GREEN

Safety Assessment of

Talc

as Used in Cosmetics

CIR EXPERT PANEL MEETING

DECEMBER 10-11, 2012

Cosmetic Ingredient Review
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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Monice M. Fiume *MMF*
            Senior Scientific Analyst/Writer
Date: November 16, 2012
Subject: Safety Assessment of Talc as Used in Cosmetics

Enclosed is the Draft Report on the Safety Assessment of Talc as Used in Cosmetics. This is the first time the Panel is seeing this document. The Scientific Literature Review, which was a collaborative effort between me and Dr. Ivan Boyer, was issued on August 21, 2012.

As explained in the Introduction, specifications for cosmetic talc state that it must be asbestos-free and that it does not contain asbestiform fibers. Because the purpose of this assessment is the safety of talc as used in cosmetics, to the best of our abilities, only studies addressing non-asbestiform talc were used.

Concentration of use data have been provided by the Council. In addition to the normal concentration of use survey, the Council also completed a survey to assess the use of talc in spray products. In this special survey, companies were asked specifically whether they use talc in spray products, and if yes, the companies were asked to provide the maximum concentration of use of talc in the spray product as well as in products in the same FDA category that are not sprays. These data are included.

This safety assessment has generated a good deal of interest, and a number of comments have been received and are included. In some of the comments, you will see reference to published studies or articles. As is standard CIR procedure, the published information is not being provided. The following is the list of comments received.
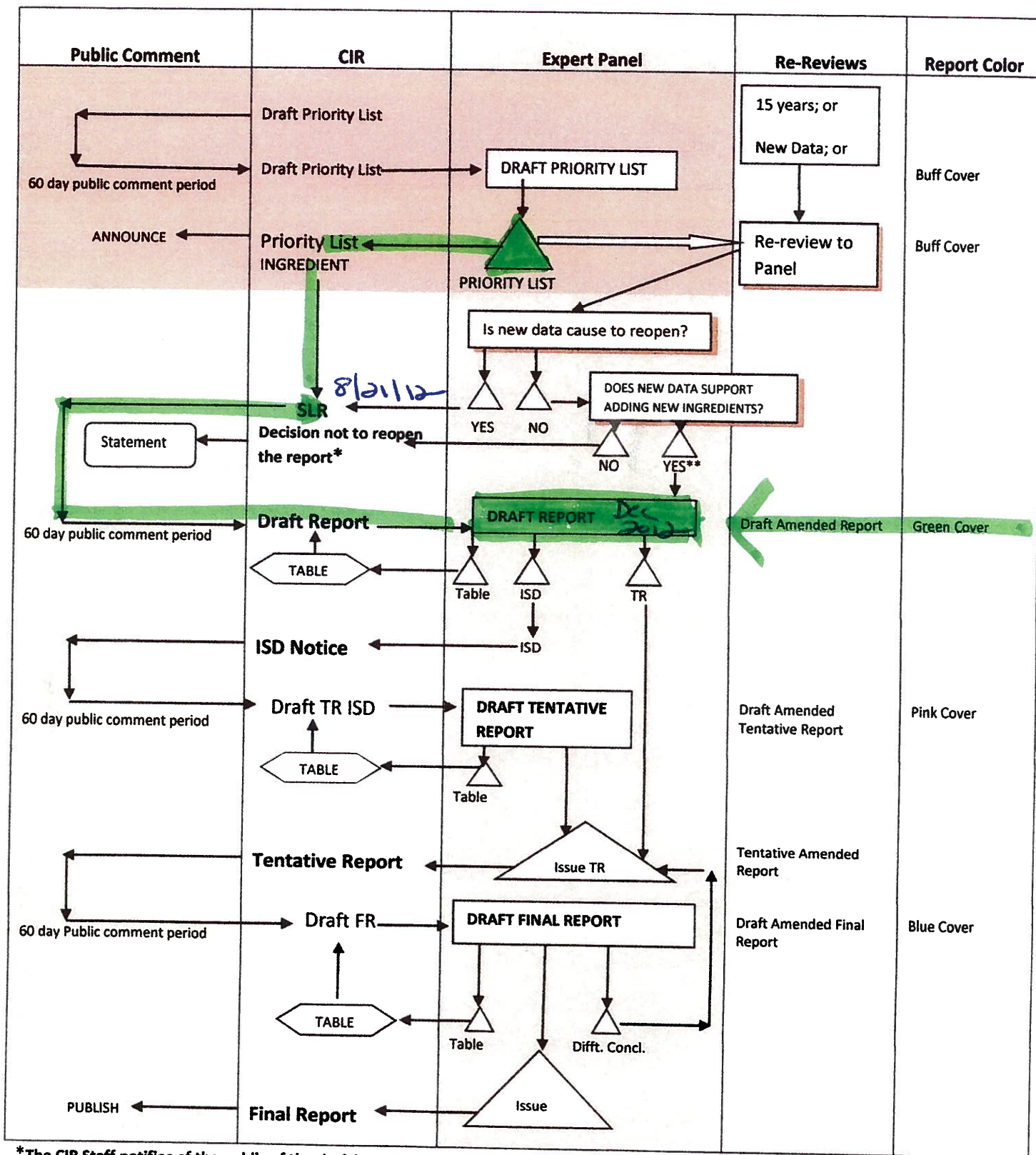
1. Comments on the Scientific Literature on Talc. Submitted by the Council on October 15, 2012.
2. Letter dated October 12, 2012 to Dr. F. Alan Andersen concerning the Scientific Literature Review on Talc as Used in Cosmetics, with attachments. Submitted on October 15, 2012 through the Council by Anonymous.
3. Initial comments on the CIR draft Scientific Literature Review for "Talc as Used in Cosmetics," dated October 19, 2012. Submitted by William G. Kelly, Jr., Center for Regulatory Effectiveness.
4. Comments dated October 19, 2012 regarding the Scientific Literature Review: Talc as Used in Cosmetics. Submitted by Dr. Michelle Wyart-Remy, EUROTALC, and Mark G. Ellis, IMA-NA.

Since this report is on a single ingredient, a data profile is not provided. As you will notice, this report contains a large amount of data. As you review the document, please don't hesitate to contact us with any questions. We are happy to provide any clarification that will assist you with your review.

If there are no additional data needs on talc, the Panel should be prepared to formulate a tentative conclusion, with the rationale provided for the Discussion, and issue a Tentative Report for public comment. If the data are not sufficient for making a determination of safety, then an Insufficient Data Announcement should be issued, listing the additional data that are needed.

SAFETY ASSESSMENT FLOW CHART

Public Comment	CIR	Expert Panel	Re-Reviews	Report Color
	Draft Priority List		15 years; or	
60 day public comment period	Draft Priority List	DRAFT PRIORITY LIST	New Data; or	Buff Cover
ANNOUNCE	Priority List INGREDIENT	PRIORITY LIST	Re-review to Panel	Buff Cover
		Is new data cause to reopen?		
	SLR	YES NO DOES NEW DATA SUPPORT ADDING NEW INGREDIENTS?		
	Decision not to reopen the report*	NO YES**		
	Statement			
60 day public comment period	Draft Report	DRAFT REPORT	Draft Amended Report	Green Cover
	TABLE	Table ISD TR		
ISD Notice		ISD		
60 day public comment period	Draft TR ISD	DRAFT TENTATIVE REPORT	Draft Amended Tentative Report	Pink Cover
	TABLE	Table		
Tentative Report		Issue TR	Tentative Amended Report	
60 day Public comment period	Draft FR	DRAFT FINAL REPORT	Draft Amended Final Report	Blue Cover
	TABLE	Table Difft. Concl.		
PUBLISH	Final Report	Issue		

8/21/12

Dec 2012

*The CIR Staff notifies of the public of the decision not to re-open the report and prepares a draft statement for review by the Panel. After Panel review, the statement is issued to the Public.

**If Draft Amended Report (DAR) is available, the Panel may choose to review; if not, CIR staff prepares DAR for Panel Review.

△ Expert Panel Decision

▭ Document for Panel Review

⇨ Option for Re-review
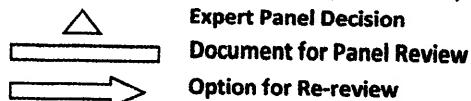
History: Talc

This report was initially started in 2009, but was eventually put on hold. It was reassigned for 2012.

The Council provided concentration of use data on January 21, 2012. In 2012, the Council completed a survey to assess the use of talc in spray products. In this special survey, companies wee asked specifically whether they use talc in spray products, and if yes, the companies were asked to provide the maximum concentration of use of talc in the spray product as well as in products in the same FDA category that are not sprays.

In January 2012, the Center for Regulatory Effectiveness provided a submission that included a large number of published studies.

August 21, 2012: Scientific Literature was posted

The following comments were received in response to the issuance of the SLR:
1. Comments on the Scientific Literature on Talc. Submitted by the Council on October 15, 2012.
2. Letter dated October 12, 2012 to Dr. F. Alan Andersen concerning the Scientific Literature Review on Talc as Used in Cosmetics, with attachments. Submitted on October 15, 2012 through the Council by Anonymous.
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December 10-11, 2012: Draft Report

The draft report was presented to the Panel.

SEARCH INFO FOR TALC (14807-96-6)

SciFinder – weekly Keep Me Posted results are received for talc

Database	Date	Search Terms/Items	# Hits/# Obtained
PubMed	3-20-12	(TALC OR 14807-96-6) AND INHALATION	89 hits/ 9 paper downloaded; 5 ordered
	3-21-12	(TALC OR 14807-96-6) AND TOXICITY	130 hits/ 1 downloaded; 4 ordered
		(TALC OR 14807-96-6) AND (IRRITATION OR SENSITIZATION)	8 hits/0 useful
	4-18-12	TALCOSIS	
	4-19-2012	PNEUMOCONIOSIS AND TALC	192/5 useful (new)
Toxnet	3-21-12	(TALC OR 14807-96-6) AND OCULAR	13 hits/0 useful
SciFinder	3-21-12	14807-96-6 AND CARCINOGENICITY (w/document-type limiters)	41 hits/ had most 1 downloaded; 1 ordered
	4-3-12	TALC AND TOXICOKINETICS (w/document-type limiters)	558 hits; 10 ordered
	4-3-12	TALC AND ABSORPTION (w/document-type limiters)	18 hits; 0 new
	4-3-12	TALC AND METABOLISM (w/document-type limiters)	264 hits; 0 new
	4-3-12	TALC AND MIGRATION (w/document-type limiters)	145 hits; 1 new order
	4-3-12	TALC AND SKIN (w/document-type limiters)	225 hits; 1 new order
	4-3-12	TALC AND INHALATION (w/document-type limiters)	140 hits; 3 new ordered
SciFinder	4-3-12	KMP (Talc by CAS #)	43 new hits/0 useful
FDA	3-23-12	21 CFR73.1550; last updated 4/1/2011 21CFR176.170; last updated 4/1/2011 21CFR182.70; last updated 4/1/2011 21CFR182.90; last updated 4/1/2011	
FDA-OTC	3-26-12	talc	OTC category skin protectant; last updated 4/7/2010
ChemPortal	3-26-12	searched CAS No.	ACToR; CCR; OECD-HPV: - no hits ESIS – IUCLID dataset; EPA – mol. wt.
OSHA	3-26-12	29CFR1910.1000 Table Z-3; last updated 7/1/1999	
ACGIH	3-26-12	Talc	used NIOSH info
OTC	3-26-12		status II for astringent drugs
Merck	3-26-12		entry found
USP	4-3-12	talc	online entry found

Many published references were received in a submission from CRE, and some published papers were received from the Council.

Ingredient Manager: Angela Howard
Date: 2/24/2009 - 10/19/09

Ingredient Name(s): **CAS RN**   **Ingredient Name(s):**
Talc   14807-96-6

Checkl	Database	Search T	Date	Hits	Notes
	PubMed	A	2/24/2009; 7/9/09		
		B	2/24/2009	1686	
		C	2/24/2009	94	
		E	7/14/2009	158	
Free	HPDB			2264	HSDB; Chem Idplus, Toxline, CCRIS, CPDB, DART, GENETOX, IRIS, ITER, LactMed, Multi-Database, TRI, Haz-Map, Household Products, TOXMAP
Free	TOXNET				
Free	NTP				
Free search/ Pay retrieval	NTIS				
Yr license	Merck	A,D	2/24/2009	1	
	FDA				Federal Register Notices
	SCCP				Opinions and EU Directives
	IPCS				
Password Required	RIFM				
Pay Service	STN				Beilstein

Date   Notes

FOIA Submitted
FOIA Results

Search Terms Key

A   Talc

B   Talc NOT pleurodesis NOT effusions

C   Talc AND ovarian cancer

D   Cas RN

E   Talc AND inflammation

F

G

Safety Assessment of

Talc

as Used in Cosmetics

Status: Draft Report for CIR Expert Panel Review

Release Date: November 16, 2012

Panel Meeting Date: December 10-11, 2012

Cosmetic Ingredient Review

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INTRODUCTION

This safety assessment presents information relevant to the safety of talc as used in cosmetic formulations. Reported functions of talc in cosmetics include abrasive, absorbent, anticaking agent, bulking agent, opacifying agent, skin protectant, and slip modifier.(Gottschalck TE & Breslawec HP, 2012)

Talc used in cosmetics does not contain asbestiform fibers. Therefore, this report will only address non-asbestiform talc. Asbestiform refers to a crystallization product of a mineral in which the crystals are thin, hair-like (practically single dimensional) fibers with enhanced strength, flexibility, and durability.(Wild P, 2006) In 1976, specifications for cosmetic talc stating that it must be asbestos-free were developed(Wehner AP, 1998a). Therefore, that year is a useful cut-off in determining what data are more likely relevant to the safety of cosmetic talc; studies before that date are likely of uncertain relevance to talc as currently used in cosmetics.

The following are conclusions from various workshops and review articles on talc. There have been a number of other published review papers on talc that are not cited here. The relevant primary references cited in the reviews are included in this safety assessment. Reviews and responses specific to the NTP study are included in the section on Carcinogenicity. The non-cosmetic issue of the prohibition of the use of talc in medical examination gloves(Food and Drug Administration (FDA), 2008a) will not be addressed in this safety assessment.

- In 1978, the Public Citizen Health Research Group contacted the Food and Drug Administration (FDA) with a letter stating their concern that talc is possibly carcinogenic and that FDA should eliminate the use of talc in drugs and cosmetics even if the results are not conclusive (letter from S.M. Wolfe and B. Gordon to D. Kennedy, FDA, Aug 1978). The FDA responded that it was studying talc and believed that any risk from talc was related to contamination by asbestos fibers (letter from D. Kennedy, FDA, to S.M. Wolfe and B. Gordon, Jan 1979).

- In 1983, the FDA received a citizen's petition from P. Douillet requesting that cosmetic talc be labeled with an asbestos warning statement, information on asbestos particle size, and the proportion of talc impurities in the product (letter from J.W. Swanson, FDA, to P. Douillet, July 1986). The FDA denied this request, stating that "there is no basis at this time for the agency to conclude that this is a health hazard attributable to asbestos in cosmetic talc. Without evidence of such a hazard, the agency concludes there is no need to require a warning label on cosmetic talc."

- In 1992, the Environmental Protection Agency (EPA) issued a "Health Assessment Document for Talc."(Environmental Protection Agency (EPA), 1992) The content of the EPA review document was similar to what would be included in a safety assessment prepared by the CIR. The review concluded that talc is not carcinogenic following inhalation exposure or intraperitoneal (i.p.), intrapleural, or intrabursal administration to rats, hamsters, and mice. However, these studies were not considered fully adequate to evaluate the carcinogenic potential of talc. The review noted that evidence from two studies suggests that talc may be an effective co-carcinogen when administered intratracheally with benzo[a]pyrene (B[a]P).

- In 1993, the National Toxicology Program (NTP) issued a report, "Toxicology and Carcinogenesis Studies of Talc (CAS No. 14807-96-6) in F344/N rats and B6C3F$_1$ Mice (Inhalation Studies)," that concluded there was *some evidence of carcinogenic activity* in male F344/rats, *clear evidence of carcinogenic activity* in female F344/N rats, and *no evidence of carcinogenic activity* in male or female B6C3F$_1$ mice exposed to aerosols of 6 or 18 mg/m^3 non-asbestiform cosmetic-grade talc in a lifetime study.(National Toxicology Program (NTP), 1993) (This study will be described in detail later in this report).

- In 1994, a public workshop titled "Talc: Consumer Uses and Health Perspectives" was organized under joint sponsorship of the FDA, the CTFA (now, the Personal Care Products Council), and the International Society of Regulatory Toxicology and Pharmacology (ISRTP).(Carr CJ (Rapporteur), 1995;Wehner AP, 1998a) The purpose of the workshop was to provide a forum for an updated discussion of the origins, manufacture, characterization, toxicology, and epidemiology of talc and related products. The principle focus was the then-latest toxicological and epidemiological studies as they related to the safe uses of talc in cosmetic products. The characteristics of cosmetic-grade talc, the history of talc use, and quality-control measures for talc were discussed, as was an appraisal of the NTP inhalation study on talc. The regulatory history of talc was also reviewed. The workshop concluded that the NTP bioassay results could not be considered a rele-

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vant predictor of human risk, and in regard to proposed association of talc exposure and ovarian cancer, the Panel found that the epidemiological data were conflicting and remain equivocal.

- In 1994, the Cancer Prevention Coalition (CPC) submitted a citizen petition to the FDA seeking labeling on all cosmetic talc products.(Cashen JA *et al.*, 1994) The requested labeling was a warning that talcum powder causes cancer in laboratory animals; frequent talc application in the female genital area increases the risk of ovarian cancer. This petition was denied.(Epstein SS, 2008)

- In 2000, talc was nominated for review in the NTP 10th Report on Carcinogens because the NTP bioassay reported clear evidence of carcinogenic activity of talc (non-asbestiform) based on increased incidences of alveolar/bronchiolar adenomas and carcinomas of the lung in female rats and because published epidemiology studies suggested that talc exposure was associated with lung cancer in pottery workers and ovarian neoplasms in women. (65 FR 17891)(2000) However, in 2005, the NTP deferred consideration of listing talc (cosmetic and occupational exposure; both asbestiform and non-asbestiform) as a carcinogen because of considerable confusion over the mineral nature and consequences of exposure to talc.(70 FR 60548)(2005) Talc has been withdrawn from review.(National Toxicology Program (NTP), 2007)

- In 2008, the CPC again submitted a petition to FDA seeking labeling on all cosmetic talc products.(Epstein SS, 2008) The requested labeling was a warning that frequent application of talcum powder in the female genital area substantially increases the risk of ovarian cancer. It does not appear that FDA has responded to this petition.

- In 2010, the International Agency for Research on Cancer (IARC) Working Group determined that there is *limited evidence* in experimental animals for the carcinogenicity of talc not containing asbestos or asbestiform fibers.(World Health Organization (WHO) International Agency for Research on Cancer (IARC), 2010) The Working Group reviewed studies in which talc of different grades was tested for carcinogenicity in mice by inhalation exposure or intrathoracic, i.p., or subcutaneous (s.c.) injection; in rats by inhalation exposure or intrathoracic or i.p. injection, oral administration, or intrapleural or ovarian implantation; and in hamsters by inhalation exposure or intratracheal injection.

- For humans, the determination of the IARC working group was that perineal use of talc-based body powder is *possibly carcinogenic to humans (Group 2B)*, and that inhaled talc not containing asbestos or asbestiform fibers is *not classifiable as to its carcinogenicity (Group 3)*.(World Health Organization (WHO) International Agency for Research on Cancer (IARC), 2010) In evaluating the carcinogenicity of talc in humans, the Working Group reviewed cohort studies of talc miners and millers, cohort and case-controlled studies examining the association of cosmetic talc use and the risk of ovarian cancer in humans, and the animal data and evidence regarding the potential mechanisms through which talc might cause cancer in humans. The Working Group found there is *inadequate evidence* in humans for the carcinogenicity of inhaled talc not containing asbestos or asbestiform fibers and there is *limited evidence* in humans for the carcinogenicity of perineal use of talc-based body powder.

Many occupational exposure studies are available that describe the effects reported in talc workers. Although the occupational exposure to talc is not at all similar to the cosmetic exposure to talc, these reports are summarized in this safety assessment to provide a total overview of available information. Occupational studies in which talc was known to contain asbestos are not included.

MINERALOGY AND CHEMISTRY

Definition and Structure

The term talc has two meanings: 1) as a mineral, the talc corresponding to the chemical formula for hydrous magnesium silicate, and 2) commercially, as a product that can be used industrially, in pharmaceuticals, and in cosmetics.(Harvey AM, 1988) The mineral talc has the formula $Mg_3Si_4O_{10}(OH)_2$(United States Pharmacopeial (USP) Convention, 2011) and a theoretical chemical composition, expressed as oxides, of 31.7% by weight (wt) magnesium oxide (MgO), 63.5% silicon dioxide (SiO_2), and 4.8% hydrogen dioxide (H_2O).(Industrial Minerals Association-North America (IMA-NA) & EUROTALC, 2012) As a cosmetic ingredient, talc (CAS No. 14807-96-6) is defined as a powdered native hydrous magnesium silicate, sometimes containing a small portion of aluminum silicate.(Gottschalck TE & Breslawec HP, 2012)

Talc belongs to the silicate subclass phyllosilicates (Muscat JE & Huncharek MS, 2008) and is a sheet silicate. The structural unit consists of three sheets, i.e., octahedrally-coordinated magnesium hydroxide groups (brucite layer) sandwiched between two layers of tetrahedrally-linked silica layers.(Rohl AN *et al.*, 1976;Grexa RW & Parmentier CJ, 1979) The apical oxygen atom positions of the tetrahedral layers are shared with one of the oxygen atom positions of the octahedral

layer.(Ross M, 1984) The composite sheets repeat every 9.4 angstroms (Å). Stacks of the triple-sheet crystalline units are held together by van der Waals forces.(Zazenski R *et al.*, 1995)   (Figure 1.)
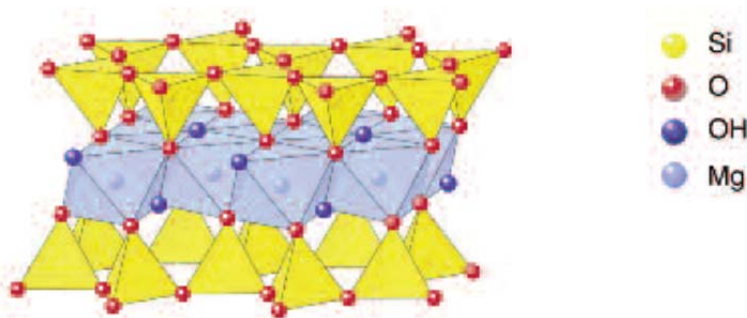

Figure 1. Schematic structure of talc(Industrial Minerals Association - Europe (IMA-Europe), 2012)

Small amounts of aluminum and iron(III) can substitute for silicon in tetrahedral sites.(Industrial Minerals Association-North America (IMA-NA) & EUROTALC, 2012) Trace amounts of nickel and small to moderate amounts of iron(II), iron(III), aluminum, and/or manganese can substitute for magnesium in octahedral sites. Such substitutions are bound within the crystal lattice and therefore do not exert any biological action. The replacement of hydroxyl groups (OH-) by fluorine may also occur.

The relationship between talc and asbestos is commonly misunderstood.(Zazenski R *et al.*, 1995) The presumption that asbestos and talc are commonly associated, or co-mined, is simply incorrect. Talc and asbestos (or even asbestiform materials) form under different geological conditions and are, at worst, separated into adjacent, but disparate, strata. Accordingly, by utilizing proper mining methodologies, asbestos contamination is avoided. Moreover, the absence of asbestos in talc is routinely confirmed in ore samples via a battery of analytical techniques.

Physical and Chemical Properties

The mineral talc is predominantly platy, with adjacent layers very weakly bonded by Van der Waals forces.(Industrial Minerals Association-North America (IMA-NA) & EUROTALC, 2012) This allows talc to be easily sheared along the plane and gives it its natural slippery feel as well as its softness. Talc is the softest mineral with a hardness of 1 on a Mohs' scale of 1 to 10.

The physical form of talc rock is related to the source and geological conditions during formation of the deposit.(Industrial Minerals Association-North America (IMA-NA) & EUROTALC, 2012) The platelet size of talc determines its lamellarity, which, in turn, is related to the genesis of talc deposits. Highly lamellar talc (informally classified as macrocrystalline talc) has large individual platelets, while microcrystalline talc has small, randomly oriented platelets. The size of an individual talc platelet can vary from 1 μm to over 100 μm, depending on the formation of the deposit.(EUROTALC, 2012)

The particle size of talc powder depends on the process used to make the powder.(Industrial Minerals Association-North America (IMA-NA) & EUROTALC, 2012) Typical cosmetic talcs have average particle sizes ranging between 4 and 15 μm when measured by sedimentation method, with only minor fractions consisting of particles considered respirable. Another source recites that the "fineness" of talc used, characterized as 200 mesh, 325 mesh, or 400 mesh (i.e., particle size distribution that allows 95-99% of the product to pass through a 200-, 325-, or 400-mesh, respectively, [74, 44, or 37 μm, respectively], when wet-out with alcohol and dispersed in water) depends on the use in cosmetics.(Zazenski R et al., 1995) For example, 200-mesh talc is preferred for body powders, while 400-mesh talc might be used for pressed powders. The cosmetic ingredient specifications for talc state that in a screen test, 100% passes through 100-mesh, 98% minimum passes through-200 mesh, and finer grades are as specified by the buyer.(Personal Care Products Council, 1989)

Physical and chemical properties of talc are summarized in Table 1.

