.2 Case-control studies

Two case-control studies of lung cancer among workers exposed to talc have been reported since the IARC review in 1987. These studies are summarized in Table 3-2. Gamble (1993) analyzed data on 22 lung cancer cases and 66 controls from the cohort of talc workers studied previously by NIOSH (Brown *et al*. 1979, Dement *et al.* 1980, Stille and Tabershaw 1982, Lamm *et al.* 1988). Talc exposure was estimated by duration of employment, and supplementary data on smoking and occupational histories were obtained by interview. Stratified analyses examining duration of employment in the talc facilities in combination with other factors did not show consistent trends in risk with increasing duration; some odds ratios were less than 1.0. Although the author interpreted the data to indicate that no excess risk was associated with talc exposure, small numbers prevented analyses of latency and exposure level, which would provide a firmer basis for conclusions. In addition, this analysis was unable to adequately separate the effects of smoking and talc exposures on the rsk of lung cancer duet to the extremely small number of non-smokers.

Chiazze *et al.* (1993) conducted a case-control study of lung cancer in a large fiberglass manufacturing plant, where exposures to asbestos, talc, silica, formaldehyde, asphalt fumes, and respirable fibers were quantitatively estimated by historical reconstruction. Age, education, marital status, and smoking also were considered in the analysis. No consistent relationship was observed between lung cancer risk and the level of talc exposure.

A third case-control study (Hartge and Stewart 1994) examined occupational risk factors for ovarian cancer. Exposures to talc and other occupational agents were identified through interviews with participants and estimated by industrial hygienists from participants' occupational histories. Ovarian cancer was not associated with occupational talc exposure in analyses controlling for age, race, parity, and previous gynecological surgery.

3.1.3 Summary

The results of recent epidemiologic studies of the cancer risks associated with exposure to talc are largely consistent with the data evaluated by IARC in 1987. Occupational studies continue to suggest a moderate increase in lung cancer mortality among workers exposed to talc dust in talc mining and milling operations and in other industrial settings where talc was used, including the rubber and paper industries. Studies of facilities where the talc was known to have contained asbestos or been of fibrous form give the strongest evidence of risk (IARC 1987a, Lamm *et al.* 1988).

No available study of workers exposed to talc includes quantitative individual-level data on the level of exposure, although measurements of dust levels and composition were reported in several studies (IARC 1987a, Wergeland *et al.* 1990). Associations between exposure and disease may be weakened through dilution of an effect by poor specificity in classifying exposure. The studies of occupational populations exposed to talc have used relatively crude exposure classifications, generally treating all workers in a facility as exposed, although some may not have had contact with talc, and evaluating exposure-

response relationships only via surrogate measures like duration of employment. Thus, the risk among truly exposed workers may be greater than reported.

Some studies of workers exposed to talc also identified other potentially carcinogenic occupational agents in the workplace. Talc miners in Vermont and Norway were potentially exposed to radon daughters in addition to talc dust; hardrock miners may also have been exposed to silica. Both agents are associated with increased risk of lung cancer and classified as carcinogenic by the IARC and the NTP, but the studies considered here did not adjust for these exposures. In Thomas and Stewart's (1987) study of the pottery industry, workers exposed to talc also were exposed to silica, so the effects of the two agents could not be separated.

The ability to control for potentially confounding exposures outside the workplace is limited in current occupational studies of workers exposed to talc. The possible influence of confounding by tobacco smoking is a concern in occupational studies demonstrating excess risk of lung cancer, especially where the excess risk is moderate. Nevertheless, an extensive empirical and theoretical literature shows that smoking is rarely an important confounder in workplace-based studies (Axelson 1988, Blair *et al.* 1985, Cornfield *et al.* 1959, Siemiatycki *et al.* 1988a,b).

3.2 Talcum powder use and ovarian cancer

The relationship between talcum powder use and ovarian cancer has been evaluated in 16 case-control studies and one cohort study. Because these epidemiological studies deal exclusively with one specific type of cancer (ovarian cancer), and because an understanding of other risk factors for ovarian cancer will enhance the interpretation of these epidemiological studies, this section also includes a brief discussion of ovarian cancer.

3.2.1 Ovarian cancer

Epithelial ovarian cancer is the leading cause of death from gynecologic malignancies in the United States (Partridge and Barnes 1999). Among women, ovarian cancer is the fifth leading cancer and the fifth leading cause of death from cancer. The American Cancer Society estimates that in 2,000, approximately 23,100 new cases will be diagnosed, and 14,000 women will die of this disease (ACS 2000, Greenlee *et al*. 2000).

The most significant risk factor for development of ovarian cancer is advancing age, although there are clear indications of genetic predisposition (familial history of the disease, often associated with the *BRCA1* and *BRCA2* genes) in at least 5% to 10% of all epithelial ovarian cancers (Partridge and Barnes 1999). Another genetic syndrome, hereditary nonpolyposis colon cancer, also has been associated with endometrial and ovarian cancer. Other risk factors for ovarian cancer include parity and breast cancer: women who have never had children are more likely to develop ovarian cancer than those who have, and women who have had breast cancer or have a family history of breast cancer are at increased risk. Early menarche and late menopause increase the risk of development of this disease. Conversely, pregnancy and the use of oral contraceptives reduce the risk of developing ovarian cancer. Likewise, both tubal ligation and

hysterectomy reduce the risk of ovarian cancer. The risk for developing ovarian cancer is 6.5/100,000 women at the age of 30 years, 13.1 at age 40, 29.8 at age 50, 43.7 at age 60, 58.1 at age 70, and 59.6 at age 80.

Epidemiologic and biologic data provide some support, although not consistent, for three hypotheses concerning the underlying pathophysiology of epithelial ovarian cancer. Two hypotheses, (1) that cancer risk is increased by frequent ovulation and (2) that cancer risk is increased by elevations in pituitary gonadotropin levels acting in concert with estrogen, are supported by studies demonstrating a reduction in ovarian cancer risk from parity, oral contraceptive use, and prolonged breast feeding. The third hypothesis, that cancer risk is increased by ovarian epithelial inflammation, is supported by studies on factors that cause ovarian inflammation, such as asbestos and talc exposures, endometriosis, and pelvic inflammatory disease. Furthermore, tubal ligation and hysterectomy, which may reduce the exposure from local genital irritants, are protective factors (Ness and Cottreau 1999).

Talc was suspected of being a risk factor for ovarian cancer based on its mineralogical and chemical similarity to asbestos, possible contamination of talc by asbestos (Rohl *et al*. 1976), published reports of postoperative talc granulomas (Eiseman *et al*. 1947, cited in Harlow and Hartge 1995), and the presence of talc particulates in ovarian tumors (Henderson *et al*. 1971, 1979, Harlow and Hartge 1995). Exposure to asbestos has been reported to be associated with an increased risk of ovarian cancers (Germani *et al*. 1999, Vasama-Neuvonen *et al*. 1999, Harlow and Hartge 1995). Epithelial changes in the ovaries of guinea pigs and rabbits receiving intraperitonel injections of asbestos products have also been observed (Graham and Graham 1967, cited in Harlow and Hartge 1995). Ovarian carcinomas are histologically similar to peritoneal mesotheliomas and, are related to asbestos exposure (Parmley and Woodruff, 1974, cited in Harlow and Hartge 1995). A number of studies have demonstrated particle migration through the fallopian tubes or retrograde menstruation (see Section 6). These observations have stimulated numerous epidemiological studies evaluating the effects of exposure to talcum powder on the risk of ovarian cancer.

3.2.2 Epidemiologic studies of talcum powder use and ovarian cancer

Only two case-control studies concerning the risk of ovarian cancer in relation to genital exposure to talc had been published at the time of the IARC 1987 review, and only one study was reviewed (Cramer *et al*. 1982) by the IARC. The second study contained inadequate information, because it was reported as a letter (Hartge *et al*. 1983). However, the literature has expanded markedly since the IARC review. Most studies of this question have used case-control designs, but one study used a prospective cohort approach. Key features of all the studies (16 case-control and one cohort) are summarized in Table 3-3.

3.2.2.1 Cohort study

Gertig *et al.* (2000) analyzed data from 76,630 U.S. women enrolled in the Nurses' Health Study to determine the association of ovarian cancer incidence with daily use of talcum powder, baby powder, or deodorizing powder in the perineal area or on sanitary

napkins. Participants reported powder use in 1982, and incident cancers were ascertained through 1996. No increase in the overall risk of ovarian cancer was associated with any type of powder use or with increasing frequency of use in analyses adjusted for an array of potential risk factors, including age, parity, smoking, body mass index, tubal ligation, and use of oral contraceptives and post-menopausal hormones. Serous-type cancer was the most common subtype (67%), with the majority of these cancers being invasive (58% of all tumors observed). Stratification by histologic subtype showed a small excess risk associated with perineal talc use for all serous tumors (borderline and invasive, RR = 1.3, 95% CI = 0.9 to 1.7, n = 84) and a significant risk for invasive serous tumors only (RR = 1.4, 95% CI = 1.0 to 1.9, n = 76). The power of this study is somewhat limited by the relatively short follow-up time of 15 years.

3.2.2.2 Case-control studies

All of the 16 case-control studies used a similar research approach, with relatively minor variations in the methods of selecting cases and controls, the risk factors that were controlled for, and the level of detail concerning talc exposure.

Every study characterized exposure to talc through interviews in which participants were asked to describe their past use of powders. Some studies used simple binary exposure indicators (Chen *et al.* 1992, Purdie *et al.* 1995, Tzonou *et al.* 1993, Godard *et al*. 1998). Others attempted to characterize exposures in more detail, examining the source of exposure through the use of powders for direct perineal application versus on clothing, sanitary napkins, or diaphragms (Cramer *et al*. 1982, Hartge *et al*. 1983, Whittemore *et al.* 1988, Harlow and Weiss 1989, Harlow *et al.* 1992, Rosenblatt *et al.* 1992, Wong *et al.* 1999, Cramer *et al.* 1999, Cook *et al.* 1997, Chang and Risch 1997, Ness *et al*. 2000), the duration and/or frequency of exposure (Whittemore *et al.* 1988, Booth *et al*. 1989, Harlow *et al.* 1992, Wong *et al.* 1999, Cramer *et al.* 1999, Cook *et al.* 1997, Chang and Risch 1997, Ness *et al*. 2000), and the use of different types of powders, such as talcum powder, baby powder, and deodorizing powder, or talc versus cornstarch (Whittemore *et al.* 1988, Harlow and Weiss 1989, Harlow *et al.* 1992, Cramer *et al.* 1999, Cook *et al.* 1997, Chang and Risch 1997). Participant interviews also provided an opportunity to collect data concerning other risk factors for ovarian cancer, so that these could be taken into account in the analysis.

Taken together, current case-control studies suggest an association of ovarian cancer with genital exposure to talc, with odds ratios (OR) in the range of 1.3 to 2.5 (Table 3-3). Among studies that considered the source of exposure, direct application of powder to the perineal region was more strongly associated with cancer than exposure via dusting other items. Two studies reported increasing cancer risk with increases in exposure level (Whittemore *et al*. 1988, Harlow *et al.* 1992), but most found no consistent increase in risk associated with higher frequency or duration of use or with multiple exposure sources. Cornstarch powders were associated with reduced cancer risk (Harlow and Weiss 1989, Cramer *et al.* 1999, Cook *et al.* 1997, Chang and Risch 1997), but results are otherwise inconsistent with respect to the risks associated with different types of powders.

The inconsistency of findings concerning the type of powder and the frequency and duration of use may be due to the challenges inherent in assessing exposure from interview data. Several authors noted inability to determine the amounts or compositions of powders as a key limitation of their approach (Harlow *et al.* 1992, Cook *et al.* 1997, Cramer *et al.* 1999). The study of Harlow *et al.* (1992) suggests that women often cannot recall details such as past use of specific brands. The formulation of commercial cosmetic powders varies over time and among brands, and women's patterns of use may vary as well. Surveys published in the late 1960s and 1970s reported that different brands of cosmetic talc varied considerably in fiberform content (tremolite and anthophyllite), ranging from less than 1% to as high as 30% (Cralley *et al.* 1968, Rohl *et al.* 1976, both cited in Harlow *et al*. 1992). However, it is not clear whether the fiberforms were asbestiforms, because of the use of nonspecific analytical techniques (Zazenski *et al*. 1995). In 1976, the cosmetic industry (CTFA 1976, cited in Harlow and Hartge 1995) agreed to voluntarily limit contamination of consumer powders. Harlow *et al.* (1992) reported a higher risk of ovarian cancer from talc use exclusively before 1960 (1.7) than use after 1960 (1.1), but this finding is compromised by the longer latency for women with earlier exposures. In contrast, Chang and Risch (1997) did not find any difference in risk associated with after-bath talc use before and after 1970.