Analytical Methods

The absence of asbestiform amphibole minerals in cosmetic talc is determined using the generally accepted method of x-ray diffraction and optical microscopy with dispersion-staining.(Nikitakis JM & McEwen GN Jr (eds), 1990b) Other

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methods for the detection of fibrous amphibole, such as transmission electron microscopy with selected area diffraction and electron microprobe, were considered but were not adopted by the cosmetics industry trade association.

Talc can also be analyzed for asbestos using polarized light microscopy and transmission electron microscopy.(Food and Drug Administration (FDA), 2012b) Infrared spectrometry, which permits detection at a 0.1% w/w minimum detection level, also can be used.(Industrial Minerals Association-North America (IMA-NA) & EUROTALC, 2012)

Free crystalline silica (quartz) in talc can be detected using differential thermal analysis, which permits detection at a 0.5 – 1.0% w/w minimum detectable level,(Nikitakis JM & McEwen GN Jr (eds), 1990c) or by x-ray diffraction.(Nikitakis JM & McEwen GN Jr (eds), 1990d)

Personal communication from WT Caneer to WH Ashton (June 1973) addressed the fact that in one study, the analytical methods used to identify the asbestos in talc were not performed and/or interpreted correctly. Misidentification of asbestos in talc can result from misinterpretation of the data obtained when performing an analytical procedure.(Krause JB & Ashton WH, 1978)

Constituents/Impurities

Associated minerals found in commercial talc products vary from deposit to deposit depending on the conditions of formation of the deposit.(Industrial Minerals Association-North America (IMA-NA) & EUROTALC, 2012) The most common minerals associated with talc are chlorite, magnesite, dolomite, calcite, mica, quartz, and fluorapatite. Amphiboles and serpentine are associated with certain specific talc deposits. These deposits are rare and historically were used for low-grade industrial applications due to the impurities present.

In 1976, the Cosmetics, Toiletry and Fragrance Association (CTFA; now known as the Personal Care Products Council [the Council]) issued purity standards for talc.(Wehner AP, 1998a) Cosmetic talc consists of a minimum of 90% hydrated magnesium silicate, with the remainder consisting of naturally associated minerals such as calcite, chlorite, dolomite, kaolin, and magnesite; it contains no detectable fibrous, asbestos minerals.(Nikitakis JM & McEwen GN Jr (eds), 1990a) Additional specifications for cosmetic talc include: 6.0% max. acid-soluble substances; 3 ppm max. arsenic (as As); 20 ppm lead (as Pb); 0.1% max. water-soluble substances; no detectable fibrous amphibole (asbestiform tremolite, etc); free crystalline silica (quartz) as specified by the buyer.

As a color additive for drugs, talc sometimes contains a small proportion of aluminum silicate. (21CFR73.1550). It is required to meet the specifications for talc in the United States Pharmacopeia (USP), and it also must contain not more than 20 ppm lead (as Pb) and not more than 3 ppm arsenic (as As). The following are the acceptance criteria for USP-grade talc: 17.0-19.5% magnesium; not more than 0.1% water-soluble substances with neutral pH; no more than 0.25% iron; not more than 10 ppm lead; not more than 0.9% calcium; not more than 2.0% aluminum; and a demonstration of an absence of asbestos(United States Pharmacopeial (USP) Convention, 2011). Talc intended for topical application is to have a total aerobic microbial count of not more than 100 cfu/g and a total combined molds and yeasts count of not more than 50 cfu/g and talc intended for oral administration is to have a total aerobic microbial count of no more than 1000 cfu/g and a total combined molds and yeasts count of not more than 100 cfu/g The acceptance criteria for food-grade talc are not more than 3 mg/kg arsenic and not more than 5 mg/kg lead, and the talc must be derived from deposits that are not associated with asbestos.(2012a)

The personal communication from Caneer to Ashton (June 1973) referred to previously referred to a study that stated that the analysis of 18 commercial talcum powders found 4-46% asbestiform mineral, with an average asbestiform content of 18%. Mr. Caneer stated that a review of the paper suggested a number of errors were present; subsequent discussions with the researchers led to admissions that errors may have been made.

Batches of cosmetic talc have been analyzed for asbestos and/or asbestiform minerals. These analyses are summarized here.

- In 1973, the results of an FDA-requested analysis of 195 samples of cosmetic talcum-type powders were presented (memo issued by A Weissler, FDA, 1973). Most of the commercial talc powders that were tested were free of any detectable amount of any asbestiform minerals. (Memo from SZ Lewin, Chemistry Department New York University, to G. Thompson, FDA, 1973). Chrysotile (trace-15%) and tremolite (trace-15%) were present in approximately 10% of the samples. X-ray diffraction, and sometimes optical or electron microscopy, were used to analyze the samples. Dr. Weissler noted that inter-laboratory analysis found good semi-quantitative agreement for tremolite (two additional laboratories), but not for chrysotile (four additional laboratories) (memo issued by A Weissler, FDA, 1973). The

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differences were thought to be due to Dr. Lewin's inclusion of mineral species that had significant differences from "classical" chrysotile.

- In 1979, the FDA analyzed samples of cosmetic talc products using x-ray diffraction (memo issued by LL Taylor, FDA, 1984). Samples found to be contaminated with tremolite or anthophyllite by x-ray diffraction were also examined by optical microscopy to determine crystal morphology. The level of detectability was 0.1% for tremolite and 2% for anthophyllite. In all cases, the amphiboles that were found were non-fibrous. None of the samples were found to contain serpentine; the limit of detectability was 1-2% using x-ray diffraction.

- In 2012, the FDA asked nine cosmetic talc suppliers for samples of their talc; four complied with the request.(Food and Drug Administration (FDA), 2012b) The FDA also selected 34 talc-containing retail products. A contract laboratory analyzed the raw material and retail products using polarized light microscopy and transmission electron microscopy, finding no asbestos fibers or structures in any of the samples. The results were limited, however, because of the limited response by the suppliers and by the number of products tested.

Production

Talc is obtained from naturally occurring rock ore.(Nikitakis JM & McEwen GN Jr (eds), 1990a) Talc commonly forms by hydrothermal alteration of rocks rich in magnesium and iron (ultramafic rocks) and by low-grade thermal metamorphism of siliceous dolomites.(Ross M, 1984) Soapstone refers to impure, massive talc rock;(Harvey AM, 1988) pure talc was once called steatite.(Piniazkiewic RJ *et al.*, 1994) Talc is typically mined in open-pit operations,(Zazenski R *et al.*, 1995) and cosmetic talcs are mined in Italy, France, Norway, India, Spain, China, Egypt, Japan, and the United States.(Schlossman ML, 2009)

Crude talc ore can be sorted (beneficiated) to improve purity of commercial products by either dry or wet processing.(Zazenski R *et al.*, 1995) In either case, the talc ore is crushed and ground to a fineness suitable for specific end-uses. A dilute talc/slurry water is conditioned for flotation by the addition of a frothing agent (often a low molecular weight alcohol), and the slurry is then processed through a series of cells through which air is pumped. This processing causes bubbles to form, and as the bubbles rise to the surface, the talc particles attach to the bubbles due to their organophilic nature; the non-talc impurities are hydrophilic and do not tend to attach to the bubbles. The float (or froth) is then collected. The process is repeated until the desired purity levels are obtained. The talc particles can be further processed by magnetic separation or acid washing to remove iron-bearing minerals, soluble salts, and metals. The talc is then filtered, washed, and dried. Cosmetic talc is typically sterilized by heat treatment.(Industrial Minerals Association-North America (IMA-NA) & EUROTALC, 2012)

USE

Cosmetic

Talc is reported to have the following functions in cosmetics: abrasive, absorbent, anticaking agent, bulking agent, opacifying agent, skin protectant, and slip modifier.(Gottschalck TE & Breslawec HP, 2012) The FDA collects information from manufacturers on the use of individual ingredients in cosmetics as a function of cosmetic product category in its Voluntary Cosmetic Registration Program (VCRP). VCRP data obtained from the FDA in 2012(Food and Drug Administration (FDA), 2012a) and data received in response to a survey of the maximum reported use concentration by category conducted by the Personal Care Products Council (Council) in 2009(Personal Care Products Council, 2010) indicate that talc is used in 2877 cosmetic formulations at concentrations up to 100%. It is used in almost every category of cosmetic product. Frequency and concentration of use data are provided in Table 2.

Products containing talc may be applied to baby skin, used in products that could be incidentally ingested, or used near the eye area or mucous membranes. Additionally, talc is used in cosmetic sprays and powders; for example, talc is reported to be used in face powders at 100%, baby powders at 99%,(Personal Care Products Council, 2010) aerosol make-up bases at up to 35%, and in aerosol deodorants at up to 30%.(Personal Care Products Councils, 2012) (Talc is not used in extremely high concentrations in spray or aerosol products because talc clogs the nozzle.(Personal Care Products Council, 2012)) These products could possibly be inhaled. In practice, 95 to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm.(Bremmer HJ *et al.*, 2006;Johnsen MA, 2004;Rothe H *et al.*, 2011;Rothe H, 2011) Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.(Bremmer HJ *et al.*, 2006;Rothe H *et al.*, 2011) There is some evidence indicating that deodorant spray products can

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release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.(Bremmer HJ *et al.*, 2006) However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.

The particle size of talc raw material varies widely by product type and by manufacturer but has "no practical significance with regard to human exposure since encapsulation by the other ingredients in the product matrices" (such as a lipstick or deodorant stick) "renders the talc constituents essentially nonrespirable".(Zazenski R *et al.*, 1995) Semi-solid matrix formulations (typically pressed powders such as blushes, eye shadows, pressed finishing powders, and base powders) incorporate binder systems. Fine talc with a larger than average particle size (200-mesh) is often preferred for use in blushes, eye shadows, and finishing powders. Loose-talc-based formulations, such as loose finishing makeup powders, baby powders, body powders, and foot powders, do not include a binder system. The majority of cosmetic talcs in loose-matrix powders contain talc particles that are of a larger diameter than those used in other cosmetic applications; for loose powders, a 200-mesh is normally used because larger platelet sizes of talc allows for better properties. In these loose powders, substantial agglomeration occurs due to electrostatic and crystalline charges on the talc powders.

While some researchers state that the inclusion of a fragrance oil may act as a minimal binder system causing further agglomeration,(Zazenski R *et al.*, 1995) another researcher found that there was no evidence that the presence of perfume in adult or baby dusting powders containing Italian 00000 grade talc or Chinese talc influenced the level of respirable talc dust.(Aylott RI *et al.*, 1979)

In the European Union, the use of talc in powdery products intended to be used for children under 3 is restricted by the requirement of labeling that warns to keep powder away from children's nose and mouth. In Canada, the inner and outer label of preparations in powder form intended for infants and children shall carry cautionary statements to the effect: "Keep out of reach of children", "Keep powder away from child's face to avoid inhalation which can cause breathing problems."(Health Canada, 2011)

Non-Cosmetic

Sterile talc is approved as a sclerosing agent.(Food and Drug Administration (FDA), 2011) Sterile talc powder is indicated for administering intrapleurally via chest-tube to decrease the recurrence of malignant pleural effusions in symptomatic patients. Talc is not allowed for use on the surface of medical gloves.(Food and Drug Administration (FDA), 2008b)

Talc is used as a color additive in drugs and is exempt from certification; it may be safely used in amounts consistent with good manufacturing practice to color drugs (21CFR73.1550). In foods, talc is used as an anticaking agent, coating agent, lubricating and release agent, surface-finishing agent, and texturizing agent.(2012a) Talc is a generally recognized as safe (GRAS) substance migrating from cotton and cotton fabrics used in dry food packaging (21CFR182.70) and as a substance migrating to food from paper and paperboard products (21CFR182.90). It is approved as an indirect food additive as a colorant (21CFR 176.170; 21CFR178.3297). The World Health Organization allocated talc (as magnesium silicate) an acceptable daily intake (ADI) of "not specified."(Joint FAO/WHO Expert Committee on Food Additives (JEFCA), 1987)

FDA determined that data are inadequate to establish general recognition of the safety of talc as an active ingredient (astringent) in over-the-counter (OTC) drug products (21CFR310.545(e)(18)(ii)).

Talc is used as a dusting powder, alone or with starch or boric acid, for medicinal and toilet preparations.(The Merck Index, 2012) It is used as an excipient and filler for pills and tablets, for dusting tablet molds, and for clarifying liquids by filtration. Talc is also used as a pigment in paints, varnishes, rubber; as filler for paper, rubber, soap; in fireproof and cold-water paints for wood, metal and stone; for lubricating molds and machinery; as glove and shoe powder; and as an electric and heat insulator. Talc is used in the leather industry, in the roofing and ceramic tile industry, as a carrier for insecticides and herbicides,(Hildick-Smith GY, 1976) and it is used in plastics.(Industrial Minerals Association - Europe (IMA-Europe), 2012)

TOXICOKINETICS

Inhalation
Non-Human

To determine the deposition, distribution, and clearance of talc, 44 female Syrian golden hamsters received a single 2-h nose-only exposure to a neutron-activated talc aerosol and sub-groups of 4 animals were then killed at 11 different intervals from 15 min to 132 days after exposure.(Wehner AP *et al.*, 1977b) The talc tested was a commercial baby powder. (Chemical characterization data were not provided). Nine unexposed control animals were used; four were killed on the day

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the test animals were exposed and five were killed on the final day of the study. The aerosol exposure system had 7 tiers of exposure ports, and the talc aerosol was passed through a cyclone elutriator to remove particles that were larger than ~10 μm in diameter; the activity median aerodynamic diameter was 6.4-6.9 μm. The mean aerosol concentration was 40 and 75 μg/l at the 15-30 and 60-90 min sampling periods, respectively. In the presentation of the results, the γ-ray counts from the controls were expressed as μg talc equivalent, and the γ-ray counts of the exposed animals were not corrected for control values.

Variations among animals killed at the same time were attributed to variations in aerosol concentration at different tiers. The mean pulmonary talc content in the lungs of test animals at various time intervals was 33.08 (15 min after exposure), 24.08 (100 min), 42.70 (4 h), 18.75 (21 h), 21.30 (2 days), 21.03 (after 4 days), 13.85 (after 8 days), and 8.95μg (after 18 days); the mean for the day 0 control animals was 1.78 μg. The biological half-life of the talc deposited in the lungs was 7-10 days. At the time of termination of the final group, i.e. 132 days, there was no statistically significant difference in the talc burden of the lungs of test (3.70 μg) and control (2.30 μg) animals. The amount of talc in the liver, kidneys, and lungs was also determined; the only statistically significant differences compared to controls in any of these organs were found in the liver; there was a decrease at 4 h compared to day 0 controls, an increase at day 36 compared to both day 0 and day 132 controls, and an increase on day 68 compared to day 132 controls. Analysis of the data using the Kruskal-Wallis test showed that there were no significant differences among the mean talc burden values for the liver, kidneys, and ovaries, including the control values, and that there was no significant trend, indicating there was no translocation of talc to these tissues. As noted, no translocation from the respiratory tract to other tissues was found in this study, and the clearance of talc from the lungs was complete within 4 months after exposure.

Oral

Non-Human

Six female Syrian golden hamsters (outbred Ela:ENG strain) were dosed by gavage with 1 ml neutron-activated talc suspended in physiological saline containing 0.6% (w/w) 1% methyl cellulose, and the animals were killed 24 h after dosing.(Wehner AP *et al.*, 1977a) The talc used was a commercial baby powder. (Chemical characterization data and particle size were not provided). Four hamsters were dosed similarly with a non-irradiated talc solution. The neutron-activated talc was exposed to an integrated neutron flux of 7×10^{16} n/cm^2 30 days prior to dosing. The skinned carcass, gastrointestinal (GI) tract, lungs, liver, kidneys, and excreta were analyzed for ^{60}Co and ^{46}Sc by γ-ray spectrometry, and the γ-ray counts were compared with those of four hamsters that were not dosed with talc.

The γ-ray counts of the tissue and excreta of the dose animals were equivalent to a total of 2.94 mg talc. Based on γ-ray counts, 74.5% of the neutron-activated talc was recovered in the feces and 23.5% was recovered in the GI tract, while 1.91% was recovered in the skinned carcass, 0.09% in the urine, 0.04% in the kidneys, and 0.02% in the liver. The amount found in the urine of the hamsters given irradiated talc was statistically significantly increased compared to the controls. No talc was recovered in the lungs.

The absorption, distribution, and excretion of orally administered talc was determined in mice, rats, and guinea pigs.(Phillips JC *et al.*, 1978) (Chemical characterization data were not provided). With all species, [^{3}H]talc was administered as a suspension in aqueous (aq.) glycerol jelly solution (10 mg/ml; 1 μCi/ml). Four LACA female mice were given a single oral dose of 40 mg/kg [^{3}H]talc. Two mice were killed at 6 h and two at 24 h after dosing. In the mice killed 6 h after dosing, 95 and 96% of the radioactivity was recovered in the large intestines and feces, 9 and 7% was recovered in the small intestines and stomach, and 0.7 and 0% in the urine of each mouse. In the two mice killed 24 h after dosing, 99 and 101% of the radioactivity was recovered in the large intestines and feces, 4 and 6% was recovered in the small intestines and stomach, and 1.3 and 1.5% in the urine of each mouse. Less than 0.005% of the radioactivity was found in the carcass of any of the mice.

Three male Wistar albino rats were given a single oral dose and three rats were given six daily oral doses by gavage of 50 mg /kg body wt [^{3}H]talc. After the last dose, urine and feces were collected every 24 h for 4 days and on day 10; the rats were then killed. Within 24 h after administration of the single dose, approximately 75% of the radioactivity was recovered in the feces and only 1% was recovered in the urine. After 96 h, a total of 95.8% of the dose was excreted in the feces and 1.7% in the urine, with a total excretion of 97.5% of the dose. No radioactivity was recovered in the liver or kidneys 10 days after a single dose of talc. On day 10 in the rats given six daily doses of [^{3}H]talc, there was no radioactivity found in the feces or livers, and there was a trace of radioactivity (<0.02%) in the kidneys of these rats.

Three female Dunkin Hartley guinea pigs were administered a single oral dose of 25 mg/kg [^{3}H]talc, and urine and feces were collected as described above; all animals were killed on day 10. Talc was excreted more slowly in the guinea pig

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than in the rat. Within 24 h after dosing, 31% of the radioactivity was recovered in the feces, and 0.2% was recovered in the urine. At 24-48 h and 48-72 h after dosing, 39% and 19% of the radioactivity, respectively, was recovered in the feces, with <0.01% of the dose being recovered in the urine at each of these time periods. Within 96 h of dosing, a total of 94.4% of the radioactivity was recovered in the feces and 0.2% was recovered in the urine, with a total of 94.6% of the dose being excreted over 96 h.

Intrapleural

Non-Human

Wistar rats were used to determine the systemic distribution of talc following intrapleural administration.(Werebe EC *et al.*, 1999) Groups of 20 rats (sex not specified) were administered 10 or 20 mg talc in 1 ml of saline as a slurry into the pleural cavity. (Chemical characterization data were not provided). Ten animals of each group were killed 24 h after instillation, and the remaining 10 animals were killed 48 h after instillation. The lungs, chest wall, liver, kidneys, spleen, heart, and brain of each animal were removed for examination. There were no gross lesions in the examined tissues. Microscopic examination revealed that the chest wall had the most common lesions, and these lesions were represented by an early pneumoconiosis characterized by stellate interstitial collections of dust-laden macrophages containing pale yellow particles associated with inflammatory infiltrate of lymphocytes with mild fibroblastic proliferation. Polarized light used to locate birefringent particles revealed "large numbers of irregular, strongly birefringence platy, acicular, and "Maltese Cross" crystals that varied in length from 5.7 – 70 μm" in the chest wall. The deposition index of talc crystals was greater in the chest wall and the lungs after administration of 10 mg (3.90 in the chest and 3.18 in the lungs) than 20 mg talc (3.58 in the chest and 2.50 in the lungs); this difference was statistically significant. (It is not stated whether these values were from the 24 h group, 48 h group, or an average of the two). Pneumoconiosis reactions were not observed in the other organs; however talc crystals were present inside of the microvessels. The researchers suggested talc was absorbed rapidly through the pleura, reaching the systemic circulation with deposition in other organs within 24 h after administration, and that the distribution was not dose-related.

TOXICOLOGICAL STUDIES

Single Dose Toxicity

Oral

The LD_{50} of talc in rats was determined to be 920 mg/kg.(Litton Bionetics, Inc., 1974) Ten male rats were dosed by gavage with 5000 mg/kg talc suspended in 0.85% saline; all 10 rats died within 24 h. Groups of 5 rats were then intubated with 50, 100, 500, 1000, 2000, or 3000 mg/kg talc in saline. All five animals dosed with 3000 mg/kg, four dosed with 2000 mg/kg, three with 1000 mg/kg, and one with 500 mg/kg talc died. (Chemical characterization data were not provided).

In another single-dose study in rats, the LD_{50} was >5000 mg/kg.(Litton Bionetics, Inc., 1974) All the animals survived dosing with 5000 mg/kg talc in 0.85% saline.

The oral LD_{50} of 18.3% talc in saline was >5000 mg/kg.(Litton Bionetics, Inc., 1974) A single oral dose of 5000 mg/kg of talc prepared as an 18.3% (w/v) suspension in saline was administered to 10 male rats. All animals survived, and there were no signs of toxicity.

Inhalation

Eight mice were placed in a box with baby powder that was circulated with compressed air.(Motomatsu K *et al.*, 1979) (Details regarding the composition of the baby powder, the amount of baby powder, or the size of the box were not provided). Two mice were removed from the box at 30-min intervals, i.e. after 30, 60, 90, or 120 min. The mice removed after 30 and 60 min recovered completely; symptoms that were observed were not specified. The mice removed after 90 min died in 5-6 h; the mice exposed for 2 h died immediately after exposure. The mice that died were necropsied, and the mucous membrane of the airway was found covered with baby powder. Microscopically, hemorrhage, edema, and desquamation of bronchial epithelium admixed with baby powder were observed.

Intrabursal

Groups of 10 anesthetized female Sprague-Dawley rats (10-15 wks of age) were given a single bilateral intrabursal injection of 100 mg/ml talc in phosphate-buffered saline (PBS), and groups of 3 age-matched, sham-operated, and sham-treated rats were used as controls.(Hamilton TC *et al.*, 1984) Asbestos-free Italian 00000 talc, composed of platy crystals ranging in size from 0.3-14 μm, was used. The animals were killed 1, 3, 6, 12, or 18 mos after dosing. There was no effect on the production of physiological concentrations of steroid hormones. Gross examination was made for all animals, and

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microscopic examination was performed 12 mos after dosing. One or both ovaries of rats dosed with talc were cystic in appearance at all time periods; no gross changes were seen in the ovaries of the control animals; the cystic structures were not derived from the ovaries but were due to distention of the bursal sac. Focal areas of papillary change were seen in the surface epithelium of four injected ovaries, but not in any of the controls. There was no correlation between the presence of foreign body granulomas and the presence of the papillary changes. No evidence of cellular lesions or of mitotic activity was seen in the non-papillary areas of the surface epithelium of injected ovaries, and neoplasia was not observed. Foreign body granulomas, without surrounding inflammation, were seen in the cortical area of five of the injected ovaries, with similar lesions in the supracapsular fat in the connective tissue matrix of the capsule. Talc was observed in the granulomas.

Intraperitoneal

The induction of fibrosis following an i.p. injection of 50 mg/kg bw non-fibrous talc in physiological saline was evaluated in six male and six female Wistar rats.(Styles JA & Tabershaw IR, 1973) A granulomatous reaction in which foreign-body giant cells containing refractile materials was observed in the rats at 1 mo after dosing; this lesion was still observed at 3 mos, but there was no fibrosis.

Groups of five female Wistar rats were used to evaluate the toxicity of talc following a single i.p. injection of 0.02, 0.1, or 0.5 g in 5 ml normal saline.(Kang N *et al.*, 1992) Although the talc was described as irregular crystalline plates, it was also stated that it could vary from all plates to all fibers. The talc was composed of 49-56% silicon dioxide, 20-22% magnesium oxide, 6-8% calcium oxide; the particle size range from 10-120 µm, with a mode of 20 µm. The control group was administered saline only. The animals were killed 7 days after dosing. There were no adhesions in the control group, but adhesions were observed, mainly in the upper abdomen, of the test animals; three animals of the 0.5 g group had mild/intermediate adhesions and four animals in the 0.5 g group had four intermediate adhesions. Talc particles could be seen in the adhesions. The parietal peritoneal mesothelium was examined microscopically using the Hautchen technique, and clusters of foci of inflammatory cells were observed scattered on the surface of the peritoneum. Again, talc particles were seen in the center of each focus of inflammatory cells. Powder deposits adherent to the viscera or omentum without adhesions were reported in three animals dosed with 0.02 g talc and in all animals dosed with 0.1 or 0.5 g talc; ascites did not occur in any of these animals.

Cellular Effects

Cellular effects in various systems are described in Table 3. There were no remarkable results found in studies examining the cellular effect of talc, such as cytotoxicity assays, assays examining the effect of talc on cell viability, or studies on the induction of apoptosis (among others).

Repeated Dose Toxicity

Repeated dose animal toxicity studies are summarized in Table 4. Dermal application of talc to shaved rabbit skin for 6 wks resulted in dryness of the skin and skin erosion. Oral administration to rats for 5 days produced minimal toxicity. In inhalation studies, exposure of mice and rats for 4 wks (25 µm particle size) resulted in macrophages in the alveolar space, with more found in the mice than the rats. In rats exposed for 3, 6, or 12 mos, minimal to slight fibrosis resulted. In hamsters, exposure by inhalation to baby powder (95% talc; 4.9 -6.0 µM) did not result in clinical toxicity, and no trends were observed. Intrapleural administration of talc (25 µm) to rats did not result in mesotheliomas; granulomas at the injection site were common. Infections occurred, but no neoplastic or perineal changes, when talc was instilled intravaginally or perineally in rats. Upon intravenous (i.v.) injection of talc (<5 µm) once weekly for 3 wks in guinea pigs, talc was found in the lungs and the liver throughout the study.

Ocular Irritation

Two unpublished ocular irritation studies were briefly summarized in the IUCLID dataset on talc.(European Commission, 2000) Talc was not irritating to the eyes of rabbits in one study and was slightly irritating to the eyes of rabbits in the other study. No details were provided.

A case study was reported in which a woman presented with a foreign body sensation and inflammation of the conjunctiva of both eyes.(Lyon F & Taylor RH, 2007) Following a biopsy and electron microscopy and electron diffraction analysis of the sample, a diagnosis of foreign body granuloma secondary to talc was made. It was postulated that the talc originated from surgical gloves from a surgery performed decades earlier.

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Granuloma Formation in the Skin

Application of talc on wounds can give rise to scab formation, possible infection, and foreign body granulomas in the dermis.(Lázaro C *et al.*, 2006) In one case study, talc powder applied to post-varicella lesions resulted in granulomas. In another case study, hundreds of granulomas of the skin developed in a patient that had open, draining furuncles and who had liberally applied talc daily.(Tye MJ *et al.*, 1966)

Occupational Exposure

Talc has a threshold limit value (TLV) (respirable fraction) of 2 mg/m^3 as a 10-h time-weighted average (TWA).(National Institute for Occupational Safety and Health (NIOSH), 2001a) The National Institute for Occupational Safety and Health (NIOSH) states the immediately dangerous to life or health (IDLH) concentration is 1000 mg/m^3. The Occupational Health and Safety Administration (OHSA) mineral dust limit for talc is 20 millions of particles per cubic foot (mppcf) of air, if containing less than 1% quartz; if ≥1% quartz is present, then the quartz limit is used (250/(%SiO$_2$ + 5) mppcf) (29CFR1910.1000 Table Z-3).

Human pulmonary effects of chronic occupational inhalation of talc include diffuse interstitial fibrosis and progressive massive fibrosis (often called complicated pneumoconiosis).(Green FHY, 2000) Depending on the composition and contaminants of talc, three forms of talc-related pulmonary effects have been described: pure talcosis, produced by exposure to talc that is free of silica and asbestiform minerals; talco-asbestosis, produced by the inhalation of talc with asbestiform fibers; and talco-silicosis, produced by exposure to talc associated with silica and other non-asbestiform fibers.(Feigin DS, 1989) A fourth talc-related disease, stemming from i.v. administration of talc, is not related to occupational exposure, but instead is usually associated with abuse of oral medications. Each form has a distinctly different radiographic appearance. The radiographic abnormalities associated with pure talcosis consist of small nodules that are usually seen in the lower pulmonary fields. Reticulations may occur, but this is less common. Pure talcosis results in pulmonary function test results that are consistent with restrictive pulmonary disease.

<u>**Effects of Occupational Exposure**</u>

Studies examining the pulmonary effects of occupational exposure to talc by talc miners and millers and by workers in industries that use talc are summarized in Table 5. Statistically significantly elevated standardized mortality ratios (SMRs) for silicosis and silico-tuberculosis were observed in an early study of talc miners and millers in the Italian Piedmont region.(Rubino GF *et al.*, 1976) The miners were employed for at least one year and the millers for at least two years in their respective occupations. Talc in this region reportedly contained no fibrous material, except for tremolite micro-inclusions. This study also found statistically significantly reduced SMRs for malignant neoplasms, including lung, bronchial and tracheal cancers. Updates of this study reported similar results, including statistically significant increases in mortality, which were attributable primarily to non-malignant respiratory diseases among the miners, no increases in SMRs for cancer, including lung cancer, and no mesothelioma cases.(Coggiola M *et al.*, 2003;Rubino GF *et al.*, 1979)

A cohort study of talc miners and millers employed for at least one year found no statistically significant SMRs for all causes, all cancers, or diseases of the circulatory system or respiratory tract.(Wergeland E *et al.*, 1990) These workers were exposed to talc and magnesite containing trace amounts of quartz, tremolite, and anthophylite. There were no lung cancer or mesothelioma cases even among the workers in the highest exposure category.

The results of several other epidemiological studies were likely confounded by the presence of up to 3% silica or 6% actinolite in the talc, exposures to high concentrations of silica with or without exposures to fibrous talc or tremolite, or concurrent exposures to radon daughters.(Katsnelson BA & Molronosova KA, 1979;Leophonte P & Didier A, 1990;Selevan SG *et al.*, 1979;Wild P *et al.*, 2002;Vallyathan NV & Craighead JE, 1981;Thomas TL & Stewart PA, 1987;Thomas TL, 1990)

A meta-analysis of studies of miners and millers who worked with non-asbestiform talc reported summary SMRs for lung cancer of 0.92 (95% CI: 0.67-1.25) for millers in five countries exposed to high levels of talc without exposure to other occupational carcinogens, and 1.2 (95% CI: 0.86-1.63) for miners in 3 countries exposed to high levels of talc as well as to silica or radon and radon daughters.(Wild P, 2006) The corresponding SMRs for death from all causes were 0.95 for the millers and 1.10 for the miners.

Studies examining radiological, lung-function, and clinical (e.g., wheezing, coughing, bronchitis) parameters in talc miners and millers and rubber workers found some statistically significant changes.(Fine LJ *et al.*, 1976;Gamble J *et al.*, 1982;Leophonte P & Didier A, 1990;Wegman DH *et al.*, 1982;Wild P *et al.*, 1995;Wild P *et al.*, 2008)

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Respirable Particles During Use

Studies on exposure during use of cosmetic talc are summarized in Table 6. Many of the researchers noted that there was a wide variation in talcing times and methods, often by the same volunteer during different applications. Reported talcing times ranged from 17 sec to 31 sec.

Case Reports

A 70-yr old non-smoking female was determined to have intense endobronchitis and airway stricture following inhalation of large amounts of cosmetic talc.(Ong TH & Takano A, 2012) The subject frequently poured a "small pile of talcum powder" into her hand and applied it to her face. Bronchoscopy showed diffuse, severe endobronchitis that extended throughout both main stem bronchi. Chest radiography and computed tomography (CT) imaging showed complete collapse of the right upper and middle lobes of the lung; the right lung was normal with the exception of scattered areas of mild bronchial wall thickening, bronchial plugging, and a few non-specific nodules. Bronchial biopsies showed edema, chronic inflammation, and fibrosis, and there were confluent foreign-body granulomata that contained birefringent crystalline material. Spectral analysis confirmed the crystals were the same composition as the talc used by the subject.

A case of chronic pulmonary granulomatous reaction was reported in a woman who applied "non-powdering talc" to her face for 20 yrs, followed by use of talcum powder 2-3 times a day during a 10-yr period, usually in an unventilated room.(Tukiainen P *et al.*, 1984) The subject had smoked for 20 yrs. The amount of powder used per year was described as two boxes, but the amount per box was not stated. Chest x-rays showed fine diffuse opacities, and anterolateral thoracotomy showed a diffuse nodular consistency. A heavy intra-alveolar and interstitial granulomatous inflammation was found at biopsy, and numerous birefringent particles were found inside the giant cells. The foreign body material contained in the granulomas was characteristic of talc. After 2 yrs follow-up, a biopsy of an enlarged lymph node showed granulomatous inflammation. It was the opinion of the investigators that this was a case of not true talc pneumoconiosis, but chronic sarcoidosis and coincidental talc deposition in the lung.

Pulmonary talcosis was reported in several cases of misuse of talcum powder in which the subjects dusted their entire body with large amounts of powder at least once a day,(Wells IP *et al.*, 1979;van Huisstede A *et al.*, 2010), including one in which an individual also dusted the bed sheets every day,(Nam K & Gracey DR, 1972) and in a case in which the powder was purposefully inhaled.(Goldbach PD *et al.*, 1982) A woman that excessively used talc for herself and her children died from rapidly progressive disease and pulmonary hypertension. Cases of accidental inhalation of large amounts of talc by infants and children have been reported, and consequences have ranged from complete recovery to death.(Cruthirds TP *et al.*, 1977;Matina F *et al.*, 2011;Motomatsu K *et al.*, 1979;Pairaudeau PW *et al.*, 1991;Pfenninger J & D'Apuzzo V, 1977;Reyes de la Rocha S & Brown, 1989) Specifics of these cases are not included because the results are not from normal, intended use of the product. Also not included in this safety assessment are reports of adverse effects due to injection of talc with i.v. drug abuse.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Oral

Orally administered talc was not a developmental toxicant in mice, rats, hamsters,(Food and Drug Research Labs., Inc, 1973b) or rabbits. (Food and Drug Research Labs., Inc, 1973a) Chemical characterization of the talc was not provided in any of these studies.

Groups of 20-22 gravid female albino CD-1 mice and groups of 20-24 gravid Wistar rats were dosed by gavage with 0, 16, 74, 350, or 1600 mg/kg bw talc as an anhydrous corn oil suspension on days 6-15 of gestation.(Food and Drug Research Labs., Inc, 1973b) Aspirin was used as a positive control in both species. The mice were killed on day 17 and the rats on day 20 of gestation and the number of implantation sites, resorptions sites, and live and dead fetuses, and the live pup body weights were recorded. In both mice and rats, the administration of up to 1600 mg/kg bw talc in corn oil had no effect on reproductive or developmental parameters and had no effect on maternal or fetal survival.

In hamsters, groups of 20-23 gravid female golden hamsters were dosed by gavage with 0, 12, 56, 260, or 1200 mg/kg bw talc as an anhydrous corn oil suspension on days 6-10 of gestation.(Food and Drug Research Labs., Inc, 1973b). The animals were killed on day 14 of gestation and examined as described previously. The administration of up to 1200 mg/kg bw talc in corn oil had no reproductive or developmental effects and had no effect on maternal or fetal survival.

Groups of 12-15 gravid Dutch-belted female rabbits were dosed orally with 9, 42, 195, or 900 mg/kg talc in corn oil on days 6-18 of gestation.(Food and Drug Research Labs., Inc, 1973a) Eight gravid negative controls were given only

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vehicle and 9 gravid positive controls were dosed with 2.5 mg/kg of 6-aminonicotinamide on day 9 of gestation. The dams were killed on day 29 of gestation. A total of 1/8, 4/15, 2/12, 5/15, and 2/13 dams of the negative control, 9, 42, 195, and 900 mg/kg dose groups, respectively, died or aborted before day 29 of gestation, and the number of live litters for these groups was 6/7, 10/11, 8/10, 10/10, and 7/11, respectively. The researchers concluded that administration of up to 900 mg/kg talc on days 6-18 of gestation "had no discernible effect on nidation or on maternal or fetal survival." The researchers also stated the number of abnormalities did not differ between test and control animals.

In a dominant-lethal study, groups of 10 male rats were dosed by gavage with a single dose or once daily for 5 days with 30, 300, 3000, or 5000 mg/kg talc.(Litton Bionetics, Inc., 1974) Saline was used as the negative control and 0.1 µg/ml triethyl melamine (TEM) (i.p.) was the positive control. (The results of the reproductive portion of the study are presented here; the genotoxicity results are presented in that section of the safety assessment). Each treated rat was mated with two previously unmated females, and 2 wks after mating, the female rats were killed and the effects on fertility and preimplanta-tion loss were determined. In the single-dose study, significant dose-related decreased in average corpora lutea and preim-plantation losses were reported in the test groups at wks 4 and 5. In the repeated dose study, significant increases in average implantations and corpora lutea were reported in the test groups at wk 6, as were significant differences in the proportions of females with 1+ or 2+ dead implants. However, the results observed at the highest dose did not vary significantly from the negative control, and no dose-response or time-trend patterns were indicated.

GENOTOXICITY
In Vitro

Talc was not genotoxic in an unscheduled DNA synthesis (UDS) assay or a sister chromatid exchange (SCE) assay in rat pleural mesothelial cells (RPMC). (Endo-Capron S *et al.*, 1990;Endo-Capron S *et al.*, 1993) Three samples of Euro-pean talc (French, Italian, and Spanish talc) were tested. The samples, which contained 90-95% talc with chlorite and dolo-mite, were asbestos-free; the mean particle size of the samples ranged from 2.6 µm (Spanish and French talc) to 4.0 µm (Italian talc). In the UDS assay, the cells were treated with 0, 10, 20, or 50 µg/cm^2 of each sample of talc for 24 h. A nega-tive reference particle controls, anatase, and two positive controls reference particles, Rhodesian chrysotile and crocidolite were used; mean particle sizes of the three talc samples were 0.7, 3.2, and 3.1 µm, respectively. The particles were dispersed in culture medium at a concentration of 560 µg/ml by sonication. None of the talc samples enhanced UDS. The negative and positive particles yielded the expected results.

In the SCE assay, RPMC were treated with 0, 2, 5, 10, and 15 µg/cm^2 of each talc sample for 48 h. Two negative reference particle controls, anatase and attapulgite, and the two positive controls reference particles named previously were used, as were the chemical controls mitomycin C in water and K_2CrO_4 in culture medium. Talc did not cause a statistically significant increase in SCEs and was not clastogenic. The negative particle controls and chemical controls gave expected results; chrysotile and crocidolite statistically significantly increased SCEs in 2/4 and 3/8 experiments, respectively.

In Vitro/In Vivo

Talc was not genotoxic in a host-mediated assay or cytogenetic assay. (Chemical characterization data were not provided in either assay). In the host-mediated assay, male ICR mice served as the host and groups of 10 animals were dosed by gavage with a single dose or once daily for 5 days with 30, 300, 3000, or 5000 mg/kg talc.(Litton Bionetics, Inc., 1974) *Salmonella typhimurium* TA1530 and G46 and *Saccharomyces cerevisiae* D3 were the indicator organisms. Saline was the negative control and 100 mg/kg dimethyl nitrosamine and intramuscular administration of 350 mg/kg ethyl methane sulfon-ate were the positive controls. For comparison, 0.01-0.25 ml talc was evaluated in an Ames test using *S. typhimurium* TA1530 and G46 and *S. cerevisiae* D3. Talc caused no significant increase in mutant or recombinant frequencies in the host-mediated assay, and it was not mutagenic in the Ames test.

Groups of 15 male albino rats were given a single dose by gavage and groups of 5 rats were dosed once daily for 5 days with 30, 300, 3000 , or 5000 mg/kg talc in the cytogenetics assay.(Litton Bionetics, Inc., 1974) Saline was used as the negative controls and 0.3 mg/kg TEM (i.p.) was the positive control. The concentrations used during the in vitro aspect of the study were 2, 20, and 200 µg/ml in human embryonic lung culture (WI-38) cells. Talc produced no significant aberrations during the in vivo or in vitro phase and was not genotoxic.

In Vivo

Talc was not genotoxic in a rat dominant lethal assay.(Litton Bionetics, Inc., 1974) (Chemical characterization data were not provided). Groups of 10 male rats were dosed by gavage with a single dose or once daily for 5 days with 30, 300,

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3000, or 5000 mg/kg talc. Saline was used as the negative controls and 0.1 µg/ml TEM (i.p.) was the positive control. There were no dose-response or time-trend patterns; talc did not induce dominant lethal mutations in this assay.

CARCINOGENICITY

In 2010, the IARC Working Group determined that there is *limited evidence* in experimental animals for the carcinogenicity of talc not containing asbestos or asbestiform fibers.(World Health Organization (WHO) International Agency for Research on Cancer (IARC), 2010) The Working Group reviewed studies in which talc of different grades was tested for carcinogenicity in mice by inhalation exposure or intrathoracic, i.p., or subcutaneous (s.c.) injection, in rats by inhalation exposure or intrathoracic or i.p. injection, oral administration, or intrapleural or ovarian implantation, and in hamsters by inhalation exposure or intratracheal injection.

For humans, the evaluation of the IARC working group was that perineal use of talc-based body powder is *possibly carcinogenic to humans (Group 2B)*, and that inhaled talc not containing asbestos or asbestiform fibers is *not classifiable as to its carcinogenicity (Group 3)*.(World Health Organization (WHO) International Agency for Research on Cancer (IARC), 2010) In evaluating the carcinogenicity of talc in humans, the Working Group reviewed cohort studies of talc miners and millers, cohort and case-controlled studies examining the association of cosmetic talc use and the risk of ovarian cancer in humans, and the animal data and evidence regarding the potential mechanisms through which talc might cause cancer in humans. The Working Group found there is *inadequate evidence* in humans for the carcinogenicity of inhaled talc not containing asbestos or asbestiform fibers and there is *limited evidence* in humans for the carcinogenicity of perineal use of talc-based body powder.

The references cited by the IARC in their review were obtained by the CIR and are referenced as appropriate in this safety assessment.

Inhalation

A bioassay using mice and rats was performed by the NTP to determine the carcinogenic potential of non-asbestiform, cosmetic-grade talc following exposure by inhalation.(National Toxicology Program (NTP), 1993) There was *no evidence of carcinogenic activity* in male or female B6C3F$_1$ mice, *some evidence of carcinogenic activity* in male F344/rats, and *clear evidence of carcinogenic activity* in female F344/N rats. The talc used was asbestos-free and virtually silica-free microtalc; scanning electron microprobe analysis of one lot of talc indicated that 1/1466 particles examined was silica, 136/1466 particles tremolite, and 1241/1466 particles were talc. More than 75% of the particles were in the 1.0 – 3.0 µm range. This study is discussed in greater detail below.

A 2-yr study was performed in mice; groups of 50 male and 50 female B6C3F$_1$ mice (7 wks old) were exposed to target concentrations of 0, 6, or 18 mg/m^3 talc for 6 h/day, 5 days/wk, for 103-104 wks. The concentrations were selected based on the results of a 4-wk inhalation study in B6C3F$_1$ mice; that study is presented in Table 4. These exposure concentrations provided a dose equivalent of 0, 2, or 6 mg/kg/day for male mice, respectively, and 0, 1.3, or 3.9 mg/kg/day for female mice, respectively. The MMAD was 3.3 ± 1.9 µm in the 6 mg/m^3 chamber and 3.6 ± 2.0 µm in the 18 mg/m^3 chamber. Groups of 40 male and 40 female mice were similarly exposed and killed at 6, 12, and 18 mos for interim microscopic evaluations. Some problems were experienced in maintaining control of the chamber concentrations, and there was a 12-wk period beginning at wk 70 during which the chamber concentrations were substantially lower than the target concentrations. Mean body wts were similar for test and control animals, and there were no clinical findings attributable to talc exposure.

Compared to the 6 mos value, the lung talc burden (normalized to control lung wt) was statistically significantly increased at 24 mos in 6 mg/m^3 males, at 12 and 24 mos in 18 mg/m^3 males, at 18 and 24 mos in 6 mg/m^3 females, and at 12, 18, and 24 mos in 18 mg/m^3 females. When lung talc burdens were normalized to exposure concentration, a statistically significant difference was observed between the 6 and 18 mg/m^3 males at 12 and 24 mos but not at 6 and 18 mos. The mouse lung talc burdens are provided in Table 7.

Changes in enzymatic activities in bronchoalveolar lavage fluid were noted mostly in the 18 mg/m^3 males and females; measured enzymatic activity was increased in the high-dose animals at 18 and 24 mos. A statistically significant increase in β-glucuronidase activity was seen as of 12 mos in the high dose animals, and at 24 mos, the activity was increased in all test groups. Lavage fluid polymorphonuclear cells were statistically significantly increased in males and females of the 18 mg/m^3 group at all times except at 12 mos; statistically significant increases were observed in some 6 mg/m^3 interim groups. The population of bronchoalveolar lavage fluid macrophages was significantly decreased in the female test groups at 24 mos. The phagocytic activity of the macrophages recovered from the lavage fluid at 12, 18, and 24 mos was statistically

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significantly decreased by exposure to 18 mg/m^3 talc. At 24 mos, there was no effect on the viability of the macrophages. Lung tissue collagen and proteinase activity were significantly increased in exposed male and female rats. At 24 mos, collagen and lung fluid collagenous peptides were statistically significantly increased in the 18 mg/m^3 group, and most proteinase activity was increased as well.

Chronic active inflammation without alveolar epithelium hyperplasia, squamous metaplasia, or interstitial fibrosis was reported in exposed mice. An accumulation of macrophages was observed in the lungs, and talc-containing macrophages were found in the bronchial lymph nodes. The incidence of pulmonary neoplasms was similar for test and control animals. In the upper respiratory tract, cytoplasmic eosinophilic droplets in the nasal mucosal epithelium occurred and were concentration-dependent. There was *no evidence of carcinogenic activity* in male or female B6C3F1 mice exposed to talc.

A lifetime study was performed in rats; groups of 50 male and 50 female F344/N rats (6-7 wks old) were exposed to the same dosing regimen and target concentrations of talc as mice until mortality reached 80% in any exposure group, i.e., males were exposed for 113 wks and females for 122 wks. (The concentrations selected were based on the results of a 4-wk inhalation study in F344/N rats; that study is described in Table 4). The MMAD was 2.7 ± 1.9 μm in the 6 mg/m^3 chamber and 3.2 ± 1.9 μm in the 18 mg/m^3 chamber. As with the mice, there was difficulty in maintaining the chamber concentrations for the rats; there was a 7-wk period beginning at wk 11 during which time the concentration for the 18 mg/m^3 group varied from 30-40 mg/m^3 and there was a 12-wk period beginning at wk 70 during which the chamber concentrations were substantially lower than the target concentrations for both groups. Groups of 22 male and 22 female rats were exposed similarly and killed at 6, 11, 18, and 24 mos for interim evaluations. Survival was similar for test and control animals. Body weights of the low dose animals were similar to controls and final body weights of the high dose animals were slightly (14%) lower than controls. Compared to controls, the absolute and relative lung weights in high dose males were statistically significantly increased in at 6, 11, and 18 mos and at study termination, in high-dose females at 11, 18, and 24 mos and at study termination, and in low dose females at 18-mos and study termination.

A concentration-related impairment of respiratory function was observed in exposed male and female rats, and the severity increased with increasing duration of exposure. In the 6 and 18 mg/m^3 males and in the 6 mg/m^3 females, the lung talc burden (normalized to control lung wt) was statistically significantly increased at 11, 18, and 24 mos compared to the 6 mos value. In the 18 mg/m^3 females, the 18 and 24 mos values were statistically significantly increased compared to the 6 mos values. When lung talc burdens were normalized to exposure concentration, a statistically significant difference was observed between the 6 and 18 mg/m^3 males at 6 and 11 mos but not at 18 and 24 mos. At 24 mos, the lung talc burden (normalized to exposure concentration) was higher in the 6 mg/m^3 males than in the 18 mg/m^3 males. In the females, the only statistically significantly difference between the low and high dose groups was at 6 mos. The interim rat lung talc burdens are provided in Table 8.

Pulmonary function was impaired (i.e., restricted) in a concentration-related manner, increasing in severity with exposure duration. After 24 mos of exposure, changes in enzymatic activities in bronchoalveolar lavage fluid were noted compared to controls; statistically significant increases in β-glucuronidase were seen in all test animals. Also, lavage fluid polymorphonuclear cells were statistically significantly increased and macrophage cells were statistically significantly decreased in all test animals; a statistically significant increase in lymphocyte cell populations was reported in all test group females. The viability and phagocytic activity of the macrophages recovered from the lavage fluid were not affected by exposure to talc. Lung tissue collagen and proteinase activity was significantly increased in exposed male and female rats.

Granulomatous inflammation occurred in most test animals, and severity increased with duration and concentration. Hyperplasia of the alveolar epithelium and focal interstitial fibrosis was statistically significantly increased at study termination; squamous metaplasia of the alveolar epithelium and squamous cysts were significantly increased in the 18 mg/m^3 females only. Talc-containing macrophages were reported in the peribronchial lymphoid tissue of the lung and in the bronchial and mediastinal lymph nodes. In the full study, the incidences of pulmonary neoplasms in male rats of the test group were similar to controls. However, in female rats of the 18 mg/m^3 group, the incidences of alveolar/bronchiolar adenoma, carcinoma, and adenoma/carcinoma (combined) were statistically significantly greater than controls; one squamous cell carcinoma was reported in this group. In the upper respiratory tract, hyperplasia of the respiratory epithelium of the nasal mucosa was observed in male test animals and accumulation of cytoplasmic eosinophilic droplets in the nasal mucosal epithelium was observed in males and female test animals; the incidence of these lesions was concentration-dependent. Benign, malignant, or complex (combined) adrenal medulla pheochromocytomas occurred with a significant positive trend in male and female rats, and the incidences in the 18 mg/m^3 group were statistically significantly increased compared to controls. The incidence of

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adrenal medulla hyperplasia was statistically significantly decreased in exposed males, but not exposed females, compared to controls. It was concluded that there was *some evidence of carcinogenic activity* of talc in male F344/rats based on an increased incidence of benign or malignant pheochromocytomas of the adrenal gland and *clear evidence of carcinogenic activity* of talc in female F344/N rats based on increased incidences of alveolar/bronchiolar adenomas and carcinomas of the lung and benign or malignant pheochromocytomas of the adrenal gland.