3.2.3 Talcum powder use and histologic subtypes of ovarian cancer

Most (85%) ovarian cancers are common epithelial tumors that are derived from the surface (coelomic) epithelium (mesothelium) and the adjacent ovarian stroma. The evidence for the surface epithelial origin is strongest for serous and endometrioid subtypes (Scully 1979). Several studies evaluated the risk of perineal talc use associated with specific histologic subtypes of ovarian cancer. Some studies reported higher risks for specific histological subtypes (Harlow *et al.* 1992, Cook *et al*. 1997, Cramer *et al*. 1999), whereas other studies reported similar risk estimates for all histologic subtypes (Cramer *et al.* 1982, Chang and Risch 1997, Wong *et al*. 1999). Nevertheless, all studies that stratified by histologic subtype reported risk estimates greater than one for serous-type ovarian tumors (Harlow *et al*. 1992 [non-significant], Chang and Risch 1997, Cook *et al.* 1997, Wong *et al*. 1999 [non-significant], and Cramer *et al.* 1999). These findings support the observation of increased risk of serous-type ovarian cancer associated with perineal talc use in the prospective cohort (Gertig *et al*. 2000). Moreover, both Gertig *et al*. (2000) and Cramer *et al.* (1999) reported a stronger risk for invasive serous-type tumors. Findings were inconsistent for other histologic subtypes of ovarian cancer. Harlow *et al*. (1992) reported a higher risk associated with endometrioid and borderline tumors, whereas other studies found either no risk associated with endometrioid tumors (Cramer *et al*. 1999, Gertig *et al*. 2000) or a risk similar to that of other histologic subtypes (Chang and Risch 1997, Cook *et al.* 1997, Wong *et al.* 1999). However, because endometrioid and mucinous cancers occurred at a lower frequency than serous cancer in these studies, the risk estimates were based on smaller numbers, resulting in imprecise assessments.

3.2.4 Talcum powder use and other risk factors related to the translocation of talc

A few studies evaluated the effects of tubal ligation and/or hysterectomy on the association between perineal talc use and ovarian cancer. Tubal ligation has been shown

to decrease the risk of ovarian carcinoma (Ness and Cottreau 1999), supporting an etiologic role for vaginal exposures to exogenous substances. Cramer *et al.* (1999) reported a positive association between perineal talc use and ovarian cancer in women who had an open genital tract (no history of tubal ligation) but not a closed one (history of tubal ligation). Whittemore *et al.* (1988) evaluated the combined effects of surgical sterilization and perineal talc use. The highest risk of ovarian cancer was experienced by talc users who had not had surgery, and the lowest risk was observed in non-users who had had surgery. Harlow *et al*. (1992) observed a significant dose-response relationship between risk and the number of talc applications only after excluding talc use that occurred after hysterectomy and tubal ligation and during nonovulatory months (test for trend, $P = 0.015$). They also reported a higher risk associated with talc use in women with clinical factors that predict ovulation (mid-cycle pain and regular period). Conversely, Gertig *et al.* (2000) did not find any greater risk of cancer associated with talc use among individuals who had not had a tubal ligation.

3.2.5 Confounding and other potential biases

The odds ratios reported in most current case-control studies were adjusted for age and parity or other indicators of reproductive history. Several studies also considered the effects of other known risk or demographic factors as potential confounders, including use of oral contraceptives, marital status, education, religion, socioeconomic status, weight, and smoking (see Table 3-3). Some studies adjusted for all factors, whereas other studies adjusted only for factors that substantially affected the risk estimate. Harlow *et al*. (1992) and Cramer *et al.* (1999) conducted stratified analysis to assess whether the cancer risk associated with talc use was modified by a variety of known risk or demographic factors. Rosenblatt *et al.* (1998) suggested that body mass index was associated with talc use and thus may be a potential confounder. However, studies that did consider body mass index or obesity reported a positive association between perineal talc use and ovarian cancer (Rosenblatt *et al.* 1992 [non-significant], Cook *et al.* 1997 [significant], and Cramer *et al.* 1999 [significant]). Although the risk estimate for any given study may be influenced by a specific confounder(s), it seems unlikely that the positive associations observed in 14 case-control studies with different populations, methods, and analyses are due to systematic confounding.

Other challenges are related to the limited state of current knowledge about the causes of ovarian cancer. Uncontrolled confounding with unidentified risk factors remains a possible explanation for odds ratios in the range reported. Nevertheless, if the association with talc actually is null, then a confounder needs to be very closely linked to talc and must have an effect on ovarian cancer risk that is greater than that estimated for talc (Harlow and Hartge 1995). Other potential biases involve participation rates, selection of controls, and recall of talc exposure. Many studies report low participation rates; however, rates were similar for most studies in the United States and did not vary differently between cases and controls (Harlow and Hartge 1995). Positive associations of perineal talc use and ovarian cancer were observed in hospital-based, hospital-town, and population-based case-control studies, arguing against selection bias.

An inherent problem in case-control studies is the potential for cases and controls to recall exposures differently. This is an important issue to consider, especially because the only prospective cohort study did not find an overall increase in for risk ovarian cancer (not stratified according to histologic subtype) associated with perineal talc use. Recall bias has a greater effect on short-term than long-term exposures and is related to the publicity about a given risk factor. Cramer *et al.* (1999*)* analyzed the percentages of exposed cases and controls from 14 case-control studies (1982 to 1999) and did not find a trend of higher rates of exposure in the more recent studies, suggesting that recall bias was not a major factor. Other arguments against a role for recall bias include the nature of talc use (trivial, long-term), the absence of association of cancer with overall (non-genital) talc use, and an increased risk of specific histologic subtypes of cancer associated with talc use (Harlow and Hartge 1995, Cramer *et al*. 1999).

3.2.6 Summary

The accumulated evidence from studies examining the risk of ovarian cancer in relation to genital exposure to talc suggests an increase in cancer risk, on the order of 30% to 60% for any exposure. The principal findings of these studies are quite consistent, despite variation in the details of duration, frequency, and route of exposure and the limitations of exposure assignments based on retrospective self-reports. Of the 16 studies, 14 reported a positive association between perineal talc use and cancer, which was statistically significant in eight studies. Studies that did not find a positive association may have been limited by the use of hospital controls with other types of cancers (Wong *et al.* 1999) and insufficient power because of the small number of exposed cases (Tzonou *et al.* 1993). Moreover, positive risk estimates remain after adjustment for confounders. The evidence for causality is weakened by the absence of exposure-response trends in most studies, but this absence may be a result of the difficulty of measuring exposures by retrospective recall. An association of ovarian cancer with genital exposure to talc is biologically plausible, given the evidence that both talc and asbestos, a close mineralogical relative, can be found in ovarian tissues (Heller *et al.* 1996a,b, IARC 1987a, Wehner 1994; see Section 6).

3.3 Talc containing asbestiform fibers and talc not containing asbestiform fibers

The limited information in the literature on talc mineralogy and asbestos content poses a key challenge in assessing carcinogenicity. Only occupational studies of workers in talc mining and milling operations and pottery production provide sufficient information to identify asbestiform talc. The evidence, derived largely from observations of excess lung cancer in these settings, indicates that talc containing asbestiform fibers is carcinogenic.

Neither occupational studies conducted outside of the talc and pottery industries nor the extensive literature concerning cancer and perineally applied talcum powder provide any characterization of talc mineralogy or morphology that could be used to determine the effects of different kinds of talc. However, because of the widespread contamination of talc and commercial talc products with asbestiform minerals, it must be assumed that "talc" without further specification of mineralogy or morphology may contain asbestos fibers. The weight of the evidence thus indicates that it would be prudent to regard such undifferentiated talc materials as carcinogenic.

The evidence from occupational studies concerning the carcinogenicity of non-asbestiform talc is extremely limited. Talc miners and millers in Italy (Rubino *et al.* 1976, cited in IARC 1987a), Norway (Wergeland *et al.* 1990), and Vermont (Selevan *et al.* 1979, cited in IARC 1987a) and some of the pottery workers studied by Thomas and Stewart (1987) were exposed to talc that did not contain asbestos.

The study of Italian talc workers gave an unequivocal indication of no excess risk, but the IARC Working Group expressed concern that the methods used to calculate expected mortality in that study may have produced the observed deficits of cancer deaths (IARC 1987a). Interpretation of the studies in Vermont and Norway presents another challenge. Both studies included talc miners and millers who all were exposed to talc dusts, but only miners were at increased risk of lung cancer. Miners, but not millers, also were exposed to radon daughters at unknown levels. Although an effect of talc cannot be ruled out, this pattern of risk would be consistent with the hypothesis that radon daughters, rather than non-asbestos-containing talc, were responsible for the excess lung cancer in these groups of miners.

In contrast, in the pottery-industry study of Thomas and Stewart (1987), the risk of lung cancer was higher among workers exposed to non-fibrous forms of talc than among workers exposed to fibrous talc. However, because all of the workers also were exposed to silica, the relative carcinogenicity of fibrous and non-fibrous forms of talc cannot be assessed from these data.

In the light of these findings, the evidence from studies of occupational exposure to non-asbestos-containing talc is not sufficient to support a conclusion that this form of talc is carcinogenic. In contrast, the evidence from studies of ovarian cancer suggests that talcum powder is a carcinogen.

Table 3-1. Occupational cohort studies of cancer published after the 1987 IARC review

Reference	Study design	Population	Exposure	Effects	Potential confounders
Lamm *et al.* 1988 U.S.	historical cohort	705 white males employed in talc production, followed 1947–1978 for mortality (same cohort studied by Dement *et al.* 1980) ref.: U.S. white males	Duration of employment in talc production plant < 1 year or > 1 year	SMR 1.7 (95% CI 1.1–2.4) for all cancer, 2.5 (1.3–4.2) for respiratory cancer, and 2.4 (1.2–4.2) for lung cancer for all workers; higher SMR for short- vs. long-term workers (3.2 vs. 1.9)	analyses include prior occupational exposures to lung carcinogens.
Thomas and Stewart 1987 U.S.	historical cohort	2,055 white males manufacturing ceramic plumbing fixtures, followed 1940–1980 for mortality ref.: U.S. white males	talc used for dusting molds; both fibrous and nonfibrous forms present	lung cancer SMR 1.4 overall, 1. 7 for fibrous talc plus silica, 2.5 for nonfibrous talc plus silica, 3.6 for 15+ years exposure to nonfibrous talc plus silica	silica
Zhang *et al.* 1989 China	historical cohort	1,624 rubber workers followed 1972–1984 for mortality ref.: district population	potential exposure to talc dust in inner-tube production	lung cancer SMR 0.5 overall, 3.8 in inner-tube department, 2.9 in curing department	solvents
Wergeland *et al.* 1990 Norway	historical cohort	389 male talc miners and millers followed 1953–1987 for cancer incidence and mortality ref.: male Norwegian pop.	facilities produced and processed non-asbestiform talc; exposure estimated by duration of employment	SMR 0.8 for all malignant neoplasms; SMR 2.1 for bladder cancer, 0.9 for lung cancer (lung cancer SMR 1.6 for miners, 0.9 for millers)	radon daughters
Straif *et al.* 1999 Germany	historical cohort	11,633 male workers in 5 rubber plants employed for at least one year and followed 1981–1991 for mortality ref.: internal control group	potential exposure to talc occurred in the weighing and mixing department	increased risk of lung and stomach cancer for workers in weighing and mixing: HRR[a] 1.9 (1.2–3.1) and 4(.0 1.9–8.3), respectively, for > 10 years' employment	asbestos, carbon black

Reference	Study design	Population	Exposure	Effects	Potential confounders
Langseth and Andersen 1999 Norway	historical cohort	4,247 women employed in a pulp and paper mill, followed 1953–1993 for incident cancer ref.: female Norwegian pop.	talc used in manufacture of paper; exposure estimated by duration of employment, year of hire	lung cancer SIR 3.0 (95% CI 1.3–5.9) for < 3 years' employment, 1.4 (0.7–2.2) > 3 years; ovarian cancer SIR 1.6 (1.1–2.3) for > 3 years' employment	mycotoxins, industrial chemicals, reproductive history (ovarian cancer)
Bulbulyan *et al.* 1999 Russia	historical cohort	3,473 women employed in printing plants, followed 1979–1993 for mortality ref.: Moscow general pop.	potential exposure to talc from paper dust in bookbinding and press areas	SMR 2.6 for cancer of esophagus, 2.5 for larynx, 0.8 for lung, 1.2 for ovarian cancer; higher SMRs for cancer of esophagus among press operators, esophagus and ovary among bookbinders	ink, benzene, alcohol

[a]HRR = age-adjusted hazard rate ratio.

Table 3-2. Occupational case-control studies of cancer published after the 1987 IARC review

Reference	Population	Exposure	Effects	Potential confounders
Gamble 1993 U.S.	22 lung cancer deaths, 66 controls from cohort of talc workers studied by Dement *et al.* (1980)	tenure in the talc plant	crude ORs 1.00 for < 5 years, 1.1 for 5–15 years, 0.8 for 15–36 years; ORs < 1.0 for smokers	asbestos-containing talc; stratified analyses include smoking, other talc work, non-talc exposures
Chiazze *et al.* 1993 U.S.	144 lung cancer deaths, 260 controls employed in a fiberglass production plant	historical reconstruction of exposure to talc, asbestos, respirable fiber, respirable silica, formaldehyde and asphalt fumes	adjusted ORs for talc 0.7 (95% CI 0.3–1.8) for 10–999 fibers/ml, 1.4 (0.4–4.5) for > 1,000 fibers/ml (referent 0)	analyses included age, smoking, other workplace substances, education, marital status
Hartge and Stewart 1994 U.S.	296 women with ovarian cancer, 343 women with unrelated conditions, matched by age and race	subject-reported occupational exposure to talc and semiquantitative ranking of exposure potential based on occupational history	no association with occupational talc exposure (OR < 1.0)	analyses included age, race, parity, gynecologic surgery

Table 3-3. Cohort and case-control studies of ovarian cancer and exposure to cosmetic talc

Reference	Population	Exposure and percent exposed (cases/controls)	Effects	Comments
Cramer *et al.* 1982 U.S.	case-control study cases: 215 women with epithelial ovarian cancer (including 39 with borderline tumors) controls: 215 women from the population matched on residence, race, and age	self-reported use of talc either as a dusting powder on the perineum or on sanitary napkins any perineal: 43/29	OR = 1.9 (1.3–2.9) for any perineal exposure OR = 3.3 (1.7–6.4) for both napkins and dusting powder use	adjusted for parity and menopausal status cases and controls compared for education, religion, marital status, parity, menopausal status; parity and menopausal status considered confounders
Hartge *et al.* 1983 U.S.	hospital-based case-control study cases: 135 women with primary epithelial ovarian cancer controls: 171 women treated at the same hospitals for conditions other than gynecologic, psychiatric, or malignant diseases or pregnancy and matched on age, race, and hospital	self-reported use of talc for any use body use (including all-over, genital [genitals, sanitary napkins, or underwear], legs only, not genital, and unknown), and on diaphragm any: 50/ 58 body: 40/46 genital: 5/2	OR = 2.5 (0.7–10.0) for genital use OR = 0.8 (0.5–1.2) for some body talc OR = 0.7 (0.4–1.1) for any talc use OR = 0.8 (0.4–1.4) for diaphragm with talc	estimate unaffected by adjustment for race, age, and gravidity limited exposure assessment small sample size

Reference	Population	Exposure and percent exposed (cases/controls)	Effects	Comments
Whittemore *et al.* 1988 U.S.	case-control study cases: 188 women with primary epithelial ovarian cancer controls: 539 women from community (259) and hospital sources (280)	self-reported use of talcum powder on perineum, sanitary pads, or diaphragms perineum, including sanitary pads and diaphragms: 52/46 perineum only: 12/10	OR = 1.5 (0.8–2.6) for use on perineum, increasing with frequency of use; no association with use on pads, diaphragms, or > 1 type of use.	adjusted for parity and oral contraceptives combined control group consisting of women from hospitals and the community
Harlow and Weiss 1989 U.S.	case-control study cases: 116 women with borderline epithelial ovarian tumors (serous or mucinous) controls: 158-age and residence-matched women identified by random-digit dialing	self-reported use of talc-containing powder for perineal dusting, on sanitary napkins, or on diaphragms any: 42/41 sanitary pad: 12/6 after bath: 29/23 deodorizing: 9/3	OR = 1.1 (0.7–2.1) for any perineal powder exposure OR = 1.9 (0.9–6.9) for sanitary pads OR = 1.3 (0.8–2.7) for use after bathing OR = 3.5 (1.2–28.7) for deodorizing powder no association for talc powder only or for use on diaphragms	adjusted for age, parity, oral contraceptives

Reference	Population	Exposure and percent exposed (cases/controls)	Effects	Comments
Booth *et al*. 1989 England	hospital-based case-control study cases: 235 women with epithelial ovarian cancer (serous 43%, mucinous 15%, endometrioid 22%, clear cell 5%) controls: 451 age-matched women from the same hospital without bilateral ooporectomy and conditions that have been related to reproductive history or oral contraceptive use (all circulatory and gynecological diseases, gallbladder and thyroid diseases, rheumatoid arthritis, malignant disease of the breast, uterus, and bladder, and melanoma)	self-reported use of talc power in the genital area (rarely, monthly, weekly, and daily) weekly : 26/18 daily: 33/32	OR = 2.0 (1.3–3.4) for weekly OR = 1.3 (0.8–1.9) for daily OR = 0.7 (0.3–1.8) for monthly test for trend (never to daily) $P = 0.05$	adjusted for age and social class

Reference	Population	Exposure and percent exposed (cases/controls)	Effects	Comments
Harlow *et al.* 1992 U.S.	case-control study cases: 235 white women with primary epithelial ovarian (borderline or malignant) cancer controls: 239 women matched by residence, race, and age and selected from the population	self-reported use of talc powder on body, underclothes, sanitary pads, and diaphragms, or by husband 49/39	OR = 1.5 (1.0–2.1) with increasing trend for total lifetime use OR = 1.7 (1.1–2.7) for direct application OR = 1.6 (1.1–2.5) for baby powder OR = 1.2 (0.6–2.5) for deodorizing powder increased risk in women with clinical predictors of ovulatory cycles (mid-cycle pain and regular period) histologic subtype type, serous 1.4 (0.9–2.2), mucinous 1.2 (0.6–2.5), endometrioid 2.8 (1.2–6.4), other 1.6 (0.8–3.3) histologic grade, greater risk for borderline (2.4) than grade 1, 2, 3, or undifferentiated (1.0, 1.5, 1.5, 1.2, respectively)	adjusted for parity, education, marital status, religion, sanitary napkin use, douching, age, weight influence of potential confounders and effect modifiers assessed first through stratification and then through unconditional logistic regression
Rosenblatt *et al.* 1992 U.S.	hospital-based case-control study cases: 77 incident cases controls: 46 inpatient women without gynecologic or malignant conditions matched by age, race, and date of diagnostic admission, unmatched cases matched *a posteriori* to controls	self-reported genital exposure to fiber, including genital bath talc and sanitary napkin exposure to talc, and diaphragm use with powder genital: 29/19 sanitary napkin: 30/14 diaphragm: 19/11	OR = 1.7 (0.7–3.9) for genital bath talc OR = 4.8 (1.3–17.8) for sanitary napkin (adjusted for weight) OR = 3.0 (0.8–10.8) for diaphragm use with powder (adjusted for live births and education)	potential confounders considered: obesity, socioeconomic, religion, reproductive status, live births, oral contraceptive use; if a potential confounder changed the OR by more than 15%, it was retained in the multivariate model small sample size

Reference	Population	Exposure and percent exposed (cases/controls)	Effects	Comments
Tzonou *et al.* 1993 Greece	hospital-based case-control study cases: 189 surgical patients with ovarian epithelial tumors controls: 200 women visiting hospital patients	self-reported perineal application of talc 3/3	adjusted OR = 1.1 (0.3–4.0)	adjusted for age, education, weight, reproductive history, smoking, coffee, alcohol, hair dyes, analgesics, tranquilizers limited power: small study size and low number of exposed subjects little information on exposure
Chen *et al.* 1992 China	population-based case-control study cases: 112 women with epithelial ovarian cancer (serous 51%, mucinous 19%, and miscellaneous 30%) controls: 224 women from general population, matched by age, residence	self-reported use of dusting powder and self-reported occupational talc exposure dusting power: 6/2	OR = 3.9 (0.9–10.6) for dusting powder OR = 0.9 (0.3–2.9) for occupational exposure	adjusted for education and parity limited power: small study size and low number of exposed individuals little information on exposure
Purdie *et al.* 1995 Australia	population-based case-control study cases: 824 women with epithelial ovarian cancer controls: 860 residence-matched women randomly selected from electoral rolls	self-reported use of talc powder 57/52	adjusted OR = 1.3 (1.0–1.5)	adjusted for parity little information on exposure

Reference	Population	Exposure and percent exposed (cases/controls)	Effects	Comments
Chang and Risch 1997 Canada	population-based case-control study cases: 450 women with primary, invasive or borderline, ovarian epithelial tumors controls: 564 women from general population matched by time and age	self-reported use of talc after bathing, on sanitary napkins 44/36	adjusted OR 1.4 (1.1–1.9) for any use; similar for use after bathing (1.3) and on pads (1.2); no consistent trend by duration or frequency histologic subtype, invasive 1.5 (1.1–2.0), borderline 1.2 (0.8–2.0), serous 1.3 (1.0–1.9), mucinous 1.6 (1.0–2.6), endometrioid 1.7 (1.0–2.8)	analyses include age, reproductive history, lactation, tubal ligation, hysterectomy, family history
Cook *et al.* 1997 U.S.	population-based case-control study cases: 313 women with invasive or borderline epithelial ovarian tumors controls: 422 age-matched women selected by random-digit dialing	self-reported use of talcum powder, baby powder, or deodorant powder on perineal area, napkins, and diaphragms, including duration any: 50/40 perineal dusting: 18/11	OR = 1.5 (1.1–2.0) for lifetime genital application with no trend for cumulative exposure OR = 1.8 (1.2–2.9) for perineal dusting only no association with other uses (napkins and diaphragms); higher risk for talcum and baby power, no association with cornstarch or deodorizing powder histologic subtype, serous 1.7 (1.1–2.5), mucinous 0.7 (0.4–1.4), endometrioid 1.2 (0.6–2.3), other 1.8 (1.1–2.8)	analyses adjusted for age further adjustment for education, income, marital status, body mass index, oral contraceptive use, or parity did not alter the estimated relative risk

Reference	Population	Exposure and percent exposed (cases/controls)	Effects	Comments
Godard *et al*. 1998 Canada	population-based case-control study cases: 170 women with primary invasive carcinoma or borderline ovarian tumors, 112 sporadic cases and 58 familial cases controls: 170 age- and ethnicity-matched women selected by random-digit dialing	self-reported use of talc and family history total cases: 11/5 sporadic: 10/5 familial: 12/5	OR = 2.49 (0.9–6.6) for use of talc on perineum in all patients OR = 2.5 (0.9–7.1) for sporadic cases OR = 3.6 (0.9–12.4) for familial cases	multivariate analysis, adjusted for all possible etiologic factors that were significant or of borderline significance in the univariate analysis: age, reproductive factors (age at menarche, age at last childbirth), oral contraceptives, tubal ligation, alcohol use limited power due to small number of exposed cases and controls and small number of cases, especially after stratification by family history limited information on talc exposure

Reference	Population	Exposure and percent exposed (cases/controls)	Effects	Comments
Cramer *et al.* 1999 U.S.	population-based case-control study cases: 563 women with epithelial ovarian tumors, including borderline controls: 523 age-matched women selected by random-digit dialing and town lists	self-reported genital exposure (use of talc, baby powder or deodorant powder in genital area, sanitary pads, or underwear) 45/36	adjusted ORs = 1.6 (1.2–2.2) for genital powder exposure, 1.7 (1.3–2.3) for genital talc, 1.5 for dusting perineum or sanitary pads no trend for frequency of use stratified analysis: no difference in risk due to talc use for different ages (< 50 vs. ≥ 50), education (< 12 years vs. ≥ 12 years), marital status, religion, weight (< 140 vs. ≥ 140), number of liveborn children (0, 1–2, 3+), oral contraceptives (< 3 mo. or never vs. ≥ 3 mo.) strata; some differences in risk for study center, hysterectomy (higher risk with hysterectomy), and family history (higher risk for family history) tubal ligation, no: 1.8 (1.3–2.5), yes: 1.0 (0.5–2.1) histologic subtype: serous borderline 1.4 (0.8–2.3), serous invasive 1.7 (1.2–2.4), mucinous 0.8 (0.4–1.4), endometrioid/clear cell 1.0 (0.7–1.6), undifferentiated 1.4 (0.7–3.1)	analyses include age, study center, tubal ligation, other powder exposure stratified analysis for the following: age, study center, education, marital status, religion, weight, use of oral contraceptives, number of liveborn children, prior tubal ligation, prior hysterectomy, family history of breast or ovarian cancer

Reference	Population	Exposure and percent exposed (cases/controls)	Effects	Comments
Wong *et al.* 1999 U.S.	cases: 499 women with epithelial ovarian cancer controls: 755 female patients with non-gynecologic cancer information on talc use: 462 cases and 693 controls	self-reported application of talcum powder to the genital region 48/45	OR = 1.0 (0.8–1.3) for genital use OR = 0.9 (0.4–2.0) for use on sanitary napkins OR = 1.1 (0.7–1.7) for both no trend for duration of use histologic subtype: papillary serous cystadenocarcinoma 1.2 (0.7–2.1) endometrioid carcinoma 1.4 (0.7–2.7) mucinous adenocarcinoma 1.5 (0.6–4.0) clear cell adenocarcinoma 1.6 (0.6–4.3) undifferentiated carcinoma 1.0 (0.6–1.6)	adjusted for oral contraceptives, reproductive history, smoking, income, education, family history, hysterectomy, tubal ligation percents of controls and cases were significantly different for the different study sites
Ness *et al*. 2000 U.S.	case-control study cases: 767 women with epithelial ovarian cancer (151 borderline and 616 invasive) controls: 1,367 women frequency-matched by age and selected by random-digit dialing	self-reported use of talc, baby or deodorizing powder, and information on duration and area of use, sanitary napkins, diaphragms genital/rectal: 21/16 sanitary napkin: 19/7 underwear: 9/7	OR = 1.5 (1.1–2.0) for genital/rectal OR = 1.6 (1.1–2.3) for sanitary napkin OR = 1.7 (1.2–2.4) underwear no increase in risk with years of use	adjusted for age, gravidity, race, family history, oral contraceptive, tubal ligation, hysterectomy, breast-feeding

Reference	Population	Exposure and percent exposed (cases/controls)	Effects	Comments
Gertig *et al.* 2000 U.S.	prospective cohort: Nurses' Health Study 121,700 nurses in 11 of the larger states, ages 30–55, married, recruited in 1976 78,630 available for analysis 307 ovarian (invasive and borderline) cases diagnosed by 1996	self-reported talc use ascertained in 1982 questionnaire, baby powder, talcum, deodorizing powder to perineal, no. of times per week, sanitary napkin use percent exposed in cohort: ever: 40 daily: 15	RR[a] = 1.1 (0.9–1.4) for ever use talc on perineum RR = 0.9 (0.6–1.3) for use on sanitary napkins no increase in risk with increasing frequency of use histologic subtypes: all serous (including cystadenocarcinoma and papillary adenocarcinoma) 1.3 (0.9–1.7), serous invasive 1.4 (1.0–1.9), endometrioid 0.9 (0.5–1.9), mucinous 0.9 (0.5–1.7)	multivariate analysis, adjusted for age, parity, oral contraceptives, tubal ligation, smoking, postmenopausal hormone use; other factors that were considered but did not affect estimates: age at menarche, duration of breast-feeding, age at menopause relatively short follow-up (15 years); ovarian cancer may have a longer latency

[a]RR = relative risk.