Responses to/Reviews of the NTP Inhalation Bioassay

- One member of the NTP Board of Scientific Counselors, Technical Reports Review Subcommittee, voted against the NTP conclusions on the carcinogenic potential of non-fibrous talc in rats.(Goodman JI, 1995) This board member asserted that talc-induced lung tumors occurred only in the group of animals that experienced the most chronic toxicity and inflammation, and that the lung toxicity data were presented as an empirical observation rather than related to the risk assessment implications of the bioassay. Additionally, it was the opinion of the board member that the evaluation of the pheochromocytomas was inadequate because the spontaneous incidence of this tumor in rats was not sufficiently addressed and that the incidence of pheochromocytomas were not treatment-related.

- At a talc workshop that was co-sponsored by the FDA, CTFA (now, the Council), and ISRTP, a unanimous consensus was reached regarding the NTP talc bioassay.(Carr CJ (Rapporteur), 1995) It was the opinion of the Panel at the workshop that "because of the extreme doses and the unrealistic particle sizes of the talc that was used, because of the negative results in mice and male rats, because of the lack of tumor excess at the low doses, and because of the clear biochemical and cytological markers of excessive toxicity in the female rats, the positive talc bioassay results in female F344/N rats were the likely experimental artifacts and nonspecific generic response of a dust overload of the lungs and not a reflection of a direct activity of talc. Given the gross differences of rodent and human lungs, the lung clearance capabilities of humans, and the possible conditions of customary human exposures, the NTP bioassay results in F344/N female rats cannot be considered as relevant predictors of human risk."

- A critical appraisal of the NTP study discussed test concentration selection and the effect of lung particle overload.(Oberdörster G, 1995) The appraisal noted that a 4-wk study, rather than a subchronic study, was used to determine the test concentrations used in the bioassay; additionally, only two test concentrations were used and exposure at these concentrations impaired lung clearance in the 4-wk study. The appraisal cited a recommendation that, instead, the long-term bioassay should be performed using three concentrations and that only the highest concentration tested should show interference with lung defense mechanisms; the two lower concentrations should not interfere with clearance and particle accumulation. It was the opinion of this appraisal that lung particle clearance in both rats and mice was impaired, resulting in altered accumulation kinetics, with long-term exposure at concentrations of 6 and 18 mg/m^3. Therefore, the maximum tolerated dose (MTD) was exceeded at both exposure concentrations, and because the MTD was exceeded, "classification of such particles with respect to human pulmonary carcinogenicity should be considered carefully". Finally, the appraisal stated that the NTP conclusion of clear carcinogenicity in female rats should be qualified by a statement indicating that the lung tumors that occurred were mostly likely produced secondary to particle overload and related chronic toxicity.

- The human exposure to respirable talc particles during normal product use (values obtained from studies by Russell et al. (1979)(Russell RS *et al.*, 1979) and/or Aylott (1979)(Aylott RI *et al.*, 1979)) compared to the exposure of rats and mice in the NTP study.(Zazenski R *et al.*, 1995) According to these researchers, based upon the determinations reported in the literature, human exposure to respirable talc particles during normal product use is approximately 2000 – 20,000 time lower than that used for rats and mice in the NTP study.

- The International Life Sciences Institute (ISLI) convened the Workshop on Relevance of the Rat Lung Response to Particle Overload for Human Risk Assessment.(Olin SS, 2000) The workshop addressed studies reporting lung tumors in rats resulting from chronic inhalation of poorly soluble, nonfibrous particles (PSPs) that are of low acute toxicity and not directly genotoxic, including non-asbestiform talc. The workshop noted that PSP-induced tumors in rats are associated with the following sequence of responses: particle accumulation, chronic active inflammation, epithelial cell hyperplasia, and metaplasia; the chronic active inflammation is associated with the emergence of neoplastic cells. It was stated that, although for direct-acting mutagens the rat appears to be a good qualitative predictor of the human lung cancer, for PSPs it appears to be more sensitive than humans and other rodent species at doses and exposure intervals that result in particle overload in the rat lung. However, because it is not known whether high lung burdens of PSPs can lead to lung cancer in humans via mechanisms similar to those in rats, "it was the consensus view of the workshop that there

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are insufficient data at present to conclude that the PSP-induced tumor response in the rat model is not relevant for human hazard identification. In other words, in the absence of mechanistic data to the contrary, it must be assumed that the rat model of tumorigenicity can identify potential carcinogenic hazards to humans."

- Another comment paper discussed the use of micronized talc in the NTP study, which resulted in a significantly reduced particle size compared to cosmetic talc, i.e., 2.7-3.2 µm instead of 6.0-6.9 µm.(Wehner AP, 2002a) The commenter stated that the use of micronized talc significantly affected the bronchopulmonary deposition and clearance characteristics of the inhaled aerosol; the micronized talc particles were deposited deeper in the lung where clearance depended on alveolar macrophages, whereas cosmetic talc particles would have deposited in the ciliated portion of the respiratory tract. The commenter also remarked on the difficulty in controlling aerosol concentrations and that the 7-wk period in which the rats were exposed to twice the intended aerosol concentration most likely aggravated an existing overload condition.

Parenteral
Intrapleural
Talc did not induce pleural tumors in rats following intrapleural injection.(Endo-Capron S *et al.*, 1990) A group of 35 Sprague-Dawley rats were given an intrapleural injection of 20 mg talc (mean size 2.6 ± 2.3 µm; no other chemical characteristics provided) and control groups were given an intrapleural injection of saline (40 rats) or no injection (38 rats). The animals were killed when moribund. No pleural tumors were observed in the test or control group. As a comparison, the researchers examined the effect of Canadian chrysotile (90% of the fibers were <8 µm in length) in 39 rats and found that 25.6% of the rats developed mesothelioma.

Intraperitoneal
Forty 6-wk old Swiss albino mice were given an i.p. injection of 20 mg of UV-sterilized commercial talc (composition not stated) in 1 ml saline, and the animals were observed until there were obvious signs of a tumor or spontaneous death.(Özesmi M *et al.*, 1985) Fifty-five control animals were injected with 1 ml physiological saline. Animals that died before 9 mos elapsed were not included. Twenty-four treated mice were included in the results. Three (12.5%) developed mesothelioma; no lymphomas were reported. Forty-six of the control animals were included in the results; three mesothelioma and one lymphoma developed (8.7% total tumors).

Forty Wistar rats were given weekly i.p. injections of 25 mg talc suspended in 2 ml saline weekly for 4 wks, and the animals were allowed to live until natural death.(Pott F *et al.*, 1974) It is stated that the talc was composed of magnesium silicate, but no other components are given; the particle size was not known. Eighty control animals were injected with saline only. Few tumors developed in the test animals; the tumor rate was 2.5%. The time to first tumor was 587 days.

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Ovarian Cancer Risk

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Particulate Migration in the Genital Tract
Migration of particles through the female genital tract has been examined as a possible explanation of the presence of talc in the ovaries. However, at the "Talc: Consumer Uses and Health Perspectives" workshop, it was stated that "available histologic and physiologic studies provide no basis to conclude that talc can migrate to the ovaries from the perineal region."(Carr CJ (Rapporteur), 1995) Because whether or not translocation is a viable theory in general, several studies on the transport of particulate matter (other than talc) are briefly summarized; mixed results were found. Studies specifically relating to talc migration then follow.

Non-Human
No translocation of bone black from the vagina to the oviducts was found in monkeys.(Wehner AP *et al.*, 1985b) Cynomolgus monkeys were restrained so that their pelvis was elevated, and 0.3 ml of a suspension of 4% bone black in 30% dextran was placed in the vaginal posterior fornix of four monkeys and 0.3 ml of a suspension of 4% bone black in physiological saline containing carboxymethyl cellulose (CMC) was placed in the vaginal posterior fornix of one monkey. Ten units of oxytocin were administered by intramuscular (i.m.) injection at the same time. The monkeys were released after 20 min. One h after deposition of the bone black, two monkeys that received suspensions in dextran and the one that received the saline with CMC suspension were anesthetized and the reproductive tract of each animal was removed; the oviducts were flushed. The remaining two monkeys were processed in the same manner 72 h after deposition. The test samples, the solutions without bone black (negative controls), and samples with a suspension of bone black (positive control) were filtered with Millipore membrane filters (0.45 µm). Particles resembling bone black were found on filters used for oviduct flushing solutions as well as the solution blanks; the numbers ranged from very few to occasional on all filters and no distinct differences in numbers or shape of these particles were apparent. The new filter blank that was examined immediately upon re-

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moval was the only sample on which no bone black particles were found. The researchers stated that these results suggest that there was no translocation of bone black from the vagina to the oviducts.

Twenty-six New Zealand white rabbits were used to examine whether starch particles migrate from the vagina to the peritoneal cavity.(Edelstam GAB *et al.*, 1997) Anesthetized rabbits were divided into an untreated control group, a group given 50 mg of a glove lubricant powder intravaginally, and a group given 50 mg of the lubricant powder and *Chlamydia trachomatis* (an inclusion former). Ovulation was then induced in all groups. After 1-4, 17, and 25 days, the rabbits were anesthetized and the peritoneal cavity was rinsed; the lavage fluids were analyzed for starch particles. Small numbers of starch particles were found on all slides. Retrograde migration was found after 3 days. The number of small particles between the treated and control groups was not statistically significantly different. Large starch particles were statistically more numerous in the two test groups compared to the controls.

Human

Sterile carbon particles were suspended in 30% dextran and 3-4 ml of the suspension was deposited into the posterior fornix of three women placed in the lithotomy position (i.e., head tilted downward at a 15° angle for horizontal) that were undergoing abdominal surgery; 1 ml (10 U) of oxytocin given simultaneously via i.m. injection.(Egli GE & Newton M, 1961) During surgery, 20-34 min after deposition of the particles, the Fallopian tubes were sutured 1 cm lateral to the uterus, excised, and then flushed with saline. Carbon particles were found in the rinsate from two of the three subjects. In a study using India ink, it was found that India ink (0.2 ml) that was injected into the uterine cavity 15 min – 24 h prior to abdominal surgery was transferred to the Fallopian tubes in 27/50 women in the proliferative phase and in 23/35 women in the secretory phase of the menstrual cycle.(de Boer CH, 1972) Injection of ink into the cervical canal often resulted in immediate back flow into the vagina; the ink reached the Fallopian tubes in 17/56 women. However, when the ink was placed into the vagina, the ink was transferred to the Fallopian tubes in only 1/18 women in the proliferative phase in 12-24 h. The ink was found to pass from the vagina to the uterus in 2/37 women; one of these woman where the ink was transferred had a lacerated cervix. (In this study, some of the women had received an i.m. injection of 2 units of oxytocin at the same time the ink was administered, but it did not appear to affect the results, and the women were placed in the Trendelenburg position after the abdomen had been opened.)

In a study using a radionuclide procedure, the migration of a particulate radioactive tracer from the vagina to the peritoneal cavity and ovaries was determined in 24 women scheduled to undergo gynecological surgery.(Venter PF & Iturralde M, 1979) The day prior to surgery, the women were placed in a supine position, and less than 3 ml of 10-15 mCi [^{99m}Tc]-labeled human albumin microspheres (HAM) were deposited in the posterior fornix. Each subject remained in a supine position for 24 h. The radionuclide material remained in place for 21 women, and in 16 of these women, "sufficiently high radioactivity levels" were determined as evidence of migration to the uterus or the Fallopian tubes and ovaries. In 14 of the 21 subjects, radioactivity was measured in adnexa separately from the uterus. Nine of the 14 subjects had "marked" radioactivity in the tubes and ovaries; the five subjects that did not had severe tubal occlusions. Another group of researchers stated that this finding may be misleading because only one radioactive label was used.(Wehner AP *et al.*, 1985b)

The migration of starch particles from powdered gloves was examined in groups of female subjects that were under-going abdominal surgery.(Sjösten ACE *et al.*, 2004) A group of 17 females was examined with powdered gloves 1 day prior to surgery and a group of 12 females was examined with powdered gloves 4 days prior to surgery. Corresponding control groups of 15 and 14 females, respectively, were examined with powder-free gloves. Peritoneal fluid was collected during surgery. The number of starch particles found in patients examined with powered gloves 1 day prior to surgery was statisti-cally significantly increased for both small and large particles at all locations of the genital tract and for large particles in the peritoneal fluid. No particles were found in two subjects examined with powdered gloves and a few particles were found in three subjects examined with powder-free gloves 1 day prior to surgery. In subjects examined with powdered gloves 4 days prior to surgery, there were statistically significantly more small and large starch particles in the cervix and uterus, but not in the Fallopian tubes or peritoneal fluid, compared to subjects examined with powder-free gloves.

A catheter was used to apply 1-2 ml of 10 ± 2 MBq-TC-99m-labeled macroaggregates of human serum albumin, 5-20 Hm in size, into the posterior vaginal fornix of 1000 women with primary or secondary infertility in the follicular phase of the menstrual cycle; 15 women were examined during the early to mid-luteal phase.(Zervomanolakis I *et al.*, 2007) The women were in a supine position, and hysterosalpingoscintigraphy (HSS) scans (a method to evaluate the transport function of uterus and Fallopian tubes) were obtained immediately and at various intervals for 4 h after application. Labeled particles were detected in the uterus at the time of the first HSS scan of every woman examined; women in both the follicular and lute-

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al phase were examined. In women in the follicular phase, radioactivity entered the Fallopian tubes on both in 15% of the subjects and on one side in 64% of the subjects; significant radioactivity entered the pelvis of 6% of the subjects. Radioactivity was not found to migrate to the Fallopian tubes of the remaining women that were in the follicular phase or in any of the women examined during the luteal phase.

Talc Migration in the Genital Tract
Non-Human

Particles of talc were identified in the ovaries of rats that received intrauterine instillation(s) of talc.(Henderson WJ *et al.*, 1986) In a pilot study, one group of four female ex-breeder Sprague-Dawley rats received one intrauterine instillation of 100 mg/ml talc in 250 µl PBS; these rats were killed 5 days after dosing. A second group of four rats received intrauterine instillations of the talc suspension on days 0, 6, and 15; two animals were killed on day 20. (Spectral analysis reported a 3:1 ratio of silicon to magnesium; it is not stated whether the talc was non-fibrous). The remaining two animals were dosed again on days 22 and 30, and killed on day 49. The ovaries of each animal were analyzed by an ashing procedure.

Two groups of 12 female ex-breeder Sprague-Dawley rats were then dosed intravaginally with 250 µl of the same talc suspension or PBS only, and two animals per group were killed 24 h, 48 h, or 4 days after dosing. Their ovaries were removed and analyzed as above. Particles of talc were found in the ovaries of the two rats of the talc group that were killed after 4 days, but not in those killed at 24 or 48 h or in the PBS-treated animals.

Radioactivity was not found in the ovaries of rabbits dosed intravaginally with talc.(Phillips JC *et al.*, 1978) Three female Large White rabbits received a single intravaginal instillation of 0.5 ml of [^{3}H]talc administered as a suspension in aq. glycerol jelly solution (10 mg/ml; 1 µCi/ml) and three were given six daily doses of the talc suspension. (Chemical characterization data were not provided). In the single-dose rabbits, urine was collected every 24 h for 3 days; the animals were then killed, the urogenital tract was dissected out, and the total radioactivity was determined in the urine, ovaries, Fallopian/ uterine tubes and cervix, the bladder, and the vagina. In the urogenital tract 72 h after dosing, radioactivity (0.004% of the dose) was only detected at the site of administration. (The limit of detection was 0.25 µg). Total recovery was not quantitated.

In the multiple-dose group, the rabbits were killed 72 h after the final dose; radioactivity was determined as described for the single-dose animals. In the urogenital tract at 72 h after the final dose, 0.035% of the radioactivity was found at the site of administration and 0.006% was found associated with the cervix and Fallopian/uterine tubes. No radioactivity was found in the ovaries.

Talc was not found to translocate from the vaginas of female cynomolgus moneys to the ovaries.(Wehner AP *et al.*, 1985b) A pilot study was first performed with two female cynomolgus monkeys. Talc samples were exposed to a calculated neutron fluency of 1.2 x 10^{17} n/cm^2, and 125 mg neutron-activated talc suspended in 0.3 ml deionized water containing 1% CMC was placed into the vaginal posterior fornix of each monkey. (Deposition was similar to that of bone black, described previously). Three days after talc deposition, the animals were anesthetized and peritoneal lavage was performed; when the peritoneal cavity was opened to collect the fluid, the lavage was repeated through the abdominal incision. Peritoneal lavage was also performed on a control animal. Radionuclide activity was determined with ^{46}Sc, ^{59}Fe, and ^{60}Co. There was no measurable translocation of activated talc from the site of deposition to the uterine cavity, oviducts, ovaries, or peritoneal cavity. (The vagina and the cervix were analyzed together). It appeared that detectable amounts of ^{60}Co were found in a portion of the oviducts of each test animal, but this was not supported by ^{46}Sc or ^{59}Fe data. Approximately 0.3 and 2.3 mg talc were found in the vaginas of the two test monkeys 3 days after instillation.

In the definitive study, six monkeys were dosed with a neutron-activated purified blend of cosmetic talc for 30 consecutive workdays.(Wehner AP & Weller RE, 1986) The animals were restrained and dosed as defined in the pilot study; additionally, 10 units of oxytocin were administered by i.m. injection once weekly. ^{46}Sc, ^{59}Fe, ^{60}Co, and ^{61}Cr were used as tracers. The peritoneal lavage was performed as above 2 days after the last talc deposition. Measurable quantities of talc were observed in the vagina + cervix sample, and the quantities ranged from 0.006 – 117 mg talc. (The researchers theorized that the wide variations were most likely due to different menstrual cycle phases). No measurable levels of talc (> ~0.5 µg) were present in the samples from the peritoneal lavage fluid, ovaries, oviducts, or body of the uterus.

Human

Talc particles were found in approximately 75% (10 of 13) of the ovarian tumors and 50% (12 of 21) of the cervical tumors during an extraction-replication technique used to examine tissue from patients with ovarian or cervical can-

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cer.(Henderson WJ *et al.*, 1971) The particles found in the ovarian tumors were located deep within the tumor tissue and were not universally dispersed; some of the particles were 1000 Å, but most ranged from 1000 Å to 2 μ. The particles found in the cervical tumor tissue were generally larger than those in the ovarian tumors; some crystals were as large as 5 μ. Additionally, many particles of talc were found concentrated in the deeper layers of a primary carcinoma of the endometrium; however, talc was not found in a secondary tumor in the ovary of the same patient. Talc particles were also found in 5 of 12 normal ovarian tissue samples removed from patients with breast cancer. (Chemical characterization data were not provided for the talc that was found; the researchers noted that no asbestos fibers were found in any of the tissues studied.)

In 100 consecutive cases of women operated on for pelvic disease at Johns Hopkins Hospital, a total of 175 normal ovaries were removed and examined for particulate matter.(Mostafa SAM *et al.*, 1985) Seventy-two cases were classified as having laminated calcifications referred to as psammoma bodies. Six examples of crystalline foreign bodies were found and examined by scanning electron microscopy; computer-assisted microscopic x-ray analysis was used to determine the elemental composition of the foreign bodies in four cases. The particles were composed primarily of magnesium and silicon; the researchers stated that in industrial North America, the most common compounds containing magnesium and silicate are talc and asbestos. Nine percent (9%) of the patients appeared to have magnesium silicate granulomas in their normal ovaries, and an additional 9% contained very similar histologic entities.

The ovaries of 24 women with benign ovarian neoplasms who were undergoing surgery at Columbia Presbyterian Medical Center between 1992 and 1993 were examined for the presence of talc using both light and electron microscopy.(Heller DS *et al.*, 1996) Twelve women reported talc application directly to the perineum or underwear and 12 women were age-matched controls. The mean number of lifetime exposures for women reporting talc use was 14,820, with a range of 4784 – 39,312 lifetime exposures. The ovaries of two stillborn fetuses were analyzed as negative controls; no talc was found in these ovaries. Sections of normal ovary from the 12 women who reported the talc use were analyzed. A linear relationship between ovarian talc particle burden and exposure was not found. Neither light nor electron microscopy values correlated with perineal talc usage. Electron microscopy counts were 0 for about half of the subjects exposed to talc as well as half of the controls; talc was observed with light microscopy in all subjects exposed to talc and 11/12 of the controls. There was a negative correlation between the values obtained by light microscopy and electron microscopy. The mean electron microscopic particle count was higher in those exposed to talc and the mean light microscopic particle count was higher in the women that did not report talc use. In one subject for which both ovaries were analyzed, both talc counts varied greatly between the right and left sides (0 vs. 1,669,000 particles/g wet tissue wt by electron microscopy and 556 vs. 6 particles by light microscopy, respectively). Asbestos was detected in the ovaries of four talc-exposed subjects and five of the control subjects.

The pelvic lymph nodes of a woman with stage III ovarian papillary serous carcinoma, with metastatic serous carcinoma in two of six right external iliac and obturator nodes, were examined using polarized light microscopy and scanning electron microscopy and x-ray spectroscopy.(Cramer DW *et al.*, 2007) The subject applied talc daily for 30 yrs to the perineum, and also applied it to underwear and sanitary napkins. She had three term deliveries followed by a tubal ligation and she did not smoke, use oral contraceptives, or, with the exception of 6 mos of progesterone therapy, use postmenopausal hormone therapy. Birefringence was seen using polarized light; three of four nodes that did not contain metastases displayed polarizing material. Examination of lymph nodes by combined scanning electron microscopy and x-ray spectroscopy revealed plate-like particulates in the 5-10 μm range within the lymph nodes; the energy dispersive x-ray spectroscopy showed a magnesium and silicate signature that was compatible with talc. Nodes from 12 other patients were examined; this case was strongest for birefringence. (Electron microscopy or x-ray spectroscopy had not been performed).

Epidemiological Studies

Numerous epidemiological studies have been performed examining the risk of ovarian cancer following talc exposure. These studies are summarized in Table 9. There is a large amount of information presented in these studies, and a variety of parameters were examined. Table 10 is a summary of the relative risk for ovarian cancer presented in case-control studies; this table only includes those studies that indicated "ever" use of talc in the perineal area, independent of the manner of use.

Analysis of Ovarian Cancer Risk in the Epidemiological Studies

Concerns about using cosmetic talc are based mainly on reports suggesting that talc may migrate from the perineum to the ovaries and the results of epidemiological studies suggesting a fairly consistent association between perineal dusting with talc powders and ovarian cancers.(Wehner AP, 1998a)

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The possibility that the hygienic use of cosmetic talc powder can cause ovarian cancer was suggested after reports that talc particles were observed in or on human ovarian tissues.(Henderson WJ *et al.*, 1971;Henderson WJ *et al.*, 1978;Henderson WJ *et al.*, 1979;de Boer CH, 1972;Egli GE & Newton M, 1961;Venter PF & Iturralde M, 1979) The proposal that talc particles can migrate from the perineum to the ovaries depends on the questionable assumption that these particles can pass from the perineum through the vagina and cervical canal, move across the uterus and against the ciliary motion of the Fallopian tubes, cross the peritoneal space between the fimbriae and ovaries, escape phagocytosis in the peritoneal space, and attach to the surface of the ovaries to accumulate in the ovaries.(Kelly WG, 2012;Carr CJ, 1995)

In addition, there is evidence that the appearance of talc particles in the ovaries is attributable to sample contamination, rather than to particle translocation, in many of the earlier studies.(Wehner AP *et al.*, 1985a;Wehner AP, 1998a) The earlier studies did not include examination of blank solution or blank filter samples as negative controls, rendering the results inconclusive as proof of translocation. A later study in which cynomolgus monkeys (*Macaca fascicularis*) were exposed intravaginally to a bone black suspension found about as many particles in the blank solutions and the filters through which they were passed as in the test samples.(Wehner AP *et al.*, 1985a)

The hypothesis that talc found in the ovaries is attributable to the contamination of tissue samples, with particles ubiquitously present in the ambient environment, during sample collection, processing, storage and/or handling, is supported by studies in which, for example, talc was observed in 100% of women with no known talc exposure, as well as in 85% of women reporting frequent perineal talc applications.(Heller DS *et al.*, 1996)

Other translocation studies have been criticized for using particles with only a single radionuclide, such as ^{99m}Tc-labeled HAM,(Venter PF & Iturralde M, 1979) which yields ambiguous results because the radiolabel leaches from such particles, leading to the untenable assumption that the leached radioactive marker represents translocated particles.(Wehner AP, 1998a;Wehner AP & Wilkerson CL, 1981;Wehner AP *et al.*, 1977b;Wehner AP *et al.*, 1984;Wehner AP, 2002b;Wehner AP *et al.*, 1985a;Wehner AP & Weller RE, 1986;Wehner AP *et al.*, 1980;Wilkerson CL *et al.*, 1977;Bolles TF *et al.*, 1973) This problem can be avoided by using more than one radionuclide, each with its characteristic leaching rate, and comparing the radionuclide/particle ratios in the bulk sample before exposure to the ratios in the tissue samples after exposure.(Wehner AP, 2002b) Only if the ratios do not change do the radionuclide data reflect particle translocation rather than radionuclide leaching.(Wehner AP, 1998a)

In a later study conducted to help address this issue, ^{46}Sc, ^{60}Co, ^{59}Fe and ^{51}Cr served as tracers in 125 mg neutron-activated talc deposited intravaginally 30 times over 45 days to ensure exposure through at least one menstrual cycle in cynomolgus monkeys.(Wehner AP *et al.*, 1985a;Wehner AP & Weller RE, 1986) The tracers were found only in the vagina-with-cervix samples collected 2 days after the 30th talc application (i.e., only at the site of deposition). They were not detected in the uterus, the entire Fallopian tubes in three sections, the ovaries, or the peritoneal lavage fluid (detection limit 0.5 μg talc; about 1/250,000 of the talc deposited with each application). The γ-ray analysis of neutron-activated talc used in this study precluded interference from sample contamination by ubiquitous environmental talc particles.(Wehner AP, 1998a;Wehner AP, 2002b)

The migration of many different types of materials, including radio-opaque contrast media and dyes, from the vagina through the cervix has been demonstrated in patients in a supine or in the Trendelenburg position, or in patients with a lacerated or a dilated cervix. In addition, the flow of menstrual blood into the Fallopian tubes (i.e., retrograde menstrual flow) is a well-known phenomenon that could help explain the movement of particles to the ovaries in some cases. However, the findings of at least one study(de Boer CH, 1972) has been interpreted as indicative of the formidable barrier that the cervix presents to the translocation of particles from the vagina to the ovaries.(Wehner AP, 1998b;Wehner AP, 2002b) Colloidal carbon black (India ink) deposited intravaginally before abdominal surgery was found in the uterus only twice in 37 patients, one of them a woman who had delivered 6 children and had a lacerated cervix. Carbon black was also found in the Fallopian tubes only in this patient. All of the patients had been placed in the Trendelenburg position (i.e., legs elevated 45 degrees and head lower than the hips) under anesthesia during surgery. The movement of the abdominal organs toward the diaphragm in this position would be expected to create a vacuum in the uterus that could facilitate the movement of material from the vagina through the relaxed cervix.