4 Studies of Cancer in Experimental Animals

4.1 Non-asbestiform talc

4.1.1 Inhalation exposure in rodents

4.1.1.1 Rats

A carcinogenesis bioassay of non-asbestiform talc was conducted in F344/N rats. Groups of six- to seven-week-old rats (49 or 50 males, 50 females) were administered non-asbestiform talc by inhalation at air concentrations of 0, 6, or 18 mg/m^3 (equivalent to doses of 0, 2.8, or 8.4 mg/kg body weight (b.w.) per day for male rats and 0, 3.2, or 9.6 mg/kg b.w. per day for female rats), five days per week, for up to 113 weeks (males) or 122 weeks (females) (NTP 1993). The median mass aerodynamic diameter (MMAD) of the particles was 2.7 μm in the low-dose chamber and 3.2 μm in the high-dose chamber. The lung talc burdens, normalized to control lung weight or exposure concentrations, are shown in Tables 4-1 and 4-2, respectively. (No measurements were taken in control animals.)

Table 4-1. Lung talc burden (normalized to control lung weight) of male and female rats exposed to non-asbestiform talc for 6 to 24 months

Talc exposure level (mg/m^3)	Duration of exposure (months)			
	6	12	18	24
	Talc burden (mg/g control lung) (mean ± SD)			
Males				
6	2.63 ± 0.24	4.38 ± 0.59*	7.31 ± 0.71**	10.45 ± 1.26**
18	10.83 ± 0.23	20.96 ± 2.04*	27.57 ± 0.91*	24.15 ± 3.41*
Females				
6	2.43 ± 0.19	4.71 ± 0.26*	7.66 ± 0.34**	9.10 ± 0.88**
18	8.34 ± 0.12	14.16 ± 3.36	24.33 ± 0.63*	29.40 ± 2.40**

Source: NTP 1993

*$P \leq 0.05$; significantly different from the 6-month group by Dunn's or Shirley's test.

**$P \leq 0.01$; significantly different from the 6-month group by Dunn's or Shirley's test.

Table 4-2. Lung talc burden (normalized to exposure concentration) of male and female rats exposed to non-asbestiform talc for 6 to 24 months

Talc exposure level (mg/m^3)	Duration of exposure (months)			
	6	12	18	24
	Talc burden (mg/g control lung per mg/m^3) (mean ± SD)			
Males				
6	0.439 ± 0.040	0.731 ± 0.098	1.22 ± 0.12	1.74 ± 0.21
18	0.602 ± 0.013*	1.165 ± 0.113*	1.53 ± 0.05	1.34 ± 0.19
Females				
6	0.406 ± 0.032	0.785 ± 0.043	1.28 ± 0.06	1.52 ± 0.15
18	0.464 ± 0.007*	0.787 ± 0.187	1.35 ± 0.04	1.63 ± 0.13

Source: NTP 1993
*$P \leq 0.05$; significantly different from the 6-mg/m^3 group by Dunn's or Shirley's test.

The lung talc burden was generally proportional to exposure concentration at each interim evaluation and increased progressively with exposure duration. This suggests that clearance of talc from the lung was not impaired, or perhaps that clearance was impaired at both concentrations. Lung function alterations were evident at 18 mg/m^3 in both sexes after 11 months of exposure and at 6 mg/m^3 in males after 11 months and in females after 18 months. The impairment was characterized by reduced lung volume, reduced compliance, and altered gas exchange and distribution. Talc deposition was accompanied by inflammation with interstitial fibrosis, hyperplasia of alveolar epithelial type II cells, and, infrequently, squamous metaplasia of the alveolar epithelium (see Table 4-3).

The mean body weights of the rats exposed to non-asbestiform talc at 18 mg/m^3 were slightly lower than those of controls after week 65. Survival did not differ between exposed and unexposed rats. No clinical findings were attributed to non-asbestiform talc exposure.

Male and female rats exposed to non-asbestiform talc at 18 mg/m^3 had significantly increased incidences of benign or malignant pheochromocytoma of the adrenal gland. Female rats exposed at 18 mg/m^3 had significantly increased incidences of alveolar or bronchiolar adenoma or carcinoma of the lung. A squamous-cell carcinoma also was seen in the lung of one female in the 18-mg/m^3 exposure group. Tumor incidences and their statistical significance are summarized in Table 4-3.

Table 4-3. Non-neoplastic and neoplastic lesions in male and female rats after lifetime inhalation exposure to non-asbestiform talc

Tumor type	No. of tumors/no. examined (average severity grade[a])		
	Non-asbestiform talc concentration in air (mg/m^3)		
	0	6	18
Males			
Lungs (non-neoplastic lesions)			
Granulomatous inflammation	2/49 (1.0)	50/50** (1.6)	49/50** (2.3)
Peribronchial histiocytic hyperplasia	0/49	12/50** (1.3)	8/50** (1.9)
Alveolar epithelial hyperplasia	5/49 (2.0)	26/50** (1.3)	38/50** (1.7)
Interstitial focal fibrosis	1/49 (1.0)	16/50** (1.2)	33/50** (1.8)
Kidney: adrenal gland (neoplastic lesions)			
Pheochromocytoma: benign	25/49	30/48	36/47**
Pheochromocytoma: malignant	3/49	3/48	7/47
Pheochromocytoma: complex	0/49	2/48	1/47
Pheochromocytoma: benign, malignant, or complex	26/49	32/48	37/47**
Females			
Lungs (non-neoplastic lesions)			
Granulomatous inflammation	2/50 (1.5)	47/48** (1.5)	50/50** (2.8)
Peribronchial histiocytic hyperplasia	0/50	8/48** (1.3)	9/50** (1.3)
Alveolar epithelial hyperplasia	2/50 (1.0)	27/48** (1.2)	47/50** (2.1)
Interstitial focal fibrosis	1/50 (1.0)	24/48** (1.5)	45/50** (2.1)
Squamous cyst	0/50	1/48	7/50**
Lungs (neoplastic lesions)			
Alveolar or bronchiolar adenoma	1/50	0/48	9/50**
Alveolar or bronchiolar carcinoma	0/50	0/48	5/50*

Tumor type	No. of tumors/no. examined (average severity grade[a])		
	Non-asbestiform talc concentration in air (mg/m^3)		
	0	6	18
Alveolar or bronchiolar adenoma or carcinoma	1/50	0/48	14/50**
Kidney: adrenal gland (neoplastic lesions)			
Pheochromocytoma: benign	13/48	14/47	18/49
Pheochromocytoma: malignant	0/48	1/47	10/49**
Pheochromocytoma: benign, malignant	13/48	14/47	23/49*

Source: NTP 1993
[a]Average severity grades of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.
*$P < 0.05$, by logistic regression test corresponding to pairwise comparisons between the controls and that exposed group.
**$P \leq 0.01$, by logistic regression test corresponding to pairwise comparisons between the controls and that exposed group.

This inhalation bioassay provided evidence for carcinogenicity of non-asbestiform talc in male and female rats based on increased incidences of benign or malignant pheochromocytoma of the adrenal gland and evidence for carcinogenicity of non-asbestiform talc in female rats based on an increased incidence of alveolar or bronchiolar adenoma and carcinoma of the lung (NTP 1993).

Female Sprague-Dawley rats received intrabursal injection of 100 µL of a suspension containing 100 mg/mL Italian talc (Hamilton *et al.* 1984). The talc suspension contained no asbestos. Sham-operated and sham-treated (vehicle only) age-matched controls were included in the experiment which used a total of 95 rats. Animals were killed at 1, 3, 6, 12, and 18 months after treatment and examined. At each time interval, 10 treated, three age-matched controls, three sham-operated, and three sham-treated animals were examined. One or both ovaries of more than half of the treated animals at each time interval were macroscopically cystic due to bursal distension compared to none in the control groups. Histological examination was conducted 12 months after treatment and identified focal areas of papillary change in the surface epithelium of four of 10 treated ovaries compared to no changes in controls. Evidence of frank neoplasia was not found in any animals. Although the papillary changes may have been caused by talc exposure, the authors suggested that long term exposure to high concentrations of steroid hormones present in the follicular fluid within the distended bursa might have been involved.

4.1.1.2 Mice

A carcinogenesis bioassay of non-asbestiform talc was carried out in $B6C3F_1$ mice. Groups of seven-week-old mice (47 to 49 males, 48 to 50 females) were administered non-asbestiform talc by inhalation at air concentrations of 0, 6, or 18 mg/m^3 (equivalent

to 0, 2, or 6 mg/kg per day for male mice and 0, 1.3, or 3.9 mg/kg per day for female mice), five days per week, for 104 weeks. The MMAD of the particles was 3.3 μm in the low-dose chamber and 3.6 μm in the high-dose chamber, with geometric standard deviations of 1.9 μm and 2.0, respectively (NTP 1993).

Body weights and survival did not differ between the exposed and unexposed mice. No adverse clinical findings or increased incidences of benign or malignant tumors were attributed to non-asbestiform talc exposure. However, increased incidences of non-neoplastic lesions were observed in the lungs of both male and female mice, as shown in Table 4-4. The character of the inflammatory lesions in the lung was similar to that seen in the rat study (Section 4.1.1.1), but the lesions were more extensive and severe in rats than in mice. Lung burdens were lower in mice than in rats, but were disproportionately elevated at 18 mg/m^3, consistent with impaired clearance and decreased macrophage function. There was no evidence for carcinogenic activity of non-asbestiform talc in male or female B6C3F$_1$ mice exposed at concentrations of 6 or 18 mg/m^3 (NTP 1993).

Table 4-4. Non-neoplastic pulmonary lesions in male and female mice following lifetime inhalation exposure to non-asbestiform talc

Tumor type	No. of tumors/no. examined (average severity grade[a])		
	Non-asbestiform talc concentration in air (mg/m^3)		
	0	6	18
Males			
Macrophage hyperplasia	3/45	46/47** (1.4)	48/48** (2.8)
Chronic active inflammation	0/45	16/47** (1.1)	40/48** (2.2)
Females			
Macrophage hyperplasia	2/46	45/48** (1.6)	43/50** (2.8)
Chronic active inflammation	0/46	25/48** (1.4)	38/50** (2.3)

Source: NTP 1993
[a]Average severity grades of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.
**$P \leq 0.01$, by logistic regression test corresponding to pairwise comparisons between the controls and that exposed group.

4.1.1.3 Hamsters

Two groups of Syrian golden hamsters (50 per sex) were exposed to talc baby powder aerosol, prepared by flotation from Vermont talc (95% w/w platy talc with trace quantities of magnesite, dolomite, chlorite, and rutile) for 30 or 150 minutes per day, five days per week, for 300 days or until death (Wehner *et al.* 1977b, 1979, both cited in

IARC 1987a). The mean total talc air concentration was 27.4 mg/m^3, with a mean respirable fraction of 8.1 mg/m^3 and an MMAD of 6 μm. The incidence of alveolar-cell hyperplasia was 25% in the groups exposed to the aerosol for 30 or 150 minutes per day for 300 days, compared with 10% in the control group. In its review, the IARC Working Group noted the inadequate duration of the study (IARC 1987a).

4.1.2 Subcutaneous administration in mice

No local tumors were observed in 50 R3 female mice exposed to talc by a single subcutaneous injection of 0.2 mL of a mixture of 8 g of talc of unspecified characterization and 20 g of peanut oil (dose about 80 mg) and observed for life (average 50% survival, 596 days) (Neukomm and de Trey 1961, cited in IARC 1987a). Similarly, no local tumors were reported (in an abstract) in 26 female Marsh mice, three months old, given 20 mg of USP-grade talc by subcutaneous injection and observed for 18 to 21 months, or in 24 saline-injected control mice (Bischoff and Bryson 1976, cited in IARC 1987a).

4.1.3 Intraperitoneal injection in rodents

4.1.3.1 Rats

No significant increase in the incidence of tumors was reported in a study in which a group of 40 female Wistar rats, 8 to 12 weeks old, was given four 25-mg doses of granular talc in 2 mL of saline at weekly intervals by intraperitoneal injection and observed until death or sacrifice (average survival time after injection, 602 days). The incidence of mesotheliomas after 587 days was 1/36 in treated animals, compared with 0/72 in saline controls (Pott *et al.* 1974, 1976a,b, all cited in IARC 1987a).

An increased incidence of tumors was reported (in an abstract) in a study in which an unspecified number of female Evans rats, three months old, were given single 100-mg doses of USP-grade talc by intraperitoneal injection and observed for 18 to 21 months. Three tumors (one lymphosarcoma, one reticulum-cell sarcoma in the peritoneal cavity, one cystadenoma of the liver) were found in the 27 talc-exposed animals examined. No tumors were found in the 26 saline controls (Bischoff and Bryson 1976).

4.1.3.2 Mice

No increased incidence of tumors was reported (as an abstract) in a study in which an unspecified number of female Marsh mice, three months old, were given single 20-mg doses of USP-grade talc by intraperitoneal injection and observed for 18 to 21 months. The incidence of intraperitoneal lymphoid tumors was not significantly different between treated animals (5/22) and saline controls (6/28) (Bischoff and Bryson 1976).