It is possible that many women have been exposed in infancy to talc used to diaper them.(Heller DS *et al.*, 1996) Infants are typically placed in a supine position and their legs separated during diapering, which could facilitate the passage of talc into the vagina. This may help explain the ubiquitous presence of talc in ovarian tissue. However, it has not been

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determined whether the hymen blocks exposure to the infant genital tract, or otherwise to what extent, if any, talc can enter the genital tract during diapering.(Muscat JE & Huncharek MS, 2008)

The results of several epidemiological studies suggested that medical procedures expected to prevent the transloca-tion of talc to the ovaries, such as tubal ligation or hysterectomy, reduce the relative risk estimates associated with talc use (Cramer DW *et al.*, 1999;Harlow BL *et al.*, 1992;Whittemore AS *et al.*, 1988;Hankinson SE *et al.*, 1993) However, in one of these studies, women who were exposed to talc for one to nine years before tubal ligation or hysterectomy appeared to have an increased risk of ovarian cancer, but not women who had talc exposure for ten or more years before their sur-gery.(Whittemore AS *et al.*, 1988) Other studies found no difference in relative risk between women who had tubal ligation or hysterectomy and women who did not have these procedures.(Chang S & Risch HA, 1997;Wong C *et al.*, 1999) One study reported inverse exposure-effect trends with duration of talc exposure after adjusting for tubal ligation.(Ness RB *et al.*, 2000) Thus, the literature provides no clear, convincing support for the hypothesis that procedures that would preclude the passage of talc particles from the perineum to the ovaries reduce the risk of ovarian cancer in talc-exposed women.

The use of talc-dusted condoms or diaphragms (including diaphragms known to have been stored in talc powder), which would clearly result in exposure close to the cervical opening, was not associated with an increased estimate of relative risk of ovarian cancer.(Rosenblatt KA *et al.*, 1992;Cramer DW *et al.*, 1999;Cramer DW *et al.*, 1982) A meta-analysis of the association between talc-dusted diaphragm use and ovarian cancer risk yielded a summary odds ratio (OR) of 1.03 (95% CI: 0.80-1.37). Overall, these studies do not support the hypothesis that talc can migrate from the perineum or the vagina to the ovaries.

Many physiological, sociological, and exposure factors have been linked to ovarian cancer, a number of them with a stronger association than the hygienic use of cosmetic talc, but causality has not been established for any of them.(Wehner AP, 2002b) The etiology of the majority of ovarian cancer cases is still unknown.

The first epidemiological investigations suggesting a link between perineal exposure to cosmetic talc and the risk of developing ovarian cancer was a population-based case-control study published in 1982.(Cramer DW *et al.*, 1982). Since then, numerous case-control studies have reported small increases in relative risk estimates of all ovarian cancers combined in women using cosmetic talc products, compared to women with minimal or no exposure, including population-based studies of similar design and hospital-based case-control studies.(Tables 9 and 10; Chart 1). Other investigations found no statistically-significant increase in risk estimates for ovarian cancer (all subtypes combined), including many case-control studies and one prospective cohort study.(Gertig DM *et al.*, 2000) Presumably the subjects in all of these studies used products that contained cosmetic grade talc, but information on fibrous content is generally lacking.

The inconsistent findings of statistically-significant associations between perineal talc use and ovarian cancer paral-lel the inconsistency of the results of studies searching for associations between talc use and specific types of ovarian tumors. Some studies found statistically-significant associations between talc use and invasive cancer(Chang S & Risch HA, 1997;Cramer DW *et al.*, 1999;Gertig DM *et al.*, 2000) while another study reported an association only between talc use and tumors of low malignant potential.(Harlow BL *et al.*, 1992) Some studies found no statistically-significant associations with all subtypes of ovarian cancer considered together, but reported statistically-significant associations with specific subtypes of ovarian cancer. For example, some studies found statistically-significant associations only with serous tumors(Cook LS *et al.*, 1997;Cramer DW *et al.*, 1999;Gertig DM *et al.*, 2000), while another reported a statistically-significant association only with endometrioid tumors(Harlow BL *et al.*, 1992)

Among the epidemiological investigations reporting a statistically-significant association, the relative risk estimates ranged between 1.0 and 2.0 and were barely statistically significant (Tables 9 and 10; Chart 1). For such low estimates, epi-demiological methods generally cannot distinguish causality from even minor confounding by measured or unmeasured risk factors or the undetected biases of investigators and subjects, especially recall bias in case-control studies.(Shapiro S, 2000;Taubes G, 1995;Muscat JE & Barish M, 1998;Rothman K, 1986)

The FDA/ISRTP panel noted that the conflicting and equivocal results of the case-control studies are attributable to potential confounders (parity, contraceptive use, ovulatory frequency, age at menarche and menopause, family history, diet and exposure misclassification) and biases (e.g., recall and publication bias) inherent in most such studies.(Wehner AP, 1998a) In particular, age, race, low parity, infertility, and a family history of ovarian, endometrial or breast cancer, are among the most likely risk factors in the etiology of epithelial ovarian cancer.(Tortolero-Luna G *et al.*, 1994)

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Others have suggested that the effects of cancer treatment and smoking can be counted among the likely confounders in the talc studies.(Huncharek M *et al.*, 2007;Huncharek M & Muscat J, 2011) One study reported a statistically-significant OR of 3.4 (p = 0.01) for ovarian cancer in women who reported consuming coffee regularly for more than 40 years, compared to women who never regularly drank coffee. This was notably greater than the OR calculated for perineal talc users in the same study (OR = 1.4; p = 0.06).(Whittemore AS *et al.*, 1988) Other unidentified risk factors for ovarian cancer could be important confounders, and several such factors combined could explain the small increases in the relative risk estimates reported for ovarian cancer in women using cosmetic talc products perineally.

In general, there have been no attempts to determine whether alternative explanations, including recall bias, yielded spurious increases in relative risk estimates in the case-control studies. Prospective cohort studies do not suffer from recall bias because the exposures are recorded before the cancers were diagnosed. The single cohort study available found no statistically-significantly association between perineal talc use and all ovarian cancer subtypes combined, but did report such an association with invasive serous ovarian cancer (RR=1.4; 95% CI: 1.02-1.91)(Gertig DM *et al.*, 2000) The ORs for serous ovarian cancer were also elevated in several case-control studies (Chang S & Risch HA, 1997;Cramer DW *et al.*, 1999;Harlow BL *et al.*, 1992;Wong C *et al.*, 1999). All of the OR estimates reported in these studies were less than 1.7.

Talc exposure probably varies over time as women age and their reasons for deciding to use talc change. Talc use might be sporadic, seasonal or change with circumstances (e.g., sexual activity and parity). Thus, a single baseline assessment of talc exposure at the start of a follow-up in the cohort study(Gertig DM *et al.*, 2000) may lead to relative risk estimates biased toward the null. The single baseline exposure assessment performed in the cohort study would be more informative if talc-usage habits or patterns were steady over time or there is a long induction period or latency between talc use and diagnosed ovarian cancer. Unfortunately, no studies have characterized either the feminine hygiene habits involving the use of cosmetic talc products in the general population (e.g., who uses talc, how often and for what reasons) or the latency of purported talc-induced ovarian cancer to enable resolving these issues.(Muscat JE & Barish M, 1998)

Moreover, the epidemiological studies, including many reporting statistically-significant but weak associations between talc exposure and ovarian cancer, used questionnaires that did not focus specifically on the subjects' use of talc or talcum powders, as distinct from non-talc powders or sprays of known (e.g., corn-starch based) or unknown compositions.(Kelly WG, 2012) Further, it is not clear that all of the subjects understood the distinction between talc or talcum powders and talc-free powders when answering the questions.

Meta-analysis has been used commonly in epidemiology in attempts to overcome the problem of weak associations.(Muscat JE & Barish M, 1998) An early meta-analysis found a statistically-significant adjusted pooled OR of 1.27 (95% CI: 1.09-1.48) for ovarian cancer in women who ever used talc in the perineal or abdominal region compared to women who never used talc, based on eight studies published from 1982-1993.(Gross & Berg, 1995) However, the authors cautioned that this statistically-significant result does not provide the basis for inferring causality because many of the studies had substantial design limitations.

A more recent meta-analysis, based on 15 case-control and one cohort study, yielded a statistically-significant overall summary relative risk of 1.33 (95% CI: 1.16–1.45).(Huncharek M *et al.*, 2003;Huncharek M & Muscat J, 2011) However, a sensitivity analyses revealed clear differences in outcome based on study design. Population-based case-control studies yielded a statistically-significant increase in the risk of ovarian cancer (RR = 1.38; 95% CI: 1.25– 1.52) for hygienic use of talc, but hospital-based case–control studies showed no statistically significant difference (RR = 1.19; 95% CI: 0.99–1.41). About 32% of the women in the hospital-based control subjects and 32% of the population-based control subjects used talc. Thus, differences in the frequency of talc use in the respective control groups cannot explain the difference in the summary outcomes for the hospital-based studies compared to the population-based studies. The authors suggested that the difference may be attributable to a bias, such as a "treatment effect" among the cases. Some of the patients with ovarian cancer will undergo treatment with radiation, chemotherapy, and/or surgery, and the side effects of such treatments may make talc use more likely in these patients.

A still more recent meta-analysis, based on 20 epidemiological studies, reported a statistically-significant overall summary relative risk of 1.35 (95% CI: 1.26–1.46).(Langseth H *et al.*, 2008;Huncharek M & Muscat J, 2011) However, a statistical test for data heterogeneity yielded a p-value of 0.036, which indicates substantial inconsistencies among the pooled studies and an invalid pooled summary relative risk estimate. Thus, the outcome of this meta-analysis provides no support for a causal association between perineal talc use and ovarian cancer.

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In general, the findings of meta-analyses are considered to be un-interpretable when there is substantial heterogeneity among the studies in the methods used, the definition of exposures and outcomes, and the confounding factors that were considered.(Greenland S, 1994;Shapiro S, 2000)

Most of the epidemiological studies that searched for an exposure-effect relationship found no trend of increasing ovarian cancer risk with increasing exposure duration or frequency or cumulative exposure, despite a fivefold difference between the lowest and the highest exposure groups (Table 10).(Muscat JE & Wynder EL, 1997)   Several of these studies reported an apparent inverse trend.(Chang S & Risch HA, 1997;Huncharek M *et al.*, 2003;Maclure M, 1993;Gertig DM *et al.*, 2000;Booth M *et al.*, 1989;Cramer DW *et al.*, 1999)   For example, one study reported relative risk estimates of 0.7, 2.0, and 1.3 for monthly, weekly, and daily exposure, respectively.(Booth M *et al.*, 1989)   Another study reported RRs of 1.84, 1.43, and 1.43, respectively, for lifetime numbers of total talc applications of <3,000, 3,000-10,000, and >10,000 (once a day for 60 years would be 21,900 applications).(Cramer DW *et al.*, 1999)   Suggestions of an exposure-effect relationship were obtained only after substantially re-categorizing the subjects. For example, a positive trend between exposure frequency was noted in one study after excluding exposures during pregnancy, during oral contraceptive use, and after sterilization.(Cramer DW *et al.*, 1999)   Overall, however, the results of the epidemiological studies are not consistent with known mechanisms of carcinogenesis, which would be expected to yield positive exposure-effect trends, and the inverse trends, in particular, are not compatible with a causal relationship between perineal talc exposure and ovarian cancer. The inverse exposure-effect relationships reported in some studies suggest that poorly understood aspects of talc usage, such as a "treatment effect," or other as yet inadequately characterized or unknown biases contribute substantially to the outcomes of the epidemiological studies. (Huncharek M *et al.*, 2003;Huncharek M *et al.*, 2007)

No plausible biological mechanism has been identified to explain how exposure to non-asbestiform talc could cause ovarian cancer.

Thirty or more years ago, cosmetic talc was purported generally to contain substantial amounts of asbestos fibers,(Cralley LJ *et al.*, 1968;Rohl AN *et al.*, 1976) which would clearly represent a carcinogenic risk. However, FDA and IARC reviewed this contention and found that it could not be substantiated.(World Health Organization (WHO) International Agency for Research on Cancer (IARC), 2010;Cralley LJ *et al.*, 1968;Krause JB, 1977;Langer AM & Nolan RP, 1989;Speil S, 1971;Weissler A, 1973)   Further, stringent quality criteria have been in place for cosmetic talc, as well as for pharmaceutical-, food- and industrial-grade talc, since 1976.(Zazenski RJ, 1998)   Meeting these criteria requires the elimination of detectable asbestos and asbestiform talc from consumer products. Thus, the increased ovarian cancer risks associated with cosmetic talc use reported in some of the more recent epidemiological studies have generally not been attributed to contamination with asbestos or asbestiform talc.

However, the potential carcinogenicity of talc has been attributed by some authors to the chemical similarity of talc to asbestos. Both substances are magnesium silicates, but they share no other characteristics in common.(Muscat JE & Huncharek MS, 2008;Wehner AP, 1998a;Zazenski RJ, 1998)   The crystal structure of chrysotile asbestos, for example, is a two-layer silica-brucite sheet forming tiny fibrils with relatively water-soluble, hydrophilic outer surfaces. The aspect ratio of the fibrils is generally considered to be critical for the carcinogenicity of asbestos. In contrast, talc consists of three-layer silica-brucite-silica sheets stacked together to form small platy packets with highly insoluble, hydrophobic surfaces. Cosmetic talc does not contain fibrils.

Alternatively, some researchers have suggested that talc in the ovaries could cause cancer, indirectly, through a talc-induced inflammatory response, analogous to the action of asbestos fibers in the lungs.(Ness RB & Cottreau C, 1999)   However, pelvic inflammatory diseases, such as endometriosis, peritonitis, and tubo-ovarian abscess formation, have not been found to be associated with increased risks of ovarian cancer. In addition, anti-inflammatory drug use did not reduce ovarian cancer risk estimates in several studies.(Bonovas S *et al.*, 2005;Merritt MA *et al.*, 2008)

Most recently, one group proposed that elevated expression of anti-MUC1 antibodies induced by perineal talc in the peritoneal lymph nodes might explain the reported associations between talc exposure and ovarian cancer.(Cramer DW *et al.*, 2005)   However, the application of talc powder to other parts of the body appears to induce anti-MUC1 antibody expression as well, and elevated anti-MUC1 antibody levels generally have not been associated with increased risks of ovarian cancer. Thus, this proposal remains highly speculative.

Talc is commonly used clinically as the active agent for pleurodesis to treat malignant and benign pleural effusions. This procedure involves introducing a talc slurry through a tube directly into the pleural space to induce fibrogenesis, which

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obliterates the space and prevents the accumulation of fluid between the pleural layers. No increase in the incidences of lung or pleural cancers has been found in multiple clinical studies involving hundreds of patients followed for decades after pleurodesis.(Chappell AG *et al.*, 1979;Weissberg D & Kaufman M, 1986;Huncharek M *et al.*, 2007)

The results of these follow-up clinical studies are consistent with epidemiological investigations reporting no statistically significant increase in mortality from lung cancer or mesothelioma in workers occupationally exposed to "pure" talc.(Rubino GF *et al.*, 1976;Wergeland E *et al.*, 1990;Leophonte P & Didier A, 1990) As stated by one author, "the likelyhood that talc could selectively induce ovarian cancer and not lung cancer at exposure concentrations orders of magnitude lower than that experienced in occupational settings, argue against its toxicity."(Muscat JE & Huncharek MS, 2008) Others have noted the absence of reports suggesting that talc inhalation is associated with either lung cancers or mesothelioma in consumers(Wehner AP, 1998a).

Accordingly, animal cancer bioassays using rodents exposed to high concentrations of talc in air indicate that talc is not a primary carcinogen. The NTP life-time inhalation carcinogenesis bioassay found a statistically significant increase in the incidence of alveolar/bronchiolar adenomas and carcinomas in female rats exposed to the highest concentration of talc (18 mg/m^3), compared to the controls.(National Toxicology Program (NTP), 1993) However, the NTP study found no ovarian lesions in female mice or rats, and no malignant respiratory-tract lesions in male rats or male or female mice at either exposure concentration (6 mg/m^3 and 18 mg/m^3). Further, the lung cancers in the female rats exposed to 18 mg/m^3 talc can be plausibly attributed to the effects of chronic pulmonary particle overload, rather to the possible carcinogenicity of talc.(Oberdörster G, 1995;Morrow PE *et al.*, 1996) The use of micronized talc in the NTP study, rather than a preparation having the substantially larger particle-size distributions of cosmetic-grade talc, probably contributed significantly to pulmonary overloading in the test animals.

The latter interpretation of the results of the NTP bioassay is supported by the results of an earlier lifetime inhalation study in hamsters. The animals were exposed to a talc baby powder aerosol at rates that exceeded those measured in infant-dusting simulations (mg-h/m^3) by 30 to 1,700 fold.(Wehner AP *et al.*, 1977c;Wehner AP, 1998a) Specifically, groups of 50 male and 50 female hamsters were exposed to the aerosol (mean concentration of respirable fraction approximately 8 mg/m^3; mass mean aerodynamic diameter 6 μm) for 3, 30 or 150 min/day until they died or for 300 days, whichever came first. The exposures had no effect on the type, incidence or degree of histopathological findings in the lungs or other tissues examined, or on body weight, survival, or any other parameter evaluated, compared with the sham-exposed controls.

Further, the injection of talc into the ovaries of rats in one study (100 μl/ovary of 100 mg 0.4-14 μm platy talc crystals/ml buffered saline) induced no cancers(Hamilton TC *et al.*, 1984)

Critical issues that call into question the validity of the statistically-significant associations reported in some of the epidemiological studies include:

- Absence of persuasive evidence that talc can migrate from the perineum to the ovaries;
- Lack of consistent statistically-significant positive associations across studies;
- Uniformly small relative risk estimates in studies reporting positive associations;
- Failure to rule out plausible alternative explanations of the statistically-significant results, including biases, confounding risk factors, and exposure misclassifications;
- Absence of statistically-significant associations between ovarian cancer and using talc-dusted diaphragms or condoms;
- Overall lack of positive exposure-effect relationships;
- Inverse trends for both duration of use and frequency of use in some studies;
- Absence of a plausible biologic mechanism;
- Lack of credible, defensible evidence of carcinogenicity from the results of epidemiological studies of occupational exposures and animal bioassays.

<h3 style="text-align:center">Co-Carcinogenicity</h3>

Parenteral
Intratracheal
Talc may be co-carcinogenic when administered intratracheally with B[a]P. Groups of 24 male and 24 female Syrian golden hamsters were dosed weekly with intratracheal instillations of 3 mg talc or 3 mg talc + 3 mg B[a]P in 0.2 ml saline for 18 wks.(Stenbäck F & Rowland J, 1978) The chemical composition of talc was 61-63% silicon dioxide, 32-34%

<p style="text-align:center">24</p>

magnesium dioxide, and 0.85-1.06% other dusts; the particle size distribution was 93% <25 μ, 86% <16 μ, 54% <10 μ, 26% <5 μ, and 2% <1 μ. Control groups were given saline only or were untreated. The animals were allowed to live until natural death or until killed when moribund. Animals given talc alone had the shortest lifespan, 46 wks, compared to the saline controls (55 wks) or talc + B[a]P animals (52 wks). The talc-only treated animals showed signs of minor respiratory disorders during treatment. In these animals, at necropsy, microscopic examination revealed pulmonary congestion and interstitial fibrosis, but no detectable dust deposits, granulomas, or mesothelial proliferations were seen. There were three tumor-bearing animals; no tumors were in the respiratory tract, although three benign lung lesions (mucoepidermoid lesions) were reported. Two forestomach papillomas, 1 thyroid adenoma, and 1 adrenal adenoma were also found. The number of tumor-bearing animals in the talc + B[a]P group was much greater; 36 animals had tumors, 33 of which were respiratory. Alveolar fibrosis and inflammation were observed in this group of animals, and tumors were found throughout the respiratory tract, primarily in the lungs. Alveolar tumors were mostly adenocarcinomas, but many of the tumors of the larynx, trachea, and lungs were squamous epithelial tumors, papillomas, or squamous cell carcinomas; 39 benign lung lesions were also reported. In addition to the tumors in the respiratory tract, 11 forestomach papillomas, 1 lymphoma, and 1 melanoma were reported for this group. Respiratory tract tumors were not found in any of the control animals, but two saline treated controls and five untreated controls had tumors, with two forestomach papillomas in saline-treated animals and two lymphomas and four forestomach papillomas in untreated controls. The effects of instillation of B[a]P alone were not investigated in this study, but the researchers noted that B[a]P is a polycyclic hydrocarbon that has a carcinogenic effect in the lungs.

In a lifetime study, groups of 48 Syrian golden hamsters were dosed once weekly with intratracheal instillations of 3 mg talc, 3 mg talc + 3 mg B[a]P, or 3 mg B[a]P only.(Stenbäck F *et al.*, 1986) The talc was defined as USP grade and contained 64-66% SiO_2, 34-36% MgO_2, and <1% other dusts; the particle size distribution of talc + B[a]P was 93% <25 μm, 54% <10 μm, 26% <5 μm, and 2% <1 μm. Dust-laden macrophages and an accumulation of interstitial cells and were observed in the talc-treated animals. A proliferation of fibrillar material, primarily elastic fibers, and multinucleated giant cells with foreign material were observed in the alveolar and interstitial spaces, and occasional accumulation of proteinaceous exudate was seen in the alveoli. No increase in collagen fibers or granulomas was observed. The severity of premalignant lesions was evaluated in the tracheobronchial and alveolar zone of the animals. No dysplasia was observed with talc alone in either zone and only slight dysplasia was seen in these zones with B[a]P only, but severe dysplasia was seen in both zones with talc + B[a]P. Slight metaplasia was observed in the tracheobronchial zone of talc-treated animals; moderate metaplasia was seen in the talc + B[a]P animals and the B[a]P only animals. Epithelial destruction in the tracheobronchial zone was moderate in all three groups. In the alveolar zone, moderate hyperplasia was observed in the talc-treated animals but only slight hyperplasia in the B[a]P only-treated animals; the severity of this lesion was severe in the talc + B[a]P animals. Talc produced a co-carcinogenic effect, inducing tumors in both the upper and lower respiratory tract, and the talc + B[a]P animals had a high incidence of peripheral tumors. Talc + B[a]P induced an increase in the number of squamous carcinomas compared to B[a]P only; adenocarcinomas predominated in the talc + B[a]P group. (The number of lesions induced by talc alone was not given).

IRRITATION AND SENSITIZATION
Sensitization
Non-Human

Talc was not a sensitizer in female Hartley guinea pigs.(Grant JBF *et al.*, 1976) Female Hartley guinea pigs (number not stated) received an intradermal injection of 10 mg sterile talc in an emulsion of 0.5 ml sterile saline and 0.5 ml Freund's complete adjuvant; six guinea pigs were dosed in the same manner with 10 mg starch glove powder. (Chemical characterization data were not provided; the talc was British Pharmacopeia-grade). Eleven control animals were injected with the emulsion only. Skin tests were then performed at various intervals by challenging all animals with suspensions starch glove powder in one ear and talc in the other. Slight cutaneous thickening was observed in all control animals 24 h after challenge with both suspensions, and the responses were similar to both talc and the starch. The response to challenge with talc in the talc test group was similar to that seen in the controls. Animals in the starch group had a statistically significantly greater response to the starch challenge compared to controls.

SUMMARY

Talc is a sheet silicate that belongs to the silicate subclass phyllosilicates. In its purest form, it is a mineral that corresponds to the chemical formula for hydrous magnesium silicate; commercially, it contains varying amounts of other minerals naturally found in the ore. Only talc that does not contain asbestiform fibers is used in cosmetics, and cosmetic talc

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must consist of a minimum of 90% hydrated magnesium silicate, with the remainder consisting of naturally associated minerals such as calcite, chlorite, dolomite, kaolin, and magnesite; it contains no detectable fibrous, asbestos minerals.

In 2012, FDA VCRP data indicated that talc was used in over 2800 cosmetic formulations and according to concentration of use data received in response to a Council survey, talc is used at up to 100% in cosmetic formulations. Talc is used in almost every category of cosmetic product, and it is used in products that may be applied to baby skin, products that could be incidentally ingested, products used near the eye area or mucous membranes, and in products that are sprayed. The particle size of talc raw material varies widely by product type and by manufacturer.

Talc has many commercial uses and it has pharmaceutical use. It is used as a color additive in drugs and is exempt from certification. Sterile talc is approved as a sclerosing agent. Talc is not allowed for use on the surface of medical gloves. It is used in the production of foods, and it is approved as an indirect food additive as a color.

Syrian golden hamsters received a single 2-h nose-only exposure to talc tested as a commercial baby powder (chemical characteristics unknown), with a median aerodynamic diameter of 6.4-6.9 µm. The biological half-life of the talc deposited in the lungs was 7-10 days. No translocation from the respiratory tract to other tissues was found in this study, and the clearance of talc from the lungs was complete within 4 months after exposure. Following oral administration of $[^3H]$talc to mice, rats, and guinea pigs, most of the radioactivity was excreted in the feces. Wistar rats were used to determine the systemic distribution of talc following intrapleural administration; the study suggested that talc is absorbed very rapidly through the pleura, reaching the systemic circulation with deposition in other organs within 24 h of administration, and that the distribution is not dose-related.

The acute oral LD_{50} of rats was 920 mg/kg in one study and >5000 mg/kg in another. In a study in which mice were placed in a box with circulated baby powder, the mice removed after 30 or 60 min recovered completely and the mice removed after 90 or 120 min died; the chemical composition, amount of powder, and size of the box were not specified. In rats dosed with a single bilateral intrabursal injection of 100 mg/ml talc and killed 1-18 mos after dosing, one or both ovaries of rats dosed with talc were cystic in appearance at all time periods; the cystic structures were due to distention of the bursal sac. Foreign body granulomas, without surrounding inflammation, were seen in the cortical area of five of the injected ovaries, and talc was observed in the granulomas. In rats, a granulomatous reaction in which foreign-body giant cells containing refractile materials was observed without fibrosis in the rats at 1 mo and at 3 mos after a single i.p. injection of 50 mg/kg non-fibrous talc. In rats dosed with a single i.p. injection of 0.02, 0.1, or 0.5 g talc in 5 ml normal saline, clusters of foci of inflammatory cells were observed scattered on the surface of the peritoneum and talc particles were seen in the center of each focus of inflammatory cells.

There were no remarkable results found in studies examining the cellular effect of talc, such as cytotoxicity assays, assays examining the effect of talc on cell viability, or studies on the induction of apoptosis (among others).

Dermal application of talc to shaved rabbit skin for 6 wks resulted in dryness of the skin and skin erosion. Oral administration to rats for 5 days produced minimal toxicity. In inhalation studies, exposure of mice and rats for 4 wks (25 µm particle size) resulted in macrophages in the alveolar space, with more found in the mice than the rats. In rats exposed for 3, 6, or 12 mos, minimal to slight fibrosis resulted. In hamsters, exposure to baby powder (95% talc; 4.9 -6.0 µM) did not result in clinical toxicity, and no trends were observed. Intrapleural administration of talc (25 µm) to rats did not result in mesotheliomas; granulomas at the injection site were common. Infections occurred, but no neoplastic or perineal changes, when talc was instilled intravaginally or perineally in rats. Upon intravenous (i.v.) injection of talc (<5 µm) once weekly for 3 wks, talc was found in the lungs and the liver throughout the study.

Talc is non- or slightly irritating to rabbit eyes. In a female subject that presented with a foreign body sensation and inflammation of the conjunctiva of both eyes, a diagnosis of foreign body granuloma secondary to talc was made.

Application of talc to wounded skin can give rise to scab formation, possible infection, and foreign body granulomas in the dermis.

Talc has a TLV (respirable fraction) of 2 mg/m^3 as a TWA. Human pulmonary effects of talc include diffuse interstitial fibrosis and progressive massive fibrosis (often called complicated pneumoconiosis). In occupational exposure studies, statistically significantly elevated SMRs for silicosis and silico-tuberculosis were observed in an early study of talc miners and millers in the Italian Piedmont region exposed to talc that contained no fibrous material except for tremolite micro-inclusions; SMRs were statistically significantly reduced for malignant neoplasms, including lung, bronchial and tracheal cancers A follow-up of this group found statistically significant increases in mortality, which were attributable primarily to non-

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malignant respiratory diseases among the miners. A cohort study of talc miners and millers exposed to talc and magnesite containing trace amounts of quartz, tremolite, and anthophylite found no statistically significant SMRs for all causes, all cancers, or diseases of the circulatory system or respiratory tract. The results of several other epidemiological studies were likely confounded by the presence of up to 3% silica or 6% actinolite in the talc, exposures to high concentrations of silica with or without exposures to fibrous talc (tremolite), or concurrent exposures to radon daughters. A meta-analysis of studies of miners and millers who worked with non-asbestiform talc reported summary SMRs for lung cancer of 0.92 (95% CI: 0.67-1.25) for millers in five countries exposed to high levels of talc without exposure to other occupational carcinogens, and 1.2 (95% CI: 0.86-1.63) for miners in 3 countries exposed to high levels of talc as well as to silica or radon and radon daughters. Studies examining radiological, lung-function and clinical parameters in talc miners and millers and rubber workers founs dome statistically significant changes.

In exposure-during-cosmetic use studies, the researchers noted that there was a wide variation in talcing times and methods, often by the same volunteer during different applications. Reported talcing times ranged form 17 sec to 31 sec. Endobronchitis and airway stricture was reported in one case in which a subject applied large amounts of talc powder to her face. In another case, a chronic pulmonary granulomatous reaction was reported in a subject who applied "non-powdering talc" to her face for 20 yrs, followed by use of talcum powder 2-3 times a day for a 10-yr period.

Talc administered orally as a suspension in corn oil was not a developmental toxicant in mice (16-1600 mg/kg on days 6-15 of gestation), rats (16-1600 mg/kg on days 6-15 of gestation), hamsters (12-1200 mg/kg on days 6-10 of gestation), or rabbits (9-900 mg/kg on days 6-18 of gestation). No dose response or time-trend pattern was observed in rats that received a single oral dose or once daily dose for 5 days of 30-5000 mg/kg talc.

In vitro, talc was not genotoxic in an UDS assay (10, 20, or 50 $\mu g/cm^2$) or a SCE assay (2, 5, 10, and 15 $\mu g/cm^2$) in rat pleural mesothelial cells. Talc was not genotoxic in a host-mediated assay in mice dosed by gavage with a single dose or once daily for 5 days with 30, 300, 3000, or 5000 mg/kg talc or cytogenetic assay in rats dosed by gavage once daily for 5 days with 30, 300, 3000 , or 5000 mg/kg talc. Talc was also not genotoxic in a dominant lethal assay in which rats were dosed by gavage with a single dose or once daily for 5 days with 30, 300, 3000, or 5000 mg/kg talc.

A bioassay using mice and rats performed by the NTP to determine the carcinogenic potential of non-asbestiform, cosmetic-grade micro-talc following exposure by inhalation, and it was concluded there was *no evidence of carcinogenic activity* in male or female B6C3F1 mice, *some evidence of carcinogenic activity* in male F344/rats, and *clear evidence of carcinogenic activity* in female F344/N rats. The mice were exposed to 6 mg/m³ (MMAD 3.3 ± 1.9 μm) or 18 mg/m³ (MMAD 3.6 ± 2.0 μm) talc for 6 h/day, 5 days/wk, for 103-104 wks. The rats were exposed to 6 mg/m³ (MMAD 2.7 ± 1.9 μm) or 18 mg/m³ (MMAD 3.2 ± 1.9 μm) talc for 6 h/day, 5 days/wk, for 113 wks (males) or 122 wks (females). Concerns have been raised about this study, including concern that micronized talc was used rather than cosmetic talc resulting in a significantly reduced particle size, that aerosol concentrations were not properly controlled, that proper procedures for dose selection were not followed resulting in the MTD being exceeded at both concentrations tested, and that the results obtained were most likely due to particle overload in the lungs.

Talc did not induce pleural tumors in rats following intrapleural injection of 20 mg talc (mean size 2.6 ± 2.3 μm). Few tumors developed in rats given weekly i.p. injections of 25 mg talc suspended in 2 ml saline weekly for 4 wks. In mice given an i.p. injection of 20 mg of UV-sterilized commercial talc in 1 ml saline,, 12.5% of than animals developed mesothelioma.

Results of studies examining particulate migration in the genital tract have been mixed. In one study using monkeys, there was no translocation of bone black from the vagina to the oviducts, however in a human study, researchers concluded that there was evidence of migration of carbon particles to the uterus of the Fallopian tubes and ovaries; another group of researchers stated that this finding may be misleading because only one radioactive label was used. In a study in rabbits, the number of large starch particles in peritoneal cavity rinsate was greater in test groups that were exposed intravaginally to glove lubricant than in controls. In human subjects, it appeared that starch particles migrated to the cervix and uterus.

In studies specific to talc migration, mixed results have also been reported. In rats, talc was found in the ovaries of rats dosed intrauterinally with talc; in rats exposed with a single intravaginal dose, talc was found in the ovaries 4 days after dosing, but not 24 or 48 h after dosing. Talc was not found in the ovaries of rabbits given six daily intravaginal doses, and there was no translocation of talc from the vaginas of monkeys to the ovaries, oviducts, or the body of the uterus. In humans, talc particles were found in 10/13 ovarian tumors and 12/21 cervical tumors; the particles found in the ovarian tumors were

generally smaller than those in the cervical tumors, i.e., 1000 Å to 2 μ versus up to 5 μ, respectively. In women with benign ovarian neoplasms, half of whom applied talc to the perineum or underwear, there was no linear relationship between ovarian talc powder burden or exposure, and neither light nor electron microscopy results correlated with controls. Electron micros- copy counts were 0 for about half of the subjects exposed to talc as well as half of the controls; talc was observed with light microscopy in all subjects exposed to talc and 11/12 of the controls.

Numerous epidemiological studies have been performed examining the risk of ovarian cancer following talc expo- sure. Many physiological, sociological, and exposure factors have been linked to ovarian cancer, a number of them with a stronger association than the hygienic use of cosmetic talc, but causality has not been established for any of them. The re- sults of several epidemiological studies suggested that medical procedures expected to prevent the translocation of talc to the ovaries, such as tubal ligation or hysterectomy, reduce the relative risk estimates associated with talc use. The use of talc- dusted condoms or diaphragms (including diaphragms known to have been stored in talc powder), which would clearly result in exposure close to the cervical opening, was not associated with an increased estimate of relative risk of ovarian cancer.

Talc may be co-carcinogenic when administered intratracheally with B[a]P. In a study in which Syrian golden hamsters were dosed weekly with intratracheal instillations of 3 mg talc or 3 mg talc + 3 mg B[a]P in 0.2 ml saline for 18 wks, it appears that talc had a co-carcinogenic effect in inducing respiratory tumors. In a lifetime study in which hamsters were dosed once weekly with intratracheal instillations of 3 mg talc, 3 mg talc + 3 mg B[a]P, or 3 mg B[a]P only, talc + B[a]P induced an increase in the number of squamous carcinomas when compared to B[a]P only; adenocarcinomas predominated in the talc + B[a]P group.

Talc was not a sensitizer in female Hartley guinea pigs.

DISCUSSION

To be developed.

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Tables

Table 1. Physical and chemical properties

Property	Description	Reference
physical appearance	essentially white, odorless, fine powder ranges from snow-white to black, including greenish-gray and shades of green, pink, and red white, apple-green, gray powder; pearly or greasy luster	(Nikitakis JM & McEwen GN Jr (eds), 1990a) (Piniazkiewic RJ *et al.*, 1994) (2007)
molecular weight	379.27	(2012b)
Mohs' hardness	1 1-1.5 (may be harder when impure)	(1999) (Ross M, 1984;2007)
crystal system	triclinic	(Ross M, 1984)
morphology	perfect (001) cleavage	(Ross M, 1984)
melting point	900-1000°C 1500°C	(National Institute for Occupational Safety and Health (NIOSH), 2001b) (EUROTALC, 2012)
pH	8.8-9.5 7.7±0.5	(Harvey AM, 1988) (Schlossman ML, 2009)
density	2.7 g/cm^3	(National Institute for Occupational Safety and Health (NIOSH), 2001c)
surface area	<20 m^2/g (B.E.T. method)	(Hamer DH *et al.*, 1976)
solubility	insoluble in water, cold acids, or in alkalies; soluble in hot concentrated phosphoric acid	(2012c)
brightness (GE)	75-95	(Harvey AM, 1988)

optical properties
    n$_x$
    n$_z$
	
	1.539-1.550
	1.589-1.600
		(Rohl AN & Langer AM, 1974)

indices of refraction	$\alpha = 1.539 - 1.550$ $\beta = 1.589 - 1.594$ $\gamma = 1.589 - 1.600$	(World Health Organization (WHO) International Agency for Research on Cancer (IARC), 2010)

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Table 2. Frequency and concentration of use – summary by exposure type and complete table in FDA format

	Number of Uses(Food and Drug Administration (FDA), 2012a)	Maximum Concentration of Use (%) (Personal Care Products Council, 2010)
Totals*	**2877**	**0.0005-100**
Duration of Use		
Leave-On	*2705*	*0.002-100*
Rinse-Off	*154*	*0.0005-70*
Diluted for (Bath) Use	*18*	*0.001-88*
Presented in complete FDA VCRP format		
Baby Shampoos	NR	7
Baby Lotions, Oils, Powders, Creams	9	99
Bath Oils, Tablets, and Salts	17	1-88
Bubble Baths	NR	0.4-2
Bath Capsules	1	NR
Other Bath Preparations	NR	0.001
Eyebrow Pencil	43	0.01-79
Eyeliner	101	0.1-90
Eye Shadow	869	20-100
Eye Lotion	13	2
Mascara	79	1-50
Other Eye Makeup Preparations	61	2-6
Perfumes	3	2
Fragrance Powders (Dusting and Talcum)	104	15-99
Sachets	3	9
Other Fragrance Preparations	10	3-9
Hair Conditioner	1	0.4
Rinses	NR	0.05
Shampoos	NR	0.04
Tonics, Dressings, and Other Hair Grooming Aids	2	10
Other Hair Preparations	1	NR
Hair Dyes and Colors	NR	0.4-13
Other Hair Coloring Preparations	1	6
Blushers	290	48-94
Face Powders	500	20-100
Foundations	201	12-76 (not spray)(Personal Care Products Councils, 2012) 1-6 (aerosol spray)
Leg and Body Paints	3	2 (aerosol spray)(Personal Care Products Councils, 2012)
Lipstick	54	3-74
Makeup Bases	44	36 (not spray)(Personal Care Products Councils, 2012) 35 (aerosol spray)
Rouges	13	NR
Makeup Fixatives	11	10
Other Makeup Preparations	102	0.8-85
Basecoats and Undercoats	5	1-7
Cuticle Softeners	1	0.004-18
Nail Creams and Lotions	NR	2
Nail Polish and Enamel	7	0.002-11
Other Manicuring Preparations	1	35
Dentifrices	1	NR
Other Oral Hygiene Products	NR	11
Bath Soaps and Detergents	51	0.001-70
Deodorant (Underarm)	18	6-85 (not spray)(Personal Care Products Councils, 2012) 1-30 (aerosol spray)
Other Personal Cleanliness Products	29	0.03-20
Aftershave Lotion	1	14
Men's Talcum	3	96
Shaving Soap (cakes, sticks, etc)	NR	0.04
Other Shaving Preparations	2	NR
Cleansing	37	0.0005-0.005
Depilatories	4	NR
Face and Neck Creams, Lotions, and Powders (excl. shaving)	32	40 (not spray)(Personal Care Products Councils, 2012) 0.4 (spray)
Body and Hand Creams, Lotions, and Powders (excl. shaving)	18	96 (not spray)(Personal Care Products Councils, 2012) 0.3 (spray)

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Table 2. Frequency and concentration of use – summary by exposure type and complete table in FDA format

	Number of Uses (Food and Drug Administration (FDA), 2012a)	Maximum Concentration of Use (%) (Personal Care Products Council, 2010)
Foot Powders and Sprays	9	0.9-97
Moisturizing Creams, Lotions, and Powders	54	3-5
Night Creams, Lotions, and Powders	7	3
Paste Masks (Mud Packs)	28	0.2-18
Skin Fresheners	2	0.002-0.2
Other Skin Care Preparations	25	0.03-20
Suntan Gels, Creams, and Liquids	1	15-41
Indoor Tanning Preparations	5	74
Other Suntan Preparations	NR	3
Summary Information – by Exposure Type		
Eye Area	*1166*	*0.01-100*
Incidental Ingestion	*55*	*3-74*
Incidental Inhalation – Spray	*46[a]*	*0.3-35%[b] (Personal Care Products Councils, 2012)*
Incidental Inhalation - Powder	*616*	*2-100*
Dermal Contact	*2724*	*0.0005-100*
Deodorants (Underarm)	*18*	*2-75*
Hair – Non-Coloring	*4*	*0.04-10*
Hair –Coloring	*1*	*0.4-13*
Nail	*14*	*0.002-35*
Mucous Membrane	*153*	*0.001-88*
Baby Products	*9*	*7-99*

*The sum of all exposure types may not equal the sum of total uses.

[a]It is not known whether or not the product is a spray.

[b]A survey was completed to assess the use of talc in spray products in which companies were asked whether or not they used talc in spray products, and if so, what is the maximum use concentrate of talc in the spray product and in products that are not sprays in the same FDA product category

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Table 3. Cellular Effects

Talc/Composition	Particle Size	Test System	Procedure	Results	Reference
talc, non-fibrous	not specified	peritoneal and alveolar macrophages	cytotoxicity assay	low cytotoxicity - cytotoxicity of talc and other dusts was compared to induction of fibrosis following i.p. injection in Wistar rats; there was a good correlation between cytotoxicity of dust to macrophages in vitro and fibrogenicity in vivo	(Styles JA & Tabershaw IR, 1973)
talc; cosmetic grade (5 samples) 1 sample with 30-35% chlorite 1 sample with 1-3% amphiboles	4 cosmetic-grade samples: 80-91.5% of the respirable dust (1.94-7.36% of the sample) was <7.5 μm; micronized cosmetic talc: 93.5% of the respirable dust (19.46% of the sample) was <7.5 μm; chlorite and amphiboles samples: 3.62 and 9.76% respirable dust, respectively	unstimulated mouse peritoneal macrophages	cytotoxicity of the 7 talc samples was determined and compared to that of a standard quartz sample and a non-fibrogenic dust (magnetite)	- all 7 talc samples were cytotoxic to macrophages, but far less so that the quartz sample; quartz content of each talc (which ranges from <0.2 – 0.7%) did not seem to affect cytotoxicity - the activity of each of talc sample was similar to that of the others and not related to particle-size distribution - the talc samples induced a statistically significantly greater release of LDH compared to magnetite, and they caused a slightly, but significantly greater release of lysosomal β-glucuronidase than of LDH from the macrophages	(Davies R et al., 1983)
talc, Italian 00000	≤10 μm	rabbit lung fibroblasts	ingestion of talc particles by fibroblasts was determined	- talc was taken up by fibroblasts, and the talc particles were observed in the cells	(Henderson WJ et al., 1975)
talc, Italian	not provided	V79-4 Chinese hamster lung cells; human alveolar Type II lung cells (A549)	cytotoxicity was determined	- 50 μg/ml was not cytotoxic to V79-4 cells - talc inhibited the growth of A549 cells, the inhibitory concentrations and extent of the inhibition were not reported	(Chamberlain M & Brown RC, 1978)
talc; composition not provided, but assumed to be cosmetic grade	not provided	OSE2a; GC1a	effect of talc on cell viability; cell cultures were incubated with 0-500 μg/ml talc for 24 – 120 h	- OSE2a cells: cell viability was statistically significantly increased with 5 μg/ml talc at 24 h and statistically significantly decreased at 200 μg/ml after 72 h and at 500 μg/ml after 24 and 72 h - GC1a cells: viability was statistically significantly increased at 5, 20, and 100 μg/ml talc after 72 h and was statistically significantly decreased at 500 μg/ml after 24 h	(BuzZard AR & Lau BHS, 2007)
as above		OSE2a; GC1a	neoplastic transformation assay	- OSE2a cells: compared to untreated controls, a statistically significant increase in the number of transformed colonies was seen at 5 and 20 μg/ml, but a statistically significant decrease in transformed cells was seen at 100 μg/ml - GC1a cells: 5, 20, and 100 μg/ml talc caused a statistically significant increase in transformed colonies	
as above		OSE2a; GC1a; human PMN	ability to induce ROS	- OSE2a and GC1a cells: initial concentration-dependent decrease in ROS generation (at 24 h); ROS generation then increased in both cell lines, and the increase was statistically significant at 20 μg/ml at 72 and 120 h and at 50 μg/ml at 120 h in the OSE2a cells and at 0.5, 20, and 20 μg/ml at 72 and 120 h and at 5 and 100 μg/ml at 120 h compared to the 24 h value - PMN: a concentration-dependent increase in the induction of ROS, and the increase was statistically significant at 0.5, 5, 20, and 50 μg/ml at 24 h and at 100 and 500 μg/ml at 24 and 72 h; the maximum ROS generation in PMN was seen at 500 μg/ml talc at 24 h, and the increase was 4-fold compared to untreated controls	

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Table 3. Cellular Effects

Talc/Composition	Particle Size	Test System	Procedure	Results	Reference
talc, composition not provided	2 μm	PMC; LAC (A549)	cells were exposed to 25, 50, and 75 μg/ml talc suspended in endotoxin-free normal saline for 24, 48, and 72 h to determine the ability to induce apoptosis	- talc induced apoptosis of LAC in a concentration- and time-dependent manner, but talc did not induce apoptosis of PMCs	(Lee P et al., 2010)
talc in endotoxin-free water (assumed to be pharmaceutical-grade)	2.1 μm	PMC	confluent PMCs were exposed to 2-64 μg/cm² sterilized talc for 24 h	- PMC viability decreased with increasing talc concentrations; viability with 64 μg/cm² was 75% - all concentrations of talc significantly stimulated the release of IL-8 and MCP-1over that of unstimulated cells - talc significantly increased chemotactic activity for neutrophils and monocytes compared to unstimulated cells; the addition of excess IL-8 or MCP-1 antibody decreased chemotaxis, but it did not return entirely to the level of unstimulated cells - talc induced C-X-C and C-C chemokine expression; the transcriptional response of IL-8 and MCP-1 expression was enhanced - talc induced intercellular adhesion molecule-1 (ICAM-1) expression on PMC	(Nasreen N et al., 1998)
as above			confluent PMC were exposed to 4 μg/cm² sterilized talc for 1-72 h; controls were exposed to 4 μg/cm² glass microspheres	- talc stimulated production of IL-8 and MCP-1 to a greater degree than did glass beads	
talc in endotoxin-free 0.89% normal saline (4.0 mg/ml) (assumed to be pharmaceutical-grade)	2.1 μm	PMC; MMC	confluent cells were exposed to 0-24 μg/cm² sterilized talc in serum-free medium for 72 h; controls were exposed to 4 μg/cm² glass microspheres; viability was determined	- PMC viability was 93% with 24 μg/cm² talc - MMC viability decreased with increasing concentration of talc; with 24 μg/cm² talc, viability ranged from 62-84% depending on the cell line	(Nasreen N et al., 2000)
as above			confluent cells were exposed to 0-24 μg/cm² talc in serum-free media for 24 h; apoptosis was determined TUNEL	- PMC did not show significant apoptosis with varying concentrations - talc induced apoptosis in MMC in a concentration-dependent manner; significance was noted at 6 μg/cm², and then plateaued	
as above			PMC/MMC confluent cells were exposed to 4 μg/cm² talc for 24-72 h; 6 μg/cm² glass microspheres were used as controls; TUNEL and DNA electrophoresis was performed	- apoptosis of PMC cells by talc did not increase with time - talc induced apoptosis in MMC in a time-dependent manner; the increase over time was statistically significant compared to controls - a typical DNA ladder indicative of apoptosis was seen with MMC but not PMC	
talc, non-fibrous; mean surface area – 16.03 m²/g	1.1 μm	LP9; IOSE	effect on cell viability was determined LP9 cells: changes in gene expression were measured with 15 and 75 μm/cm² at 8 h and 15 μm/cm² at 24 h; IOSE cells: changes in gene expression were measured with 75 μm/cm² at 8 and 24 h	- non-toxic to IOSE cells at up to 75 μm²/cm² and to LP9 cells at ≤163 μm²/cm²; toxicity seen with ≥243 μm²/cm² - LP9 cells: low conc. of talc increased expression of 1 gene at 8 h and no changes at 24 h, while elevated expression levels of 30 genes were seen at 8 h with high conc. - IOSE: no significant mRNA changes	(Shukla A et al., 2009)