4.1.4 Intrapleural and intrathoracic administration in rodent

4.1.4.1 Rats

No significant increase in the incidence of tumors was reported (in an abstract) in a study in which an unspecified number of female Evans rats, three months old, were given single 50-mg doses of USP-grade talc by intrathoracic injection. After 18 to 21 months, 7/30 treated animals had reticulum-cell sarcomas or lymphomas. The incidences of these tumors were 8/32 and 7/32 in saline and untreated controls, respectively (Bischoff and Bryson 1976, cited in IARC 1987a).

Single 40-mg doses of one of seven grades of refined commercial talc, from separate sources, in hardened gelatin were administered to groups of 30 to 50 female Osborne-Mendel rats, 12 to 20 weeks old, by intrapleural implantation. Animals similarly treated with unspecified nonfibrous, "noncarcinogenic" materials, as well as untreated animals, were used as controls. Rats were observed for two years. The incidences of pleural sarcoma for the different grades of talc (1 through 7) are summarized in Table 4-5 (Stanton *et al.* 1981, cited in IARC 1987a).

Table 4-5. Incidence of pleural sarcoma in rats injected with seven grades of refined commercial talc

Talc grade	No. examined/ no. with tumors (percentage)	
1	1/26	(3.8)
2	1/30	(3.3)
3	1/29	(3.4)
4	1/29	(3.4)
5	0/30	(0)
6	0/30	(0)
7	0/29	(0)
Controls (untreated)	3/491	(0.6)
Controls (nonfibrous, "noncarcinogenic" materials)	17/615	(2.8)

Source: Stanton *et al.* 1981, cited in IARC 1987a

4.1.4.2 Mice

An increased incidence of tumors was reported (in an abstract) in a study in which an unspecified number of male Marsh mice, three months old, were given single 10-mg doses of USP-grade talc by intrathoracic injection. After 18 to 21 months, 5/47 treated animals had two adenocarcinomas and three lymphoid tumors of the lungs, compared with 0/48 in saline controls (Bischoff and Bryson 1976, cited in IARC 1987a).

4.2 Asbestiform talc

The IARC reviewed the carcinogenic potential of asbestiform substances via various routes in various species up to 1987. The studies reviewed used Italian talc and

commercial talc (IARC 1987a). The IARC also reviewed studies in which asbestiform fibers or different forms of asbestos (amosite, anthophyllite, crocidolite, chrysotile), without regard to mineralogy, were used (IARC 1977, 1987b). For evaluation of the carcinogenicity of asbestiform talc, asbestos is considered a reasonable surrogate, in part, because asbestos is the generic term for all naturally occurring fibers of mineral silicates of the serpentine and amphibole series (IARC 1977) (see Section 1).

The carcinogenicity studies for asbestos and asbestiform dusts evaluated by the IARC (1977, 1987a) are summarized in Table 4-6.

Table 4-6. Studies of the carcinogenicity of commercial and Italian talc and various types of asbestos in experimental animals

Chemical form	Exposure	Species (strain, no. tested	Tumor incidence and type (no. observed/ no. examined)	Control tumor incidence and type (no. observed/ no. examined)	Reference
Oral administration					
Talc (commercial)	50 mg/kg per day for life	rats (Wistar, 50)	3/45, liver cell carcinomas	2/49, liver cell carcinomas	Gibel *et al*. 1976
Talc (Italian)	100 mg/day for 100 days	rats (Wistar, 32)	1 gastric leiomyosarcoma	0/16	Wagner *et al*. 1977a[a]
Asbestos filter material containing 52.6% chrysotile	50 mg/kg per day for life	rats (Wistar, 50)	12/42, malignant tumors	2/49, liver cell carcinomas	Gibel *et al*. 1976
Chrysotile	100 mg/day for 100 days	rats (Wistar, 32)	1 gastric leiomyosarcoma	0/16	Wagner *et al*. 1977a[a]
Inhalation exposure					
Talc (Italian)	10.8 mg/m^3	rats (Wistar)	1/24, lung adenoma	0/24	Wagner *et al*. 1977a
Chrysotile	80 mg/m^3	rats	25/72, lung tumors	0/39	Gross *et al*. 1967
Chrysotile	49 mg/m^3	rats	no tumors	no controls	Reeves *et al*. 1971
Chrysotile	5 mg/m^3	rats (Charles River, 69)	2 lung carcinomas 1 pleural mesothelioma	no controls	Reeves *et al*. 1974
Chrysotile (Canadian)	12 mg/m^3	rats (CD Wistar)	17/137, lung tumors 4/137, mesotheliomas	0/126	Wagner *et al*. 1974
Chrysotile (Rhodesian)	12 mg/m^3	rats (CD Wistar)	30/144, lung tumors 0/144, mesotheliomas	0/126	Wagner *et al*. 1974
Chrysotile	50 mg/m^3	rats	5%, 2 lung carcinomas 1 mediastinal fibrosarcoma	no controls	Reeves 1976
Chrysotile	10.8 mg/m^3	rats (CD Wistar)	1/24, adenocarcinoma of the lung	0/24	Wagner *et al*. 1977a
Crocidolite	49 mg/m^3	rats	2/31, carcinoma of the lungs	no controls	Reeves *et al*. 1971

Chemical form	Exposure	Species (strain, no. tested	Tumor incidence and type (no. observed/ no. examined)	Control tumor incidence and type (no. observed/ no. examined)	Reference
Chrysotile	150–300 million particles/mL	mice (AC/F_1 hybrid)	58/127, pulmonary adenomas	80/222, pulmonary adenomas	Lynch *et al*. 1957
Crocidolite	5 mg/m^3	rats (Charles River, 69)	5 lung carcinomas	no controls	Reeves *et al*. 1974
Crocidolite	12 mg/m^3	rats (CD Wistar)	16/141, lung tumors 4/141, mesotheliomas	no controls	Wagner *et al*. 1974
Crocidolite	50 mg/m^3	rats	14% malignant tumors of the lung	no controls	Reeves 1976
Crocidolite	48 mg/m^3	guinea pigs (32)	no tumors	no controls	Reeves *et al*. 1974
Crocidolite	48 mg/m^3	rabbits (20)	no tumors	no controls	Reeves *et al*. 1974
Crocidolite	48 mg/m^3	gerbils (68)	no tumors	no controls	Reeves *et al*. 1974
Amosite	49 mg/m^3	rats	no tumors	no controls	Reeves *et al*. 1971
Amosite	5 mg/m^3	rats (Charles River, 69)	2 pleural mesotheliomas	no controls	Reeves *et al*. 1974
Amosite	50 mg/m^3	rats	5% malignant tumors of the lung and pleura	no controls	Reeves 1976
Amosite	12 mg/m^3	rats (CD Wistar)	11/146, lung tumors 1/146, mesotheliomas	0/126	Wagner *et al*. 1974
Anthophyllite	12 mg/m^3	rats (CD Wistar)	16/145, lung tumors 2/145, mesotheliomas	0/126	Wagner *et al*. 1974
Intrapleural implantation					
Talc (Italian)	20 mg	rats (Wistar, 48)	0/48, mesotheliomas	no mesotheliomas	Wagner *et al*. 1977a
Chrysotile	67 mg	rats (Sprague-Dawley)	mesotheliomas	no controls	Donna 1970
Chrysotile	10 mg	rats	2/12, mesotheliomas	no controls	Reeves *et al.* 1971

Chemical form	Exposure	Species (strain, no. tested	Tumor incidence and type (no. observed/ no. examined)	Control tumor incidence and type (no. observed/ no. examined)	Reference
Chrysotile (Rhodesian)	40 mg	rats (Osborne-Mendel)	60%, mesotheliomas	no controls	Stanton and Wrench 1972
Chrysotile (Russian)	3 x 20 mg	rats	37.5%, mesotheliomas	no controls	Pylev and Shabad 1973
Chrysotile (Russian)	3 x 20 mg	rats	31/67, mesotheliomas	no controls	Shabad *et al*. 1974
Chrysotile	1 mg	hamsters (50)	0/50, mesotheliomas	no controls	Smith and Hubert 1974
	10 mg		4/50, mesotheliomas		
	25 mg		9/50, mesotheliomas		
Chrysotile	20 mg	rats (Wistar, 48)	18/48, mesotheliomas	no controls	Wagner *et al*. 1977a
Chrysotile (Canadian)	20 mg	rats (CD Wistar)	30%, mesotheliomas	no controls	Wagner *et al*. 1977b
Chrysotile (Rhodesian)	20 mg	rats (CD Wistar)	19%, mesotheliomas	no controls	Wagner *et al*. 1977b
Crocidolite	67 mg	rats (Sprague-Dawley)	mesotheliomas	no controls	Donna 1970
Crocidolite	10 mg	rats	1/3, mesotheliomas	no controls	Reeves *et al.* 1971
Crocidolite	40 mg	rats (Osborne-Mendel)	60%, mesotheliomas	no controls	Stanton and Wrench 1972
Crocidolite	20 mg	rats (CD Wistar)	61%, mesotheliomas	no controls	Wagner *et al*. 1977b
Crocidolite	1 mg	hamsters (50)	2/50, mesotheliomas	no controls	Smith and Hubert 1974
	10 mg		10/50, mesotheliomas		
Crocidolite	16 mg	Rabbits	2/130, mesotheliomas	no controls	Reeves *et al.* 1971
Amosite	67 mg	rats (Sprague-Dawley)	mesotheliomas	no controls	Donna 1970
Amosite	40 mg	rats (Osborne-Mendel)	60%, mesotheliomas	no controls	Stanton and Wrench 1972
Amosite	1 mg	hamsters (50)	0/50, mesotheliomas	no controls	Smith and Hubert 1974

Chemical form	Exposure	Species (strain, no. tested	Tumor incidence and type (no. observed/ no. examined)	Control tumor incidence and type (no. observed/ no. examined)	Reference
	10 mg		4/50, mesotheliomas		
Amosite	20 mg	rats (CD Wistar)	36%, mesotheliomas	no controls	Wagner *et al*. 1977b
Anthophyllite	10 mg	hamsters (50)	3/50, mesotheliomas	no controls	Smith and Hubert 1974
Anthophyllite	20 mg	rats (CD Wistar)	34%, mesotheliomas	no controls	Wagner *et al*. 1977b
Intratracheal instillation					
Chrysotile	12 mg + 4.5 mg BaP	hamsters	7 pulmonary adenomas 7 pulmonary carcinomas 10 tracheobronchial papillomas among 31 animals	no controls	Smith *et al*. 1970
Chrysotile (Russian)	2 mg + 0.144 mg BaP	rats	6/21, lung papillomas, epidermoid carcinomas, reticulosarcomas, pleural mesotheliomas	no controls	Shabad *et al*. 1974
	2 mg + mg BaP		6/11, tumors		
Intraperitoneal injection					
Chrysotile	20 mg	rats (Charles River CD)	3/11, peritoneal mesotheliomas	no controls	Reeves *et al*. 1971
Chrysotile[b]	100 mg	rats (Wistar)	40%, tumors	no controls	Pott *et al*. 1972
Chrysotile (Rhodesian)	2 mg	rats (Wistar)	16%, tumors[c]	no controls	Pott *et al*. 1976a
	6.25 mg		77%, tumors[c]		
	25 mg		81%, tumors[c]		
	100 mg		55%, tumors[c]		
Crocidolite	20 mg	rats (Charles River CD)	3/13, peritoneal mesotheliomas	no controls	Reeves *et al*. 1971

Chemical form	Exposure	Species (strain, no. tested	Tumor incidence and type (no. observed/ no. examined)	Control tumor incidence and type (no. observed/ no. examined)	Reference
Crocidolite	25 mg	rats (Sprague-Dawley, 50/sex)	31/50, mesotheliomas in males 34/50, mesotheliomas in females	no controls	Maltoni and Annoscia 1974
Crocidolite	2 mg	rats (Wistar)	39%, tumors	no controls	Pott *et al*. 1976b
Amosite	20 mg	rats (Charles River CD)	0/13, peritoneal mesotheliomas	no controls	Reeves *et al*. 1971
Chrysotile	2, 6.25, 25, 100 mg	mice (NMRI, 540)	mesotheliomas	no mesotheliomas	Pott *et al.* 1976a
Crocidolite	2, 6.25, 25, 100 mg	mice (NMRI, 540)	mesotheliomas	no mesotheliomas	Pott *et al.* 1976a
Glass fiber	2, 6.25, 25, 100 mg	mice (NMRI, 540)	mesotheliomas	no mesotheliomas	Pott *et al.* 1976a
Subcutaneous injection					
Chrysotile (Rhodesian)	75 mg	rats (Wistar)	1/33, local tumors	no controls	Pott *et al*. 1976a
Intraovarian injection					
Talc (Italian)	100 mg/mL	rats (Sprague-Dawley	no tumors	no tumors	Hamilton *et al.* 1984[d]

Source: cited in IARC 1977 except as noted
[a]Cited in IARC 1987a.
[b]Milled to 99% < 3 μm.
[c]Mesotheliomas, spindle-cell sarcomas, poly-cell sarcomas, carcinomas, and reticulum-cell sarcomas.
[d]Not cited in IARC.

4.3 Summary

Inhaled non-asbestiform talc was associated with increased incidences of benign or malignant pheochromocytoma of the adrenal gland in male and female rats and with an increased incidence of alveolar or bronchiolar adenoma and carcinoma of the lung in female rats. Inhaled non-asbestiform talc did not cause tumors in female rats at the lowest exposure concentration (6 mg/m^3) or in male and female $B6C3F_1$ mice or Syrian golden hamsters. The lungs of the male and female rats and mice showed signs of marked toxicity, characterized by inflammation, focal fibrosis, and hyperplasia, suggestive of impaired clearance. Although no definite determination was made, the lung burden data suggested that clearance was not significantly impaired.