Abbreviations: GC1a = normal ovarian granulosa cells; IL-8 = interleukin-8; IOSE = human ovarian epithelial cells; LAC = lung adenocarcinoma cell line; LDH = lactate dehydrogenase; LP9 = human mesothelial LP9/TERT-1 cells; MCP-1 = monocyte chemotactic protein-1; MMC = human malignant mesothelioma cells; OSE2a = normal ovarian epithelial cells; PMC = human pleural mesothelial cells; PMN = polymorphonuclear neutrophils; ROS = reactive oxidative species; TUNEL = terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end labeling

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Table 4. Repeated Dose Toxicity Studies

Talc/Composition	Particle Size	Dose/Conc	Animals; #/grp	Dose Duration	Procedure	Results	Reference
DERMAL							
commercial talcum powder; composition not provided	not provided	amount applied was not specified	domestic rabbits 5M/5F (test grp) 4M/4F (controls)	1x/day 6wks	- the powder was sprinkled on the shaved skin of the dorsal surface of the body trunk, and then spread evenly over the site - it does not state that the site was wrapped - blood chemistry values were measured at the termination of dosing	- all animals developed skin dryness - signs of skin erosion were observed - no clinical signs were observed - compared to control values: - alanine transaminase, aspartate transaminase, glutamyl transferase, amylase, and potassium ion values were statistically significantly decreased - cholesterol, high density lipoproteins, triglycerides, bilirubin, and glucose values were statistically significantly increased	(Wadaan MAM, 2009)
ORAL							
talc; composition not provided	not provided	29.6% in saline 5000 mg/kg/day	5 rats	5 days	no additional details	minimal signs of toxicity were observed	(Litton Bionetics, Inc., 1974)
Italian talc, 00000 grade; 92% talc (by wt), 3% chlorite, 1% carbonate minerals; 0.5-1% quartz	25 μm (mean particle size); upper size, 70 μm	100 mg/day in feed	Wistar rats 16M/16F (talc and chrysotile) 8M/8F (controls)	101 days over 5 mos	super-fine chrysotile asbestos (SFA chrysotile)-fed and untreated controls were used; 2 animals/group were killed 3 mos after dosing, all other animals lived until natural death	- talc: mean survival (from start of feeding), 614 days; 1 leiomyosarcoma of the stomach, 2 sarcomas of the uterus - chrysotile: mean survival, 619 days; 1 possible leiomyosarcoma of the stomach, 1 sarcoma of the uterus, 1 lymphosarcoma - controls: mean survival, 641 days; 1 adrenal adenoma	(Wagner JC et al., 1975)
INHALATION							
asbestos-free talc; 19.2-19.4% Mg	MMAD, 2.7 ± 0.1 μm; 79% of the talc by mass had an aerodynamic diameter <5 μm	target: 0, 2, 6, or 18 mg/m³ actual: 0, 2.2, 5.7, or 20.4 mg/m³	B6C3F1 mice 10M/10F	4 wks 6 h/day 5 days/wk	- multi-tiered inhalation chambers were used; animals were killed 24 h after the last exposure; lung burdens were measured in half of the animals and the other half were used for microscopic examination - this study was used to determine the exposure concentrations for a 2-yr NTP bioassay	- lung burden averaged 0, 100, 290, and 1020 μg talc/g lung for control, low, mid, and high dose, respectively; lung burdens normalized for lung wt and exposure conc: n/a, 46, 51, and 50 μg talc/g lung/mg/m³, respectively - no exposure-related abnormalities were seen at necropsy; microscopically, the only exposure-related lesion was a modest, diffuse increase in free macrophages within the alveolar space; the macrophages, which were focally aggregated, contained talc particles	(Pickrell 1A et al., 1989;National Toxicology Program (NTP), 1993)

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Table 4. Repeated Dose Toxicity Studies

Talc/Composition	Particle Size	Dose/Conc	Dose Duration	Procedure	Animals: #/grp	Results	Reference
asbestos-free talc; 19.2-19.4% Mg	MMAD, 3.3 ± 0.1μm; 79% of the talc by mass had an aerodynamic diameter <5 μm	target: 0, 2, 6, or 18 mg/m³ actual: 0, 2.3, 4.3, or 17 mg/m³	4 wks 6 h/day 5 days/wk	as above - this study was used to determine the exposure concentrations for a lifetime NTP study	F344/Crl rats 10M/10F	- lung burden averaged 3, 70, 170, and 720 μg talc/g lung for control, low, mid, and high dose, respectively; lung burdens normalized for lung wt and exposure conc: n/a, 30, 39, and 42 μg talc/g lung/mg/m3, respectively; normalized low dose value was statistically significantly greater than mid and high dose values - the increase in talc lung burden with exposure concentrations may be attributable to overwhelming the capacity of the respiratory tract to clear particles at 6 and 18 mg/m3 exposures - no exposure-related abnormalities were seen at necropsy; microscopically, the only exposure-related lesion was a modest, diffuse increase in free macrophages within the alveolar space; fewer macrophages were seen in the exposed rats than in the exposed mice; the diffusely scattered macrophages contained talc particles	(Pickrell JA et al., 1989;National Toxicology Program (NTP), 1993)
Italian talc, 00000 grade; 92% talc (by wt), 3% chlorite, 1% carbonate minerals; 0.5-1% quartz	25 μm (mean particle size); upper size, 70 μm	10.8 mg/m³ (mean) approximately 40% respirable	7.5 h/day 5 days/wk	animals (6/cage) were exposed to talc dust; SFA chrysotile controls were treated similarly at each time frame; untreated controls were used; some animals were killed 10 days or 1 yr after final exposure, and the remainder lived until natural death	Wistar rats	mean fibrosis scoring scale: 1 – nil; 2 – minimal; 4 – slight; 6 – moderate; 8 - severe (for use below)	(Wagner JC et al., 1975)
		cumulative 3 mos dose=4100 mg/m³h	3 mos	8 animals were killed 10 days and 8 were killed 1 yr after exposure	24M/24F	- mean fibrosis score 10 days/1 yr after talc exposure: 2.2/2.4; chrysotile: 2.8/2.2; controls: 1.8/1.6 - over 50% of the animals were alive at 28 mos	
		cumulative 6 mos dose=8200 mg/m³h	6 mos	6 animals were killed 10 days after and 4 talc and chrysotile animals and 3 control animals were killed 1 yr after exposure	12M/12F	- mean fibrosis score 10 days/1 yr after exposure - talc: 2.7/3.4; chrysotile: 3.0/3.2; controls: 1.9/1.5 - most test animals died by 28 mos; there were no lung tumors in the talc or control group and 1 adenomatosis in the chrysotile group	
		cumulative 12 mos dose=16,400 mg/m³h	12 mos	6 animals were killed 10 days after exposure and 4 talc and chrysotile animals and 3 control animals were killed 1 yr after exposure	12M/12F	- mean fibrosis score 10 days/1 yr after exposure - talc: 3.4/4.6; chrysotile: 3.2/4.2; controls: 1.3/1.9 - most test animals died by 28 mos; in the lungs, 1 adenoma was found in the talc group; 3 adenomas, 2 adenomatosis, and 1 adenocarcinoma was found in the chrysotile group; there were no lung tumors in the controls	
commercial (talc) baby powder; 95% (w/w) platy talc with trace quantities of carbonates (magnesium and dolomite) and platy chlorite and rutile	MMAD, 4.9 μm	37.1±7.4 μg/l (MTAC) respirable fraction: 9.8± 2.4 μg/l cumulative dose: 3 min: 14.6 mg·h/m³ 30 min: 146 mg·h/m³ 150 min: 732 mg·h/m³	30 days 3, 30, or 150 min/day 5 days/wk	single tier exposure; animals lived until natural death	Syrian golden hamsters, 50M/50F; controls, 25M/25F	- no statistically significant difference in survival time among groups, but there was a significant difference btwn males and females within grps; no clinical signs of toxicity to talc - the type, incidence, and severity of lesions indicated no trend toward a dose-response and no statistically significant differences between exposed and control groups	(Wehner AP et al., 1977c)

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Table 4. Repeated Dose Toxicity Studies

Talc/Composition	Particle Size	Dose/Conc	Dose Duration	Procedure	Animals; #/grp	Results	Reference
	MMAD, 6.0 μm	27.4±3.4 μg/l (MTAC) respirable fraction: 8.1±1.0 μg/l 30 min: 1210 mg·h/m³ 150 min: 6060 mg·h/m³	until natural death or 300 days (max); 30 or 150 min/day 5 days/wk	single tier exposure; animals lived until natural death	Syrian golden hamsters; 50M/50F 25M/25F controls	- no statistically significant difference in survival time among grps, but there was a significant difference btwn males and females within all grps; no clinical signs of toxicity to talc - the type, incidence, and severity of lesions indicated no trend toward a dose-response and no statistically significant differences between exposed and control groups; the incidence of focal alveolar cell hyperplasia (25% in treated grps; 10% in controls) appeared to be affected by treatment, but a two-way weighted analysis showed no significant association	(European Commission, 2000)
talc; "technical" or "pharmaceutical" grade	not provided	30-383 mg/m³	9 mos; 6 h/day, 6 days/wk	details were not provided	rats; number not provided	None of the animals died as a specific consequence of exposure.	
INTRAPLEURAL							
Italian talc, 00000 grade; 92% talc (by wt), 3% chlorite, 1% carbonate minerals; 0.5-1% quartz	25 μm (mean particle size); upper size, 70 μm	20 mg in physiological saline; 50 mg/ml	until natural death	injection into the right pleural cavity; saline and SFA chrysotile controls were used	Wistar rats 24 M/24 F	- talc: mean survival, 655 days; no mesotheliomas; injection-site granulomas were common; small pulmonary adenoma in one rat, but no other lesions in the lung - saline: mean survival, 691 days; no mesotheliomas - chrysotile: mean survival, 598 days; 18 mesotheliomas	(Wagner JC et al., 1975)
INTRAVAGINAL AND PERINEAL							
talc; composition not provided	not provided	100 mg in 0.5 ml saline	daily for 3 mos	talc was administered perineally (in aerosol form) or intravaginally; controls were untreated or given intravaginal administration of saline baseline cervicovaginal smears were obtained at study initiation; all animals were killed at study termination	Sprague-Dawley rats; 7 F	- all animals in both test groups developed infection: intravaginal test group: 5 had vulvovaginitis, 6 had endometritis, 4 had pelvic infection, and 3 had ovary infections (7 ovaries) perineal group: all had vulvovaginitis, 4 had endometritis, 5 had pelvic infection, 4 had ovarian infection (8 ovaries), 2 developed salpingitis and tubal inclusion saline controls: 1 had endometritis untreated controls: 2 had vulvovaginitis and endometritis with infection in both ovaries, and 1 of these animals developed salpingitis - no neoplastic change was found	(Keskin N et al., 2009)
INTRATRACHEAL							
talc dust from a mill in Vermont; <1% quartz; no fibrous material	MMAD, 7.5 μm; percentage mass <5 μm was 26%	0.15 ml/100 g bw of the dust in 0.9% NaCl containing 13.3 μg/ml rabbit surface active material; 0, 0.15, 0.75, or 3.75 mg/100 g bw	single exposure	the suspension was instilled intratracheally - dose-response study; results 1 day after exposure -biochemical and cellular indicators of injury in BAL were measured	hamsters, 6	- no significant effect on macrophage numbers - PMN numbers were elevated - lactate dehydrogenase, peroxidase and albumin levels increased in a dose-dependent manner	(Beck BD et al., 1987)

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Table 4. Repeated Dose Toxicity Studies

Talc/Composition	Particle Size	Dose/Conc	Animals; #/grp	Dose Duration	Procedure	Results	Reference
		3.75 mg talc/100 g bw	hamsters, 4 (exposure) or 3 (controls)		- time course experiment; measurements made 1, 4, 7, and 14-days after treatment in broncho-alveolar lavage fluid	- PMN values approached control levels at 4-14 days post-exposure - peroxidase values approached control values by day 7 post-exposure - albumin levels decreased rapidly after exposure - chronic toxic effects on macrophages were observed	
INTRAVENOUS							
approx. 61% SiO_2, 32% MgO, 1% Al_2O_3	<5 μm	25 mg in 0.5 ml physiological saline	male guinea pigs, 24 test animals 8 controls	3 doses; given on days 0, 7, and 15	i.v. injection into the thigh vein in the hind leg; 2 test animals and 1 control were killed at 8 different intervals (from 1-150 days) after the last dose	- 8 animals died immediately after the 2nd and 3rd doses - gross observations: no significant abnormalities in the liver; moderate enlargement of the abdominal lymph nodes at study termination; varying degrees of congestion in the lungs developing early and persisting throughout - some particles lodged in the alveolar capillaries of the lung; by day 15, many small focal areas of macrophages and lymphocytes developed near the alveolar capillaries, and an increased density of talc particles was seen - talc particles were observed in the lungs and in the liver throughout the study, and in the abdominal lymph nodes at day 30+; no talc was seen in the tracheobronchial lymph nodes, but a moderate degree of lymphopoiesis was observed at various times	(Dogra RKS *et al.*, 1977)

Abbreviations: BAL = bronchoalveolar lavage fluid; conc = concentration; grp = group; MMAD = mass median aerodynamic diameter; MTAC = mean total aerosol concentration; PMN = polymorphonuclear neutrophils

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Table 5. Pulmonary effects of occupational exposure

Tale Composition and Particle Size (if given)	Study Population and Location	Timeframe examined	Procedure/Parameters Measured/Limitations	Findings	Reference
			Mining and Milling		
- some chlorite and quartz; very minor to trace amounts of magnesite and dolomite; no amphibole or chrysotile minerals were detected	- 1346 millers, 438 miners, and an equal number of age-matched controls from the town of Alba (>1 yr in job) - mine location: Italy - Germanasca and Chisone Valley (Piedmont)	employees that began work btwn 1921-1950 – followed until 1974	historic prospective study - cumulative exposure for each worker was estimated from the results of successive determinations of air dust content from 1948+ (until retirement or June 30, 1974) - Exposure Levels by distribution of total number of inhaled particles (cumulative exposure for each worker was estimated from the results of successive determinations of air dust content and quantified by calculating an appropriate value of the total amount of inhaled particles during the employment period) <u>Miners</u> level 1: 566 – 1699 mppcf/yr (n=405) level 2: 1700 – 5665 mppcf/yr (n=423) level 3: 5666 – 12,750 mppcf/yr (n=518) <u>Millers</u> level 1: 25 - 41 mppcf/yr (n=163) level 2: 142 - 424 mppcf/yr (n=144) level 3: 425 - 906 mppcf/yr (n=131) <u>Limitation</u> - possible lack of comparability of the occupational and control groups for comparing mortality - smoking status was not known	- by observed vs. expected comparison, the observed overall mortality of miners and millers was significantly lower than expected - there was no relationship found between the ratio of observed to expected deaths and the interval between first exposure and death - among different exposure classes, the ratio did not increase with increasing exposure for miners: **- respiratory disease (all except TB) (SMR = 1.38), silicosis (SMR = 2.01), and silico-TB (SMR = 1.58) were statistically significantly greater than expected** -break-out by exposure showed increasing ratios with increased exposure for these diseases - break-out by interval between first exposure and death showed increasing ratios with increasing latency-yrs for respiratory diseases (all except TB); it was noted that for silicosis with or without TB, the ratios were unchanged over time because of the absence of pneumoconiosis in controls, but the number of observed cases showed a constant increase with latency - researchers noted that the trends in dose and latency and the different incidences of silicosis suggests that the inducing factor was silica, not talc -incidence of malignant neoplasms: *- all (SMR = 0.771, of the lungs, bronchus and trachea (SMR = 0.46), and of other sites (SMR = 0.58) were statistically significantly lower than expected* - break-out by interval between first exposure and death for all malignant neoplasms and lung cancer showed a decrease with increasing latency - an increasing trend was observed for cancer of the larynx *- CV disease was statistically significantly lower than expected (SMR = 0.75)* for millers: *- CV disease was statistically significantly lower than expected (SMR = 0.78)* - there were no consistent trends observed for any cause of death - break-out by interval between first exposure and death indicated that the ratio of all tumors increased with increasing latency, but the number of observed deaths was still less than expected	(Rubino GF *et al.,* 1976)

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Table 5. Pulmonary effects of occupational exposure

Talc Composition and Particle Size (if given)	Study Population and Location	Timeframe examined	Procedure/Parameters Measured/Limitations	Findings	Reference
- composition as above - dust counts represented particle sizes of 0.5 – 5.0 µm	- 1260 miners and 418 millers in above study	as above	- because of the concern stated above, i.e. the possible lack of comparability of the occupational and control groups for comparing mortality, expected death rates were recalculated using the death rates of the Italian male population as the standard death rate - the mortality patterns for 1946-1974 were examined using the rates relevant to 1951 for the first 5 yrs	Miners - **the observed cause of death for "all causes" (SMR = 1.25); non-malignant respiratory diseases (SMR = 3.29) (primarily pneumoconiosis), and TB (SMR = 1.98) were statistically significantly increased** - there were 58 cases of pneumoconiosis and 13 cases of TB-associated with pneumoconiosis - an increasing trend with increasing exposure was observed for pneumoconiosis and TB - at the highest exposure level, ~20% of total deaths were due to pneumoconiosis, with or without TB - the researchers stated that the high frequency of pneumoconiosis in miners was attributable to the high content of free silica in the air dust, which was as high as 18% in drilling operations	(Rubino GF et al., 1979)
- non-asbestiform talc	- 1795 males; 1244 miners and 551 millers (>1 yr employment) - mine location: Val Chisone, Turin Italy	1946 - 1995	update of study described above - total mortality and selected cause of death; those with a significant increase are given (shown as SMR (95% CI)) - no information was provided on smoking status	Millers - **the observed cause of death for "all causes" was statistically significantly increased (SMR = 1.2)** - the observed cause of death was increased but NS for non-malignant respiratory diseases (SMR = 1.5) and TB (SMR = 2.0) - there were only 3 cases of pneumoconiosis and 1 case of TB-associated with pneumoconiosis - there was no consistent trend with increased exposure level Miners **all causes: 1.3 (1.2 – 1.4)** **oral cavity cancers: 6.1 (3.9 – 9.1)** **respiratory tract diseases: 3.1 (2.5 – 3.7)** **digestive tract diseases: 1.4 (1.0 – 1.8)** **cirrhosis: 1.8 (1.3 – 2.5)** - SMR for lung cancer was not significantly increased; 1.1 (0.7 – 1.5) Millers **oral cavity cancers: 3.3 (1.3 – 6.9)** - SMR for lung cancers was 0.7 (0.3 – 1.2)	(Coggiola M et al., 2003)
			- mortality by duration of exposure was examined	- for all miners and millers, no trend in risk with exposure was observed for any of the causes of death - **when miners only were examined, an increasing trend in risk with increasing exposure was observed for non-neoplastic respiratory disease (i.e., silicosis); <10 yrs exposure, the SMR was 2.8 (1.7-4.6); 10-20 yrs exposure, 2.8 (1.7 –4.2); >20 yrs exposure, 3.2 (2.5 – 4.1)**	
			- mortality by time since first exposure (latency) was examined	for all miners and millers, **a direct trend was observed only for non-neoplastic respiratory disease; at <20 yrs latency, SMR was 1.5 (0.7-2.6); 20-30 yrs, 2.4 (1.5 -3.4); >0 yrs, 2.4, 1.9– 3.0)**	

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Table 5. Pulmonary effects of occupational exposure

Talc Composition and Particle Size (if given)	Study Population and Location	Timeframe examined	Procedure/Parameters Measured/Limitations	Findings	Reference

- non-asbestiform talc, trace amounts of quartz, tremolite, and anthophyllite
- fibers had been detected near the detection limit for optical microscopy
	- 94 miners (>1 yr employment)
	- 295 millers (>2 yr employment)
	-mine located in Norway; the mean value for radon daughter exposure was 3.5 pCi/l at the worksite
		1935 – 1972 (millers)
		1944 – 1972 (miners)
			- levels of dust exposure were not registered during the actual period; samples collected from 1980-1982 demonstrated great variability between job category and workplace:
			mine: 0.94 – 97.35 mg/m³
			mill: 1.4 – 54.1 mg/m³
			
			Limitations
			- numbers were too small for further conclusions on cause-specific mortality or to form inferences on particular cancer types
				- for combined miners/millers, SMRs were <1 for all causes, all malignant neoplasms, and diseases of the respiratory system
				  - for miners only, obs > exp for number of malignant neoplasms
				- for combined miners/millers, cancer incidences at all sites, lung, prostate, and intestine, SIRs were <1; SIRs for incidences of kidney, stomach, and bladder cancers were 1.2% (95% CI, 0.1 - 3.4), 1.1 (95% CI, 0.41-2.15), and 2.1 (95% CI, 0.8-4.3)
				  - for miners only, obs > exp for cancer incidence at all sites, stomach, lung, prostate, and other sites
				  - for millers only, obs > exp for cancer incidence of the bladder
					(Wergeland E et al., 1990)

- no asbestos in samples - free silica levels were <0.25% for nearly all bulk talc samples - free silica detectable only in occasional air samples - talc shards and ribbons were seen in talc bulk and airborne dust samples - significant quantities of magnesite, chlorite, and dolomite - traces of calcite, biotite, ankerite, phlogopite	- 225 millers, 163 miners (all males; 47 were included in both groups) (>1 yr employment) - Vermont mines (radon daughter levels ranged from trace quantities to 0.12 working levels; single measurements up to 1.0 working levels have been measured)	1940 – 1975	- U.S. mortality rates were used; data from 1940 – 1967 were obtained and deaths after 1967 were extrapolated - however, because Vermont rates (1949-1975) for non-malignant respiratory diseases and respiratory cancer deaths are greater than U.S. rates, comparisons were made for these causes of deaths with those expected using Vermont rates; cause-specific expected deaths for the study population were obtained by applying death rates, calculated from yearly tallies of deaths and census data, to the person-yrs of observation of the cohort members Limitations - selection bias from radiographic monitoring of talc workers; the bias is most likely small - no data on smoking habits were available	- there were 90 talc-worker deaths observed and 77.32 expected (NS) - for all talc workers, the observed number of deaths for total non-malignant respiratory which was specific for ONMRD ,excluding influenza and pneumonia were statistically significantly increased - 9 of the 11 workers with ONMDR had radiographic reading consistent with pneumoconiosis - the possibility of an interactive effect between cigarette smoking and talc exposure was discussed Miners - **deaths due to respiratory malignant neoplasms were statistically significantly increased** - this increase was also found using Vermont data Millers - **deaths due to total non-malignant respiratory diseases and ONMRD (7 observed/0.89 expected U.S.) were statistically significantly increased** - this increase was also found using Vermont data	(Selevan SG et al., 1979)
- milled product is a talc-chlorite mixture - contains 0-3% quartz	- 1070 male workers at a milling site in the French Pyrenees (>1 yr employment) - local (1968+) and national mortality rates were used for comparison	1945-1994	- a nested case-control study protocol was used - two case control studies were set up for each cohort: a lung-cancer study and a study of non-malignant respiratory disease - occupational histories and smoking information was collected by an external interviewer	- the researchers stated that because excess lung cancer mortality was observed for miner and not millers suggests that additional etiologic agents, alone or in combination with talc dust, affects miners - the SMR for all causes of death (1968+) was 0.93 - the SMR for non-malignant respiratory diseases was 0.27 - the incidence of pneumoconiosis was 0 - the SMR (obs/exp) for all cancers was 0.73, for stomach cancer was 0.40 (0.38-2.75, and for lung cancer was 1.06 (0.43-2.19)	(Wild P et al., 2002)

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Table 5. Pulmonary effects of occupational exposure

Talc Composition and Particle Size (if given)	Study Population and Location	Timeframe examined	Procedure/Parameters Measured/Limitations	Findings	Reference
- milled product is talc-chlorite or talc-dolomite - contains 0.5-4% quartz	- 542 male workers from three mines and their respective mills in the Styrian Alps (>1 yr employment - mortality rates of Styria were used for comparison	1972-1995	- work histories were abstracted from company records; smoking history was obtained from a variety of sources	- the SMR for all causes of death was 0.75 - the SMR for non-malignant respiratory diseases was 1.06 **- the SMR for pneumoconiosis was 5.56 (95% CI; 1.12 – 16.2); 3 cases were observed** - the SMR for all cancers was 1.02, for stomach cancer was 1.18 (0.38-2.75), and for lung cancer was 1.23 (0.76-1.89)	(Wild P et al., 2002)
	- cohort: 40 cases; 39 French and 1 Austrian - 44 controls; 41 French and 3 Austrian		Nested case-control study for respiratory disease	Cumulative exposure to talc (y·mg/m^3): <100; OR = 0.22 100-400; OR = 1.00 400-800; OR = 1.97 ≥800; OR = 2.53 - mortality increased with exposure **all cases: OR =1.08 (1.02 - 1.16)** pneumoconiosis: OR = 1.17 (0.99 – 1.38) COPD: OR = 1.02 (0.86 – 1.2)	
	- cohort: 30 cases; 23 French and 7 Austrian - 88 controls; 67 French; 21 controls		Nested case control study for lung cancer	Cumulative exposure to talc (y·mg/m^3): <100; OR = 0.86 100-400; OR = 1.07 400-800; OR = 0.60 ≥800; OR = 0.73 - a relationship between mortality and exposure was not observed	
- did not contain tremolite; only amphibole mineral was non-asbestiform actinolite (one bed at ≤6%); ≤42% carbonate minerals, 0.2-1.6% quartz	- workers from a company in Russia that mined, ground, and processed talc; total number of cases not stated (>3 yrs at plant) - the "other population" were matched non-cancer/non-worker deaths from the same town	1949 – 1975	- estimated the death rate by relating the number of deaths from cancer of cases to the number of man-yrs of work for all employees during the same period - the calculated death rates were compared with the analogous death rate for the controls	**- RR of death from tumors of all sites was 5.1 (p < 0.001) for males and 6.4 (p<0.001) and females** **- RR of death from lung cancer was 4.5 (p<0.02) for males** and 9.3 (NS) for females - for lung cancer of male workers compared to controls, the death rate of those <59 yrs old was 2x greater, of those 60-69 yrs old was 6.51x greater, and of those 70+ yrs old was 40.02x greater **- RR of death from gastric cancer was 3.7 (p<0.02) for males and 6.3 (p<0.05) for females**	(Katsnelson BA & Molronosova KA, 1979)