Italian and commercial talc (both presumably containing asbestiform fibers) did not significantly increase the incidences of tumors in rats when given orally or via intrapleural injection; a leiomyosarcoma was found in one study after oral exposure of rats to Italian talc. However, asbestiform dusts (chrysotile, crocidolite, amosite, anthophyllite), as toxicological surrogates for asbestiform talc, caused tumors of the lungs (mostly mesotheliomas) following inhalation, intrapleural, intrathoracic, intratracheal, or intraperitoneal exposure. Chrysotile induced unspecified pulmonary tumors and mesothelioma in rats and pulmonary adenoma in mice via inhalation exposure; dose-dependent mesothelioma in rats and hamsters via intrapleural implantation; pulmonary tumors in rats via intratracheal instillation; and mesothelioma, spindle-cell sarcoma, poly-cell sarcoma, carcinoma, and reticulum-cell sarcoma in rats via intraperitoneal injection. Crocidolite and amosite caused similar tumors in these species by similar routes of administration. Anthophyllite caused lung tumors and mesothelioma via inhalation in rats and via intrapleural injection in rats and hamsters. Orally administered asbestos filter material containing 52.5% chrysotile was associated with the development of pulmonary carcinoma and adenoma, reticulosarcoma, hepatic-cell carcinoma, cholangioma, papilloma of the forestomach, and mammary fibroadenoma. A leiomyosarcoma was found in rats orally exposed to chrysotile.

5 Genotoxicity

5.1 Non-asbestiform talc

The IARC reviewed the literature through 1986 for genotoxicity of talc, including asbestiform talc (IARC 1987a). Genotoxicity information on talc in the IARC review was limited to a single unpublished study conducted by Litton Bionetics in 1974. The IARC did not indicate whether the talc used in this study was asbestiform or non-asbestiform. Talc did not induce mutations in *Salmonella typhimurium*, in *Saccharomyces cerevisiae,* or in a host-mediated assay; did not induce chromosomal aberrations in human WI38 cells; and did not induce dominant lethal mutations in rats (Litton Bionetics 1974, cited in IARC 1987a). Genotoxicity data from the IARC review are summarized in Table 5-1.

The NTP (1993) report cited the IARC report regarding genotoxicity data and reiterated that no published genotoxicity studies of talc and only one unpublished report could be found. In the one published study of non-asbestiform talc identified in a search of published literature from 1986 to the present, no genotoxic effects were observed (Endo-Capron *et al.* 1993).

Table 5-1. Genetic and related effects of talc exposure reviewed in IARC (1987a)

Test system	End point	Results	References
Prokaryotic			
Salmonella typhimurium	reverse mutation (strains *TA1530, his G46*)	negative	Litton Bionetics 1974
Lower eukaryotic *in vitro*			
Saccharomyces cerevisiae (D3)	gene mutation	negative	Litton Bionetics 1974
Mammalian *in vitro*			
Human WI38 cells	chromosomal aberrations (2–200 μg/mL)	negative	Litton Bionetics 1974
Mammalian *in vivo*			
Mice	host-mediated assay (30–5,000 mg/kg b.w.)	negative	Litton Bionetics 1974
Rats	chromosomal aberrations or dominant lethal mutations (30–5,000 mg/kg b.w.)	negative	Litton Bionetics 1974

Source: IARC 1987a

5.1.1 Non-mammalian systems

No information on the genotoxicity of talc in prokaryotic systems, plants, or lower eukaryotic systems was found in the published literature.

5.1.2 Mammalian Systems

5.1.2.1 In vitro *assays*

Sister chromatid exchange in rat pleural mesothelial cells

Rat pleural mesothelial cells were exposed to one of three talc samples, attapulgite or anatase (negative controls), or chrysotile or crocidolite asbestos (positive controls) (Endo-Capron *et al.* 1993). The talc samples contained 90% to 95% talc, with chlorite and dolomite accounting for the remaining 5% to 10%, and contained no asbestos fibers. Sister chromatid exchanges (SCEs) were not induced by talc, but were induced by the asbestos positive controls.

Unscheduled DNA synthesis in rat pleural mesothelial cells

Rat pleural mesothelial cells were exposed to one of three talc samples, attapulgite or anatase (negative controls), or chrysotile or crocidolite asbestos (positive controls) (Endo-Capron *et al.* 1993), as described above. Unscheduled DNA synthesis was not induced by exposure to talc or the negative controls, but was induced by exposure to the asbestos positive controls.

5.1.2.2 In vivo *assays*

No information on the genotoxicity of talc in whole animals was found in the published literature.

*5.1.3 Other tests (*in vivo *and* in vitro*)*

High-purity talc dust was moderately cytotoxic in mouse peritoneal macrophages, suggesting that talc might be fibrogenic *in vivo* (Davies *et al.* 1983, cited in Wehner 1994).

5.2 Asbestiform talc

As discussed above, the IARC did not indicate whether the talc used in the one available unpublished study was asbestiform or non-asbestiform (Litton Bionetics 1974, cited in IARC 1987a). No genotoxic effects were found in that study. No additional genotoxicity studies for talc were identified in NTP (1993).

A search of the literature published after 1986 did not identify any specific genotoxicity study for asbestiform talc. However, a general review of the genotoxicity of fibers, with an emphasis on asbestos fibers, was identified (Jaurand 1997). This review noted that until recently, fibers were considered to be nongenotoxic carcinogens, because earlier studies failed to demonstrate positive results in gene mutation assays. However, assays have been adapted for investigating genetic effects of fiber exposure, and evidence for genotoxicity is accumulating. Therefore, genotoxicity data derived from studies with asbestos and other mineral fibers are summarized in this section as applicable to asbestiform talc (see Table 5-2).

Table 5-2. Genetic effects of asbestiform fibers

Test system	Test fiber	End point	Results	References
Prokaryotic				
S. typhimurium	chrysotile, crocidolite, amosite, anthophyllite	reverse mutation (strains TA1538 and TA1535)	negative	Chamberlain and Tarmy 1977
S. typhimurium	tremolite	reverse mutation (strain TA102)	negative	Athanasiou *et al.* 1992
S. typhimurium	chrysotile	reverse mutation (strain TA102)	negative	Faux *et al.* 1994
S. typhimurium	crocidolite	reverse mutation (strain TA102)	positive	Faux *et al.* 1994
S. typhimurium	crocidolite (0.4 and 0.8 mg), chrysotile (0.4 mg)	DNA adducts (strain TA104)	positive	Howden and Faux 1996
E. coli	chrysotile, crocidolite	gene mutation	negative	Chamberlain and Tarmy 1977
E. coli	tremolite	gene mutation	positive	Cleveland 1984
Lower eukaryotic *in vivo*				
D. melanogaster	nontremolite, crocidolite	female germ-line aneuploidy	negative	Osgood and Sterling 1991
D. melanogaster	chrysotile, amosite	female germ-line aneuploidy	positive	Osgood and Sterling 1991
Mammalian *in vitro*				
Rat lung fibroblasts (RFL-6)	crocidolite (2.5 µg/cm^2)	DNA adducts	positive	Howden and Faux 1996
Mouse mesothelioma cells (C3H10T1/2)	crocidolite (25–200 µg/cm^2)	DNA breaks	positive	Turver and Brown 1987
Rat alveolar Type II cells	amosite (25–250 µg/cm^2)	DNA breaks	positive	Kamp *et al.* 1995
Rat embryo cells	crocidolite (0.05–2 µg/cm^2)	DNA breaks (nick translation)	positive	Libbus *et al.* 1989
Rat pleural mesothelial cells	chrysotile and crocidolite (2, 4, and 10 µg/cm^2)	unscheduled DNA synthesis	positive	Renier *et al.* 1990
Rat pleural mesothelial cells	chrysotile and crocidolite (up to 40 µg/cm^2)	unscheduled DNA synthesis	positive	Dong *et al.* 1994
Rat hepatocytes	chrysotile (10 and 100 µg/mL)	unscheduled DNA synthesis	negative	Denizeau *et al.* 1985

Test system	Test fiber	End point	Results	References
Hamster tracheal epithelial cells	chrysotile (1–3 µg/mL), crocidolite (1–10 µg/mL)	DNA breaks	negative	Mossman *et al.* 1983
Chinese hamster lung cells	chrysotile, crocidolite, amosite	mutations at *hgprt* locus	weak positive	Huang 1979
Chinese hamster ovary cells	crocidolite	mutations at *hgprt* locus	negative	Kenne *et al.* 1986
Syrian hamster embryo cells	chrysotile, crocidolite	mutations at *hgprt* and Na^+/K^+ ATPase loci	negative	Oshimura *et al.* 1984
Rat liver cells	chrysotile, crocidolite, amosite	mutations at *hgprt* locus	negative	Reiss *et al.* 1982
Human cells *in vitro*				
Premyelocytic leukemia cells (HL60)	crocidolite (50 µg/mL)	8-OHdG DNA adducts[a]	positive	Takeuchi and Morimoto 1994
Lung epithelial cells (A549)	crocidolite (1.5 and 3 µg/cm^2)	8-OHdG DNA adducts[a]	positive	Chao *et al.* 1996
Lung epithelial-like cells (WI26)	amosite (25 and 250 µg/cm^2), chrysotile (250 µg/cm^2)	DNA breaks	positive	Kamp *et al.* 1995
White blood cells	crocidolite (10–500 µg/mL)	DNA breaks	positive	Faux *et al.* 1994
Bronchial epithelial cells	amosite and crocidolite (25 µg/mL)	DNA breaks	negative	Fornace *et al.* 1982
Mesothelial cells (TSV40)	amosite (10, 25, and 100 µg/cm^2)	DNA breaks	negative	Kinnula *et al.* 1994
Mesothelial cells	amosite (1, 10, and 100 µg/mL)	DNA breaks	negative	Gabrielson *et al.* 1986
Human–hamster hybrid (AL cells)	chrysotile, crocidolite	mutations at *hgprt* and *S1* loci	negative (*hgprt*) positive (*S1*)	Hei *et al.* 1992, 1995
Lymphocytes	crocidolite, erionite	mutations at *HLA-A* locus	negative	Both *et al.* (1994)
Lymphocytes	chrysotile (50 µg/mL)	mutations at *HLA-A* locus	positive	Both *et al.* 1994
Mesothelioma cells	crocidolite	mutations at *HLA-A* locus	negative	Both *et al.* 1995

Test system	Test fiber	End point	Results	References
Mammalian *in vivo*				
Swiss albino mice	chrysotile (20 mg/kg per day)	chromosomal aberrations in male germ cells	negative	Rita and Reddy 1986

Source: Jaurand 1997
[a]8-OHdG = 8-hydroxydeoxyguanosine.

5.2.1 Prokaryotic systems

5.2.1.1 Gene mutation in Salmonella typhimurium

Most *S. typhimurium* reverse mutation assays of asbestiform fibers were negative (see Table 5-1); however, crocidolite was reported to induce mutations in the TA102 strain (Faux *et al.* 1994, cited in Jaurand 1997).

5.2.1.2 Gene mutation in Escherichia coli

Cleveland (1984, cited in Jaurand 1997) reported that naturally occurring tremolite asbestos increased the frequency of mutant colonies in *E. coli* when tested in the presence or absence of an exogenous rat liver S9 metabolizing system. The frequency of mutant colonies was higher in the assay using S9. The author suggested that some unknown mutagen may have been introduced with the asbestos and was metabolized by S9.

5.2.2 Plants

No information on the genotoxicity of asbestiform fibers in plant systems was found in the published literature.

5.2.3 Lower Eukaryotic eukaryotic systems

5.2.3.1 Germ-line aneuploidy in Drosophila

Germ-line aneuploidy was reported in female *Drosophila melanogaster* fed certain types of asbestos suspended in a 2% sucrose-water solution for three days (Osgood and Sterling 1991). Chrysotile at concentrations of 5 or 25 mg/mL was the most effective and induced both chromosome gain and chromosome loss. Amosite also induced a statistically significant increase in aneuploidy at 25 mg/mL, inducing chromosome loss in eight of nine tests. Crocidolite and non-asbestiform tremolite did not significantly increase aneuploidy.

5.2.4 Mammalian systems

5.2.4.1 In vitro assays

Asbestos and other fibers tested in various *in vitro* assays induced DNA and chromosome damage but, in most studies, did not induce mutations.

Gene mutation at the hgprt locus in mammalian cell cultures

Jaurand (1997) reported negative results for mutation at the hypoxanthine-guanine phosphoribosyl transferase (*hgprt)* locus in Chinese hamster ovary cells, Syrian hamster embryo cells, adult rat liver cells, and human–hamster hybrid AL cells (see Table 5-3). A weak positive response was noted for Chinese hamster lung cells.

Chromosome damage in rodent and human cells

Chromosome damage was found in rodent and human cells exposed to asbestos or other fibers (Jaurand 1997). Damage included chromosome breaks, micronucleus formation, and aneuploidy, as summarized in Table 5-3. Positive results were less frequent in human cells than in rodent cells.

Table 5-3. Chromosome damage in cells exposed *in vitro* to mineral fibers

Test system	Test fiber	End point	Results (no. positive/ no. of studies)
Rodent cells (Chinese hamster ovary and lung cells, Syrian hamster embryo cells, rat tracheal and mesothelial cells)	crocidolite	chromosomal aberrations, micronuclei	7/8
	chrysotile	chromosomal aberrations, micronuclei	10/10
	amosite, tremolite, erionite, glass fibers	chromosomal aberrations, micronuclei	8/9
	crocidolite	aneuploidy	12/12
	chrysotile	aneuploidy	8/8
	amosite, tremolite, erionite, glass fibers, refractory ceramic fibers	aneuploidy	8/8
Human cells (bronchial epithelial cells, lymphocytes, lymphoid cells, mesothelial cells)	crocidolite	chromosomal aberrations, micronuclei	1/5
	chrysotile	chromosomal aberrations, micronuclei	2/6
	other fibers (other asbestos types and glass fibers)	chromosomal aberrations, micronuclei	2/5
	crocidolite	aneuploidy	2/6
	chrysotile	aneuploidy	4/7
	other fibers (other asbestos types and glass fibers)	aneuploidy	3/5

Source: Jaurand 1997

Sister chromatid exchange in rat pleural mesothelial cells

As described in Section 5.1.2.1, exposure of rat pleural mesothelial cells to chrysotile or crocidolite asbestos increased the frequency of SCEs (Endo-Capron *et al*. 1993).

Unscheduled DNA synthesis in rodent and human cells

As described in Section 5.1.2.1, exposure of pleural mesothelial cells to chrysotile or crocidolite asbestos induced unscheduled DNA synthesis (Endo-Capron *et al.* 1993).

Several studies have reported that asbestos fibers caused DNA breaks and unscheduled DNA synthesis, and some have reported negative results (Jaurand 1997). Overall, positive results have been reported more frequently for nonhuman than human cells (see Table 5-3). These effects may be cell-type specific (Jaurand 1997).

5.2.4.2 In vivo *assays*

Chrysotile asbestos was suspended in water and orally administered to male Swiss albino mice at 20 mg/kg b.w. per day for 60 days (chromosomal aberration assay) or 35 days (sperm morphology assay). Control animals received distilled water. After the animals were killed, meiotic preparations from the testes were prepared and examined for chromosomal aberrations and abnormal sperm. There was no evidence that exposure to asbestos resulted in chromosomal aberrations or abnormal sperm (Rita and Reddy 1986).

5.3 Summary

Non-asbestiform talc was found to be nongenotoxic (NTP 1993). The IARC identified one unpublished report regarding genotoxic effects of talc, and only one study published since the IARC review was identified. Non-asbestiform talc did not induce mutations *in vitro* in *Salmonella typhimurium* or *Saccharomyces cerevisiae* or *in vivo* in a host-mediated assay and a dominant lethal assay in mice. It also did not induce chromosomal aberrations in human WI38 cells or SCEs or unscheduled DNA synthesis in rat pleural mesothelial cells.

No genotoxic effects of talc with or without asbestiform fibers were reported in the published literature, including the IARC review. However, many genotoxicity studies were identified for asbestos and other mineral fibers. These studies indicated that asbestos and other mineral fibers may be associated with DNA and chromosome damage. Genetic effects reported most frequently and consistently included the following: (1) DNA adducts in bacteria and cultured rodent and human cells, (2) unscheduled DNA synthesis in cultured rodent cells, (3) DNA breaks in cultured rodent and human cells, (4) aneuploidy in cultured rodent cells, and (5) chromosomal aberrations in cultured rodent cells. Assays for aneuploidy and chromosomal aberrations in cultured human cells gave inconsistent results, gene mutation assays in bacteria and cultured mammalian cells gave mostly negative results, and chromosomal aberrations were not induced in germ cells from adult male Swiss albino mice.

6 Other Relevant Data

6.1 Non-asbestiform talc

6.1.1 Deposition, clearance, and retention

Size, shape, surface chemistry, cytotoxicity, and other factors influence the deposition, clearance, retention, and toxicity of inhaled particles (Reger and Morgan 1990, NTP 1993, Wehner 1994, Wylie *et al.* 1997). Talc particles usually are platelike or granular but also may be fibrous. In addition, depending on the source and grade of talc, various nonfibrous and fibrous mineral contaminants may be present, including calcite, dolomite, chlorite, quartz, carbonates, and asbestos (De Vuyst *et al.* 1987, Silicosis and Silicate Disease Committee 1988). The most common types of asbestiform fibers found within talc deposits include tremolite, anthophyllite, and chrysotile (IARC 1977). Gastrointestinal absorption of ingested talc is unlikely. There was no evidence that ingested talc was absorbed by rats, mice, guinea pigs, or hamsters (IARC 1987a). It is noteworthy, however, that talc particles, presumably ingested, have been found in stomach tumors and the subserosal stroma of hernia sacs in humans (Henderson *et al.* 1975, Pratt *et al.* 1985, both cited in IARC 1987a).

The deposition and retention of inhaled talc particles in the lungs depends on several factors, such as the ventilation rate and particle size and shape. Particles deposited in the ciliated part of the upper respiratory tract probably are transported out of the lungs and swallowed (Wehner 1994). Some particles deposited deeper in the lung might be cleared by macrophages; however, chronic exposure to dust particles could overwhelm these clearance mechanisms, resulting in long-term retention and lung disease (Silicosis and Silicate Disease Committee 1988). During autopsy, talc particles have been found in the lungs of urban residents, farmers, asbestos miners, drug addicts, and others (IARC 1987a). Pickrell *et al*. (1989) used a computer simulation model to predict lung burdens in rodents and humans following chronic exposure to talc aerosols. Humans were projected to retain higher lung burdens than rodents exposed to the same talc aerosol, because of a higher deposition fraction and lower clearance (Pickrell *et al.* 1989). However, rodent lung burdens may have been underestimated by the model, because clearance rates were assumed to remain constant over the two-year simulation. Particulate analysis of lung tissue and bronchoalveolar lavage fluid from individuals exposed to talc and other particulates demonstrate that talc particles and talc bodies are prevalent in lung tissues many years after exposure (Johnson *et al.* 1986, De Vuyst *et al.* 1987, Dodson *et al.* 1995).

In hamsters, 6% to 8% (20 to 80 µg) of the inhaled amount of talc particles with a median diameter of 6.4 µm to 6.9 µm were deposited in the alveolar region (Wehner *et al*. 1977a,b, cited in IARC 1987a). These researchers reported a biological half-life of 7 to 10 days, with no translocation of talc particles outside the lungs. Alveolar clearance was complete four months after exposure. The IARC Working Group noted that the unusually short clearance time may relate to limitations in the sensitivity of the detection methods and the large size of the particles. Rats exposed to talc aerosols with a mean particle size of 25 µm for periods up to 12 months retained levels proportional to the cumulative

exposure in the lungs (Wagner *et al.* 1977b, cited in IARC 1987a). Pickrell *et al.* (1989) reported that the amount of talc retained in the lungs of rats and mice following inhalation exposure for 20 days increased with increasing concentration. The mass median aerodynamic diameter of the talc aerosol was 3.0 µm. Talc particles deposited in the lungs of Syrian golden hamsters were not distributed to other tissues (Wehner *et al.* 1977a,b, 1979, cited in IARC 1987a).

Werebe *et al.* (1999) demonstrated that talc could be rapidly absorbed through the pleural tissues of rats and distributed throughout the body via the systemic circulation. In this study, talc was placed directly into the pleural space through a catheter.

There is some evidence from both human and animal studies that talc is able to migrate through the female genital tract to the ovaries and peritoneal cavity (Wehner 1994, Whysner and Mohan 2000). Talc particles have been found in human ovaries and ovarian tumors (Henderson *et al.* 1971, Heller *et al.* 1996a, Chang and Risch 1997, Cramer *et al.* 1999). Henderson *et al.* (1971) examined tumor tissues taken from patients with ovarian or cervical cancer. No asbestos particles were found in any of the tissues; however, talc particles were identified in 10 of 13 of the ovarian tumors and in 12 of 21 of the cervical tumors. The talc particles were found deep within the ovarian tumor tissue and ranged in size from 1,000Å to 2 µm. Talc particles in the cervical tumors were as large as 5 µm. Talc particles also were found in 5 of 12 normal ovarian tissues removed from patients with breast cancer. Heller *et al*. (1996a) did not find a correlation between ovarian talc particle burden and exposure history; however, they did report a higher mean electron microscopic particle count in talc users. Factors other than exposure history that may contribute to the ovarian particle burden include method of application, type of talc, undocumented exposures, and uneven distribution within the ovarian parenchyma.

Egli and Newton (1961, cited in Lauchlan 1994) placed India ink in the vaginas of women just prior to hysterectomy. Particles of carbon black from the ink were found at the fimbriated end of the oviduct by the end of the operation, thus indicating that particles were able to migrate through the genital tract. Green *et al.* (1997) provided further support for the theory that talc particles could migrate through the female genital tract. Tubal sterilization and hysterectomy significantly reduced the risk of ovarian cancer, suggesting that contaminants such as talc may gain access to the peritoneal cavity through patent fallopian tubes.

Henderson *et al*. (1986) demonstrated that talc particles could migrate from the vagina and posterior uterus to the ovaries in rats. Talc particles were suspended in phosphate buffered saline (100 mg/mL, total volume 250 µL) and placed in the uterus or vagina of Sprague-Dawley rats. Four rats received a single uterine instillation (sacrificed on day 5), two rats received further treatments on days 6 and 15 (sacrificed on day 20), and two rats received further treatments on days 6, 15, 22, and 30 (sacrificed on day 49). Six rats received intravaginal instillation. Two rats each were sacrificed 24 hours, 48 hours, and four days after treatment. Talc particles were found in the ovaries of all animals that received intrauterine exposure and in both rats sacrificed four days after intravaginal exposure. Talc particles were not found in the ovaries of rats within 48 hours of intravaginal exposure.

Other animal studies do not support the theory that particles can be translocated from the vagina to the ovaries (Wehner *et al.* 1985, 1986, Boorman and Seely 1995). Wehner *et al.* (1985) placed 0.3 mL of a 4% bone black suspension in the vaginas of five cynomolgus monkeys (*Macaca fascicularis*). The oviducts were examined one hour (three animals) or 72 hours (two animals) after treatment and did not show evidence of translocation. In a separate experiment, two monkeys received 125 mg of neutron-activated cosmetic talc suspended in 0.3 mL of deionized water. These animals were examined three days later by peritoneal lavage. No measurable translocation of talc particles occurred. In a follow-up study, Wehner *et al.* (1986) investigated whether or not multiple vaginal depositions of neutron-activated talc would result in translocation to the uterus or beyond. Six monkeys were treated with 30 applications (125 mg of talc suspended in 0.3 mL of physiological saline solution) in 45 days. Abdominal lavage was performed two days after the final treatment. The ovaries, oviducts, uterus, and vagina with cervix also were examined. Talc was found only in the vagina and cervix, indicating that translocation did not occur.

Boorman and Seely (1995) randomly selected 10 female rats from the control and exposure groups from the NTP (1993) study. Histological slides of lung and ovarian tissues were examined for talc partilces. Talc particles were identified in the lungs of exposed rats but were not found in the ovaries or ovarian bursa from any of the rats. In this case, lifetime exposure to talc aerosols did not result in deposition of talc particles in the ovary of Fischer 344/N rats. These researchers noted that the animals and cages were often covered with talc; therefore, there was ample opportunity for oral, respiratory, and perineal exposure.

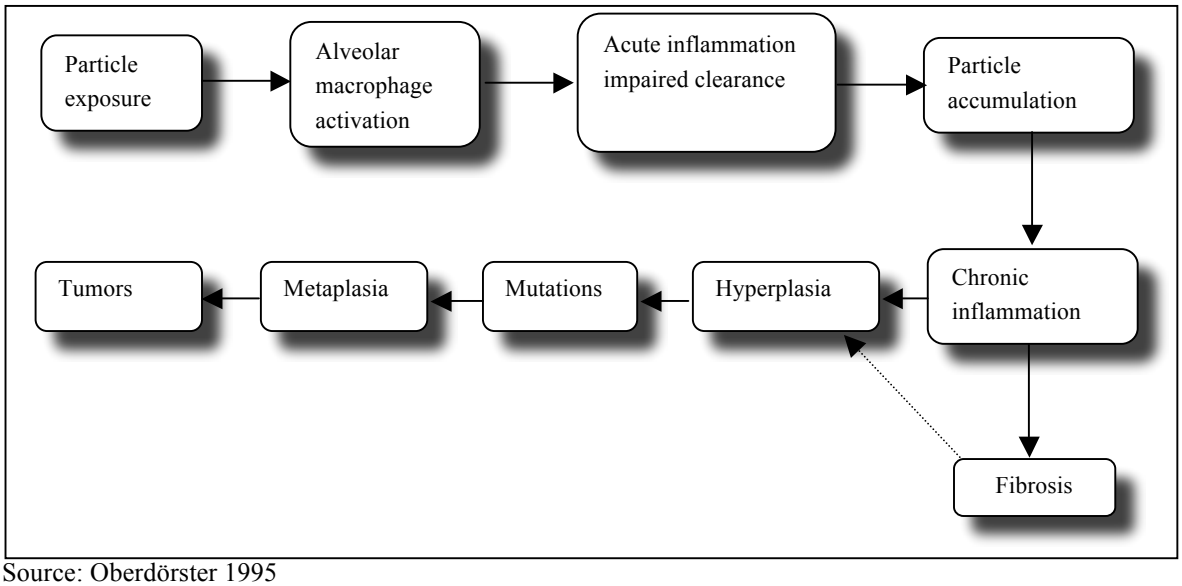
6.1.2 Possible mechanisms

The NTP (1993) concluded that there was some evidence of carcinogenic activity of non-asbestiform, cosmetic-grade talc in male F344/N rats, based on an increased incidence of pheochromocytoma of the adrenal gland. There was clear evidence of carcinogenic activity in female F344/N rats, based on increased incidences of alveolar or bronchiolar adenoma and carcinoma of the lung and pheochromocytoma of the adrenal gland. However, the relevance of these results to humans has been questioned (Goodman 1995, Oberdörster 1995, Zazenski *et al.* 1995). The probable mechanism for increased pheochromocytoma in rats exposed to talc aerosols is not clear, but two general hypotheses were presented by the NTP (1993). The increased incidence may be a non-specific effect of stress resulting from chronic pulmonary inflammation. The adrenal medulla, as a modified sympathetic ganglion, reacts to both neural and hormonal stimuli in the secretion of catecholamines. If prolonged stress were to increase the rate of occurrence or growth of proliferative lesions in the adrenal medulla, similar exposure-related increases in pheochromocytoma incidences might be expected. Alternatively, cytokines released from macrophages or other cells in the lung might be responsible for the increased incidence of pheochromocytoma.

Lung tumors were not induced in male rats or in male or female mice in the NTP (1993) study. Pulmonary inflammation and toxicity were much less in the mice than in the rats. Chronic granulomatous inflammation, alveolar epithelial hyperplasia, squamous

metaplasia, squamous cysts, and interstitial fibrosis were observed in both male and female rats. Goodman (1995) and Oberdörster (1995), on further analysis of the NTP data, suggested that these data indicated that lung clearance mechanisms were overwhelmed, leading to lung overload and marked chronic lung toxicity. The NTP (1993) reported that exposure-normalized data showed that lung talc burdens were generally proportional to exposure concentration and suggested two interpretations: that increasing the exposure concentrations did not substantially impair clearance mechanisms or that clearance mechanisms were impaired similarly at both exposure concentrations. Marked hyperplasia and fibrosis have been linked to tumorigenesis (Dungworth 1994, cited in Oberdörster 1995). A proposed sequence of events is illustrated in Figure 6-1 (Oberdörster 1995). Under the conditions of the Oberdörster scenario, exposure to non-asbestiform talc that does not result in marked chronic lung toxicity would not likely cause tumors (Goodman 1995). Estimates of human exposure to talc particles under normal conditions of use (normal face or body powdering by adults; diapering use for infants) were well below concentrations expected to result in lung toxicity (Zazenski *et al.* 1995).

Figure 6-1. Proposed sequence of pulmonary events associated with lung overload



Source: Oberdörster 1995

6.2 Asbestiform talc

6.2.1 Deposition, clearance, and retention

The deposition, clearance, and retention of asbestiform talc or asbestos are similar to those of non-asbestiform talc (see Section 6.1.1).

During autopsy, talc particles have been found in the lungs of urban residents, farmers, asbestos miners, drug addicts, and others (IARC 1987a). Particulate analysis of lung tissue and bronchoalveolar lavage fluid from individuals exposed to talc and other particulates, including asbestos, suggests that talc particles, asbestos fibers, and

ferruginous bodies (coated talc or asbestos fibers) are prevalent in lung tissues many years after exposure (Johnson *et al.* 1986, De Vuyst *et al.* 1987, Dodson *et al.* 1995).

Deposition, retention, and clearance of inhaled asbestos in laboratory animals were shown to vary according to the type of asbestos. Retention of amphibole particles in the lung was proportional to the concentration of respirable dust. Chrysotile lung burdens did not increase with dose, and chrysotile particles were deposited and retained in the lungs in lower amounts than amphibole particles. Following six months' exposure to various amphiboles, clearance rates after 18 months ranged from 41% to 74%. Clearance rates for chrysotiles were much lower, but could not be determined exactly, because of their low occurrence in the lungs (IARC 1977). These findings are consistent with human data. In most cases, amphibole fibers predominate in human lung tissues (IARC 1987b). However, humans were reported to have a higher deposition fraction and lower clearance rate than rats (Pickrell *et al.* 1989).

There is some evidence that asbestos fibers injected into the pleural space of rats could translocate to the liver and other tissues (IARC 1977). Asbestos fibers also were detected in the ovaries of 9 of 13 women with household asbestos exposure and in 6 of 17 women who had no known exposure to asbestos (Heller *et al.* 1996b).

6.2.2 Possible mechanisms

Talc inhalation has been associated with three distinct forms of pulmonary disease: talcosilicosis, talcoasbestosis, and talcosis (Wehner 1994). Talcosilicosis and talcoasbestosis are associated with exposure to talc containing a high silica content and asbestiform fibers, respectively. Talcosilicosis is identical to silicosis, and talcoasbestosis is essentially identical to asbestosis, including malignancy. Talcosis is associated with heavy and prolonged exposure to pure talc and has most often been associated with occupational exposures. Clinical features of talcosis are consistent with restrictive pulmonary disease (Wehner 1994).

The exact mechanisms by which fibers induce lung cancer or mesothelioma are not completely understood. The biological activity of fibers is related to many factors, including fiber geometry and chemistry, persistence in the lungs, and chemical composition and surface reactivity. Current evidence indicates that fibers may act as direct or indirect carcinogens. The following sections focus on possible mechanisms or modes of action associated with talcoasbestosis, as inferred from asbestosis.

6.2.3 Fiber dimensions and mineralogy

The results of some studies indicate that the fibrous structure is related to cancer induction (IARC 1977, Browne 1991). Evidence from both animal and human data indicates that fibers shorter than 5 μm are not carcinogenic, whereas fibers longer than 8 μm and with a width less than 0.25 μm have been considered the most hazardous. In some studies, non-asbestiform fibers, including glass fibers, with diameters less than 0.5 μm have induced mesotheliomas. Furthermore, carcinogenicity studies in laboratory animals suggest that asbestiform tremolite causes tumors, but non-asbestiform tremolite does not (Reger and Morgan 1990). However, Wylie *et al.* (1997) suggested that

mineralogical composition, rather than fiber size, plays an important role in the toxicity of mineral fibers. They compared the cytotoxic and proliferative effects of fibrous talc and asbestos on hamster tracheal epithelial and rat pleural mesothelial cells. Three talc samples, containing varying amounts of talc fibers and asbestos, were used in the study. Talc fibers accounted for 62% to 99% of the total fibers in the sample that were greater than 5 μm in length. Both cell types were less sensitive to talc than to asbestos, even though the talc samples contained fibers that were similar to the asbestos fibers in size and shape.

6.2.4 Direct genotoxic activity

Three possible mechanisms for direct genotoxic activity of asbestiform fibers were identified by Voytek *et al.* (1990). The first mechanism involves penetration of the target cell by asbestos fibers and direct interaction with macromolecules, including DNA. The second mechanism involves binding of asbestos to tubulin. Tubulin is necessary for chromosomal separation during cell division; therefore, interference with this protein could lead to aneuploidy. Data showing that asbestos may cause DNA breaks, unscheduled DNA synthesis, and aneuploidy are summarized in Section 5. The third mechanism involves transfection of viral DNA or DNA fragments into the genome of a normal cell. At high concentrations (3 to 10 mg/mL), asbestos fibers may interact with DNA fragments and carry them into the cell for insertion into genomic DNA. DNA fragments have been found outside of cell membranes. Furthermore, inflammatory reactions induced by asbestos fibers result in cellular destruction, which can release degraded DNA fragments. The inserted DNA could alter the expression of cellular oncogenes, or the transfected DNA could contain oncogenes. However, it is uncertain whether concentrations of asbestos fibers (carriers) and DNA fragments at asbestos deposition sites would be sufficient for this to occur *in vivo* (Voytek *et al.* 1990).

6.2.5 Indirect genotoxic activity

Browne (1991) reviewed the pathogenesis of asbestosis, including lung cancer and mesothelioma, and concluded that the malignant changes may not result from a direct genotoxic action. Persistent inflammatory reactions are produced by inhalation of fibers too long to be completely ingested by phagocytes. Interaction of macrophages with the longer fibers results in lifelong release of lysosomal enzymes, reactive oxygen species, and growth factors; however, inflammatory reactions induced by exposure to shorter fibers are transient. According to Browne (1991), the data suggest that asbestosis, lung cancer, and mesothelioma result from chronic proliferation, destruction of the normal tissue architecture, and disruption of the protective mechanisms following exposure to longer asbestiform fibers.

There is evidence that ferrous iron present in some asbestos fibers can generate reactive oxygen species by reduction of oxygen to form the superoxide free radical (Voytek *et al.* 1990, Martin *et al.* 1997). Hydrogen peroxide and the hydroxyl free radical may be formed from the superoxide free radical. Asbestos fibers also may transfer electrons directly to cell surfaces or macromolecules within the cell, leading to genetic damage and mutations. For example, heat treatment of chrysotile asbestos fibers (6 μm in length) reduced their cytotoxicity to human fibroblasts and bovine alveolar macrophages.

Subsequent irradiation of the fibers restored the cytotoxic effects. A possible explanation is that heat treatment caused the release of metastable electrons within the asbestos minerals, which were restored by irradiation (Valentine *et al.* 1983, cited in Voytek *et al.* 1990).

The airway epithelium responds to particulate exposure through inflammatory reactions (Martin *et al.* 1997, Voytek *et al.* 1990). Inflammation of the airway epithelium results in cell injury and regeneration and the accumulation of macrophages and polymorphonuclear leukocytes. These cells release growth-stimulating factors and release reactive oxygen species after phagocytosis. Reactive oxygen species can induce mutations in the dividing cells, leading to malignant transformation (Voytek *et al.* 1990, Martin *et al.* 1997). Evidence suggests that nonfibrous particles and short fibers are not as active as long fibers in stimulating generation of reactive oxygen species. Because reactive oxygen species are short-lived, it has been suggested that more stable secondary molecules derived from reactive oxygen species are likely to be involved in DNA damage (Jaurand 1997).

All types of asbestos, as well as some manmade vitreous fibers, produce the hydroxyl free radical in buffered solutions. Treatment of both cell-free systems and cell cultures with asbestos has produced 8-hydroxydeoxyguanosine (8-OHdG). Although the role of this hydroxylation product in carcinogenesis is uncertain, 8-OHdG can cause miscoding errors during DNA replication that result in mutations (Jaurand 1997).

6.2.6 Asbestiform fibers as cancer promoters

Chrysotile asbestos promoted tumors in F344 rat trachea transplanted to the retroscapular region of eight-week-old isogeneic recipients (Voytek *et al.* 1990). Pellets containing 12.5 to 100 μg of dimethylbenz[*a*]anthracene (DMBA) were placed in the lumina of the transplants and removed after four weeks. Chrysotile asbestos (200 μg) was then placed in the lumina. Carcinomas were increased in animals initially treated with nontumorigenic doses of DMBA (25 or 50 μg) and exposed to asbestos fibers at the transplantation site (Topping and Nettesheim 1980, cited in Voytek *et al.* 1990).

Asbestos fibers may interact with membrane phospholipase C, causing an influx of calcium ions into the cell and subsequent activation of protein kinase C, which stimulates reactive oxygen species and plays a key role in signal transduction involving activation of oncogenes, cellular growth, and tumor promotion (Voytek *et al.* 1990). However, in one study, amosite asbestos fibers failed to induce reactive oxygen species in human lung mesothelial cells, and free-radical scavengers did not alter the cytotoxic effects (Gabrielson *et al.* 1986, cited in Voytek *et al.* 1990). Cell type differences, experimental conditions, and fiber characteristics might explain this discrepancy.

6.3 Summary

Ingested or inhaled non-asbestiform talc particles are unlikely to be absorbed into the systemic circulation and distributed to other parts of the body. Inhaled talc particles may persist for years within the lungs. The current data indicate that inhaled non-asbestiform

talc is unlikely to pose a cancer risk to humans under exposure conditions that do not impair clearance mechanisms or cause chronic lung toxicity.

Ingested or inhaled asbestiform talc particles are unlikely to be absorbed into the systemic circulation and distributed to other parts of the body. Inhaled asbestiform talc particles may persist within the lungs for years, eventually precipitating chronic pulmonary disease. Fiber dimensions and mineralogy have been identified as important factors related to toxicity. Short fibers are less effective in stimulating production of reactive oxygen species. Long, thin fibers are generally regarded as the most toxic. Talc fibers were reported to be less toxic than asbestos fibers of similar dimensions. The current data indicate that inhaled talc containing asbestiform fibers induces effects in the lungs that are essentially identical to those associated with asbestosis. Asbestiform minerals may induce cancer by directly or indirectly interacting with DNA or may act as a tumor promoter. Direct genotoxic effects have not been demonstrated *in vivo*; however, evidence is accumulating that fibers are genotoxic agents. Chronic inflammation and phagocytosis were identified in the majority of studies as critical events.

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Appendix A: IARC Monographs on the Evaluation of the carcinogenic Risk of Chemicals to Humans. Silica and Some Silicates. V 42. 1987. A-1 – A-41.

Appendix B: IARC Monographs on the Evaluation of the carcinogenic Risk of Chemicals to Humans. Talc. Suppl. 7. 1987. B-1 – B-2.

Appendix C: IARC Monographs on the Evaluation of the carcinogenic Risk of Chemicals to Man. Asbestos. V 14. 1977. C-1 – C-103.

Appendix D: IARC Monographs on the Evaluation of the carcinogenic Risk to Humans. Overall Evaluation of carcinogenicity: An Updating of IARC Monographs. Suppl. 7. 1987. D-1 – D-12.