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Table 5. Pulmonary effects of occupational exposure

Talc Composition and Particle Size (if given)	Study Population and Location	Timeframe examined	Procedure/Parameters Measured/Limitations	Findings	Reference
- minimal amounts of crystalline silica and asbestiform minerals - contained chlorites and carbonates	- 7 miners/millers - 8 adult age-matched by decade male controls - Vermont mines	4-27 yrs of exposure (timeframe not stated)	- lifetime exposure to talc ranges from 12 – 5930 mppcf - pulmonary tissue from deceased talc workers was examined and compared to pulmonary tissue of controls	- lungs of 4 workers exposed for 4-19 yrs exhibited **focal and diffuse fibrosis with accumulations of talc**, but chest x-rays were negative for pneumoconiosis - lungs of 3 workers exposed for 19, 26, and 27 yrs had **areas of diffuse confluent fibrosis and talc** - 2 workers exposed for 27 yrs had positive chest x-rays; the chest x-ray was not available for the remaining worker - extensive pulmonary fibrosis was found in the patient exposed for 27 yrs (5930 mppcf); large amounts of silicon and aluminum were found in the lungs - the severity of lesions and the concentrations of magnesium and silicon in the lungs compared top controls increased with duration of exposure - circumscribed granulomas were not observed	(Vallyathan NV & Craighead JE, 1981)
- talc was essentially free from silica and asbestos - geometric mean exposure was 1.8 mg/m³ respirable dust	- 116 miners and millers over the age of 25 in 3 Vermont plants - avg. yrs. employed was 8.5	1975-1976	- exposure levels were >3.0 mg/m³ respirable dust - a medical history, including questions pertinent to the respiratory system, and smoking history were obtained - pulmonary function tests were performed - an appropriate control group was not available; observed values were compared to predicted values from a standard pop. - chest x-rays were taken in 100 of the subjects Limitations - the follow-up interval is short and the overall range of exposures within the study may be too narrow to detect exposure-related effects in the small study pop. - effects on pulmonary function in non-smokers was not associated with lifetime or current talc exposure after a relatively short avg. yrs. Employed; longer follow-up would be needed before concluding there is no effect of talc on non-smokers at this exposure level	- **observed/predicted FEV₁ (FEV%) and MMEF (MMEF%) were significantly reduced** - yrs of employment and talc-yrs (i.e., lifetime dust exposure) were significantly associated with decreased FEV₁/FVC and MMEF%, but not with FVC% or FEV% - a 43.3% prevalence of any chest x-ray abnormality was observed; with a third being diffuse parenchymal opacities or pleural abnormalities - 12 subjects had small round opacities and 9 had small irregular opacities; there was a statistically significant association with talc-yrs	(Wegman DH *et al*, 1982)
- contained talc, chlorite, and a small quantity of dolomite - 0.5-3% free silica (<1% particle size distribution <10 µ) - does not contain asbestos	- 176 millers from Luzenac, France (cross-sectional study)	1978	- cross-sectional study	- 46 workers (27%) had pneumoconiosis - 36 of the cases were slight - 10 of the cases had higher profusion or large opacities - intensity and duration of dust exposure were linked to radiologic signs of pneumoconiosis	(Leophonte P & Didier A, 1990)

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Table 5. Pulmonary effects of occupational exposure

Talc Composition and Particle Size (if given)	Study Population and Location	Timeframe examined	Procedure/Parameters Measured/Limitations	Findings	Reference
	- dust exposed workers - local and national pop. were used as controls	1945-1981	- retrospective study, completed by a prospective study until 1988	- difference in life expectancy of dust-exposed workers compared to the local and national pop. was NS - differences in mortality due to cancer, including lung and digestive system cancers,, were NS - in a cohort or workers deceased between 1970-1981 compared to 97 age-matched controls, the mortality ratio for chronic respiratory diseases was 2.4; a follow-up in 1998 confirmed these results	
	- 39 pneumoconiotic workers; 6 had profusion equal to 2 or 3 - 39 matched for smoking and age non-dust exposed controls		- respiratory function was compared	- VC, TLC, and single breath TCO were statistically significant decreased in pneumoconiotic subjects compared to controls	
	- 8 hospitalized pneumoconiotic workers		- a bronchoalveolar lavage was performed	-hypercellularity was observed, with a significant increase in neutrophilic and eosinophilic PMN leukocytes - numerous talc particles were found in all lavage fluids, including uncoated plate-like particles (0.5 – 40 µm) and atypical ferruginous bodies)	
3 mines - MT: free silica content was below the limit of detection (<0.8%) ; no fibers; NC: 1.5% free silica; acicular particles (aspect ratios 5-100:1 and some diameters <0.1 µm); TX: 2.2% free silica; tremolite and antigorite fibers (0.5-3 µm in length) - geometric mean concentrations of respirable dust in samples (mg/m³) for miners and millers was 0.66 and 1.1 (MT), 0.45 and 1.56 (TX), 0.14 and 0.26 (NC)	-177 talc workers from MT, 71 from TX, 51 from NC - since there were no differences among regions by age, smoking, or exposure groups, the populations were combined - were compared to 1140 blue collar workers (males and females from NC in electronics, synthetic textiles, bakeries, and bottling plants)	avg. from 3 plants: 5.5 (TX), 6.6 (MT), and 10.1 (NC) yrs (timeframe not stated)	- cumulative exposure (mg/m³ x yrs) was 1.21 for MT, 2.64 for TX, and 0.28 for NC - all workers completed a respiratory questionnaire - chest x-rays were taken and sputum was collected Limitations - workers examined were only those currently working - length of the working history was a relatively short time for the development of occupationally-related symptoms - estimating past exposure was a problem	prevalence of dyspnea - 6% in non-smokers, 10% in ex-smokers, 3% in smokers; 5% total (prevalence was increased with age; no demonstrated association with cumulative exposure) prevalence of pleural thickening - 0% in non-smokers; 4% in ex-smokers; 9% in smokers; 5% total (tendency to increase with age; no demonstrated association with cumulative exposure) - cumulative exposure was not significant for any of the lung function tests parameters examined and compared to blue-collar controls - cough: 20.3% of test v. 16.7% controls - phlegm: 20.3% of test v. 17.3% of controls - dyspnea: 5.8% of test v. 7.5% of controls - bilateral pleural thickening: 6.3% of test v. 0.4% of controls mean percent predicted pulmonary function compared to 292 controls FEV_1: 99.7 FVC: 101.0 peak flow: 97.9 FEF_{50}: 94.1 FEF_{75}: 84.5	(Gamble J et al., 1982)

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Table 5. Pulmonary effects of occupational exposure

Talc Composition and Particle Size (if given)	Study Population and Location	Timeframe examined	Procedure/Parameters Measured/Limitations	Findings	Reference
- non-asbestiform talc-chlorite mixture	- 398 subjects from talc facilities in the Styrian alps, Austria - >5 yrs continuous employment btwn 1989-2001	1988-2003	- in the French mill, overall exposure decreased from a geometric mean exposure of 1.95 mg/m^3 (GSD3.9) in 1986 to 0.80 mg/m^3 (GSD 4.3) in 2003; the high GSDs are due to different exposures based on job - in the Austrian mill, the 1988-1995 geometric mean exposure was 0.75 mg/m^3 (GSD 3.67); in 1996, it was 0.30 mg/m^3 (GSD 3.25) - lung function parameters were measured, with the following confounders: pack-yrs; apparatus used to determined respiratory function; gender; gender-specific age and height; medical histories - regression coefficients (95% CI) are presented Limitations - the symptoms questionnaire was only used a mean of two times at the French site and less at the Austrian site - the mean duration of follow-up was <5 yrs	Total cumulative exposure per 10 yrs mg/m^3 FEV$_1$ (ml): -6.58 (-13.81 to 0.65) FVC (ml): -7.71 (-15.45 to 0.03) FEV$_1$/FVC (%): 0.000 (-0.090 to 0.090) Cumulative exposure at inclusion per 10 yrs mg/m^3 FEV$_1$ (ml): -7.26 (-14.65 to 0.13) FVC (ml): -8.47 (-16.38 to -0.57) FEV$_1$/FVC (%): -0.004 (-0.096 to 0.087) Cumulative exposure since inclusion per 10 yrs mg/m^3 FEV$_1$ (ml): 7.75 (-25.49 to 40.99) FVC (ml): 10.24 (-28.22 to 48.70) FEV$_1$/FVC (%): 0.105 (-0.364 to 0.574)	(Wild P *et al.*, 2008)
			- prevalence of self-declared respiratory symptoms, including the following confounders: pack-yrs of cigarettes for chronic bronchitis and usual cough and/or phlegm and age for dyspnea - ORs (95% CI) are presented	Total cumulative exposure per 10 yrs mg/m^3 chronic bronchitis: 1.014 (0.963-1.068) usual cough or phlegm: 1.021 (0.993.-1.050) dyspnea: 1.040 (0.997-1.087) Cumulative exposure at inclusion per 10 yrs mg/m^3 chronic bronchitis: 1.032 (0.985-1.081) usual cough or phlegm: 1.014 (0.983-1.046) dyspnea: 1.031 (0.985-1.080) Cumulative exposure since inclusion per 10 yrs mg/m^3 chronic bronchitis: 0.473 (0.193-1.158) usual cough or phlegm: 1.250 (0.986-1.584) dyspnea: 1.405 (0.870-2.257)	
			radiograph results were examined - ORs (95% CI) are presented - profusion: using the Standard X-rays, the profusion (concentration) of small opacities is classified on a 4-point major category scale (0, 1, 2, or 3), with each major category divided into three, giving 12 ordered subcate-gories of increasing profusion; category 0 refers to the absence of small opacity and category 3 represents the most profuse	Initial cumulative exposure per 10 yrs mg/m^3 **profusion ≥ 0/1: 1.056 (1.031-1.085)** **profusion ≥1/0: 1.060 (1.028-1.095)** pleural abnormalities: 1.036 (0.960-1.119) Cumulative exposure since inclusion per 10 yrs mg/m^3 profusion ≥ 0/1: 0.917 (0.838-1.004) profusion ≥1/0: 0.858 (1.028-1.095) pleural abnormalities: 1.145 (0.980-1.336)	

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Table 5. Pulmonary effects of occupational exposure

Talc Composition and Particle Size (if given)	Study Population and Location	Timeframe examined	Procedure/Parameters Measured/Limitations	Findings	Reference
the talc ore contained chlorite, aluminum, some dolomite (<3%), some quartz (<3%), and traces of calcite, apatite, pyrite, and mica - amphiboles were not been detected	- 166 millers (158 M/8 F) from a talc-producing factory in SW France	workers employed 1989-1990	- geometric mean exposure at the time of the study was 1.87 mg/m³ (GSD, 2.5 mg/m³) - each subject was given a standardized questionnaire and questioned about smoking and occupational history during their annual medical check-up - a chest radiograph that had been taken between 1982-1987 was reviewed - 139 subjects had a second radiograph in 1992 - the prevalence of self-reported symptoms (as %) according to cumulative exposure were determined Limitations - less than optimal quality of the spirometric tests that led to the exclusion of 30 subjects - standardized functional variables according to cumulative exposure were determined	<u>≤20 y mg/m³ (n=46)</u> chronic bronchitis: 0% chronic cough or phlegm: 8.7% dyspnea: 4.4% wheeze: 4.4% <u>20-50 y mg/m³ (n=25)</u> chronic bronchitis: 4% chronic cough or phlegm: 20% dyspnea: 8% wheeze: 4% <u>50-150 y mg/m³ (n=54)</u> chronic bronchitis: 13% chronic cough or phlegm: 35.7% dyspnea: 17% wheeze: 3.7% <u>>150 y mg/m³ (n=41)</u> chronic bronchitis: 2% chronic cough or phlegm: 14.6% dyspnea: 14.6% wheeze: 0% <u>≤20 y mg/m³ (as mean (SD)) (n=36)</u> FVC: 1.33 (1.28) FEV: 1.22 (1.21) FEV/FVC: 0.25 (0.70) MMEF: 0.66 (1.58) <u>20-50 y mg/m³ (n=20)</u> FVC: 0.82 (1.04) FEV: 0.77 (1.22) FEV/FVC: 0.27 (0.79) MMEF: 0.36 (1.41) <u>50-150 y mg/m³ (n=44)</u> FVC: 1.10 (1.07) FEV: 0.74 (1.17) FEV/FVC: -0.04 (0.80) MMEF: -0.19 (1.15) <u>>150 y mg/m³ (as mean (SD)) (n=36)</u> FVC: 0.65 (1.03) FEV: 0.50 (1.06) FEV/FVC: 0.24 (0.75) MMEF: -0.06 (1.12)	(Wild P et al., 1995)

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Table 5. Pulmonary effects of occupational exposure

Talc Composition and Particle Size (if given)	Study Population and Location	Timeframe examined	Procedure/Parameters Measured/Limitations	Findings	Reference
			- radiological opacities at the first radiograph - given in terms of cumulative exposure to talc	any opacity including 0/1 coefficient: 0.33 OR (95% CI): **1.39 (1.06-1.84)** any opacity excluding 0/1 coefficient: 0.97 OR: **2.65 (1.25-5.64)** - 4 pleural abnormalities were reported at the first reading - the prevalence of small opacities was higher in the second radiograph, with 11 new opacities compatible with pneumoconiosis (1/0 or above)	
Plant Workers					
Rubber Workers					
non-fibrous talc; <2 fibers/cc - <1% free silica - avg dust concentrations ranged from 0.47 – 3.55 mg/m³, with most jobs exposed to <1 mg/m³	- 80 talc workers (15.9 yrs avg. length of employment) and 189 non-exposed rubber workers (13.4 yrs avg. length of employment) (average talc exposure, i.e. "dust yrs", was 9 yrs) - plant location not specified	1972-1974	- subjects were asked about medical, occupational, smoking, and respiratory histories - pulmonary function tests were performed - exposure to talc was evaluated by respirable mass sampling - 28 workers were studied for acute change in $FEV_{1.0}$ and FVC for one shift - pulmonary function changes related to talc exposure were measured in white workers >24 yrs old -chest x-rays were taken in most exposed workers	- there were no significant differences between exposed and non-exposed workers in age, smoking, or socioeconomic or ethnic factors - statistically significant increases in cough for 3 mos and phlegm for 3 mos (chronic bronchitis symptoms) and wheezing most days and nights (an obstructive respiratory disease symptom) were observed in exposed workers; none of the workers had dyspnea - talc had no acute effect on ventilatory capacity - talc workers had lower (NS) FVC standardized flow rates and a lower ratio of $FEV_{1.0}$ to FVC; the flow rate/FVC at 12.5% FVC was statistically significantly decreased in exposed workers -for workers of >10 yrs, residual $FEV_{1.0}$ was statistically significantly decreased in exposed workers - none of the chest x-rays were definitely consistent with classical talc pneumoconiosis	(Fine LJ *et al.*, 1976)

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Table 5. Pulmonary effects of occupational exposure

Talc Composition and Particle Size (if given)	Study Population and Location	Timeframe examined	Procedure/Parameters Measured/Limitations	Findings	Reference
			Pottery Plant Workers		
non-fibrous talc	- white men from 3 ceramic plumbing fixture plants (>1 yr employment)	employed during 1939-1966	- workers were exposed to both silica and talc - mortality from 1940-1980 was examined Limitations - information on smoking patterns was not available	- with high silica/non-fibrous talc exposure, there was a statistically significant increase in SMR for lung cancer (SMR=2.54) and non-malignant disease mortality (SMR=2.20) - with high silica/no talc exposure, the increase was only seen for non-malignant respiratory disease (SMR=2.64) **- with non-fibrous talc, SMRs for lung cancer were statistically significant increased with 5-14 and 15+ yrs duration of exposure and -14 and 15+ yrs since first talc exposure** - SMRs for non-malignant respiratory diseases were statistically significant increased with <5, but not 5-14 or 15+ yrs duration of exposure and with 5-14, but not >15, yrs since first talc exposure **- the researchers postulated that non-fibrous talc was related to excess lung cancer, and that it was possible that silica might act as a co-factor or promoting agent**	(Thomas TL & Stewart PA, 1987;Thomas TL, 1990)

Abbreviations: CI = confidence interval; CV = cardiovascular; exp = expected; FEF = forced expiratory flow; FEV = forced expiratory volume; FVC = forced vital capacity; GI = gastrointestinal; GSD = geometric standard deviation; MMEF = maximum mid-expiratory flow; NS = non-statistically significant; obs = observed; ONMRD = other non-malignant respiratory disease; OR = odds ratio; PMN = polymorphonuclear cells; pop. = population; RR = relative risk; SD = standard deviation; SIR = standardized incidence ration; SMR = standardized mortality ratio; TB = tuberculosis; TCO = transfer factor for carbon monoxide; VC = vital capacity

Bolded text was used to highlight statistically significant increases
Italicized text was used to highlight statistically significant decreases

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Table 6. Exposure During Cosmetic Talc Use

Study Population	Test Article	Measurement Device	Study Conditions	Procedure	Respirable Amount	Other Results	Reference
infant exposure simulation; number not given	commercial talcum powder (composition not defined)	gravimetric dust sampler	simulated	- powder was dusted into a shallow tray from a height of 7-13 cm - the air inlets of the sampler were placed where the baby's nose would be, as well as 40 cm above the tray (representing mother's exposure); the dust concentration was similar for the mother and the infant	0.10 mg/min/m³	10 s dusting period: total median dust concentration - 0.243 mppcf 65 s settling period: median dust concentration - 0.124 mppcf median exposure/application: 0.1752 mppcf-min median weekly exposure (5 applications/day): 0.102 mppcf-h	(Hildick-Smith GY, 1976)
48 infants	commercial talcum powder (composition not defined)	10 mm nylon cyclone	actual	-mothers diapered infants, applying powder in their usual method -the cyclone inlet was held next to the baby's head, approx. 4" above the change mat - procedure was repeated 3x in succession and the mean of the 3 runs was used; was performed over two 4-day periods	0.19 ± 0.084 mg/m³	avg. use/exposure: 0.88 g exposure time: 0.52 min TWA: 0.095 ± 0.039 mg·min/m³	(Russell RS et al., 1979)
adults, 23 males and 21 females	commercial talcum powder (composition not defined)	10 mm nylon cyclone	actual	- subjects applied powder in their usual manner in an anteroom - a headband with an attached 10-mm cyclone positioned at the level of the nose was worn - performed over two 4-day periods	2.03 ± 1.49 mg/m³	avg. use/exposure: 8.84 g exposure time: 1.23 min TWA: 1.727 mg·min/m³	(Aylott RI et al., 1979)
infant simulation; 4 subjects	baby powder with: - Chinese talc - Italian 00000 grade talc (cosmetic talcs; both perfumed and unperfumed; Chinese and Italian perfumed talc contained 0.045 and 0.2% perfume, respectively)	for respirable dust: cyclone elutriator/filter head system with 25-mm diameter filter; allowed sampling of all particles <1 μm, 50% of 5-μm particles, and no 7-μm particles for total dust: cyclone removed and open filter holder with a 37 mm filter	simulated	- in a 3.7 x 2.8 m room, adult subjects used a doll to simulate powdering during diapering - the sample collection unit was on a table next to the doll's head -the "doll's nose" was approx. 15-30 cm from the sampling point - sampling time was 5 min -2 trials at 1 h intervals	Chinese, perfumed: <0.1-0.9 mg/m³ unperfumed: <0.1-0.9 mg/m³ Italian, perfumed: <0.1-0.3 mg/m³ unperfumed: <0.1-0.5 mg/m³	- there were no major differences among concentrations of respirable dust - mean concentration of respirable talc (for Chinese and Italian perfumed and unperfumed talcs) – 0.21 mg/m³ - respirable talc accumulated during 4 samplings: 0.005-0.3 mg/m³ - no evidence that perfume affected amount of respirable talc - mean talcing time: 19-21 s	(Aylott RI et al., 1979)
4 female subjects	loose face powder: - Chinese talc - Italian 00000 grade talc - Italian micronized-grade talc (cosmetic talcs; all unperfumed)	as above	actual	- in a 2 x 1 m room, subjects applied powder in their normal manner (a small window was open during application) - the application puff was only dipped once in the powder - the subject's nose was approx.. 15 cm from the sampling point - sampling time was 5 min - 2 trials at1- h intervals	Chinese: <0.1-1.1 mg/m³ Italian: <0.1-0.8 mg/m³ Italian, micronized: <0.3-1.7 mg/m³	with the exception of micronized talc, there were no major differences among concentrations of respirable dust - mean concentration of respirable talc (for Chinese and Italian perfumed and unperfumed talcs) – 0.48 mg/m³ - respirable talc accumulated during 4 samplings: 0.1-0.4 mg/m³ - no evidence that perfume affected amount of respirable talc - mean talcing time: 17-19 s	

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Table 6. Exposure During Cosmetic Talc Use

Study Population	Test Article	Measurement Device	Study Conditions	Procedure	Respirable Amount	Other Results	Reference
4 female subjects	adult dusting powder: - Chinese talc - Italian 00000 grade talc (both perfumed and unperfumed) - Italian micronized-grade talc, unperfumed (cosmetic talc)	as above	actual	- in a 2.3x 2 m room, subjects applied powder in their normal manner - the subject's nose was approx.. 30-90 cm from the sampling point - one experiment with unperfumed Italian talc was performed at >90% humidity - sampling time was 5 min - particle size analysis was performed for un-perfumed Italian 00000 and micronized talc - 2 trials at 1 h intervals	Chinese, perfumed: $0.3\text{-}2.6\ mg/m^3$ unperfumed: $0.5\text{-}1.8\ mg/m^3$ Italian, perfumed: $0.4\text{-}1.7\ mg/m^3$ unperfumed: $0.5\text{-}2.6\ mg/m^3$ high humidity: $0.2\text{-}0.8\ mg/m^3$ Italian, micronized: $0.6\text{-}3.3\ mg/m^3$	-with the exception of micronized talc, there were no major differences among concentrations of respirable dust - mean concentration of respirable talc (for Chinese and Italian perfumed and unperfumed talcs) – $1.13\ mg/m^3$ - mean concentrations of micronized talc were $1.9\ mg/m^3$ - respirable talc accumulated during 4 samplings: $0.3\text{-}2.5\ mg/m^3$ - total talc with cyclone removed: Italian 00000 unperfumed, 2.7-4.8 mg/m^3; Italian micronized, 0.2-1.5 mg/m^3 - total talc with cyclone removed: Italian 00000 unperfumed, 2.7-4.8 mg/m^3; Italian micronized, 0.2-1.5 mg/m^3 - total talc with open filter: Italian 00000 unperfumed, 8-27 mg/m^3; Italian micronized, 10-17 mg/m^3 - detectable background levels of respirable talc were found only with micronized talc (0.6-1.6 mg/m^3) and Italian talc (<0.1-1.0 mg/m^3) at high humidity - no evidence that perfume affected amount of respirable talc - particle size analysis demonstrated that most particles were between 1 and 8 µm - mean talcing time: 27-31 s	(Hildick-Smith GY, 1976)
adult consumers and miners	consumer – cosmetic talc; miner – talc dust	not stated	actual	comparison between adult consumer's 1 min daily exposure and a miner's 8 h daily exposure		-consumers: weekly exposure resulting from use lasting 10 s, with 65 s settling time, would be 0.102 mppcf-h of talc dust/wk -miners: assuming a max. daily exposure of 20 mppcf talc dust, weekly exposure would be 890 mppcf-h -exposure of miners about 8000 x greater than that of consumers (calculations were not provided)	

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Table 7. Lung Talc Burden in Mice   (National Toxicology Program (NTP), 1993)

	Male		Female	
Evaluation	**6 mg/m³**	**18 mg/m³**	**6 mg/m³**	**18 mg/m³**
Normalized to Control Lung Weight (mg talc/g control lung)				
6 mos	0.415 0.114 (2)	1.41 ± 0.29 (4)	0.524 ± 0.056 (4)	1.35 ± 0.24 (4)
12 mos	1.084 ± 0.130 (4)	9.00 ± 1.45* (4)	0.707 ± 0.170 (4)	6.17 ± 1.39* (4)
18 mos	0.426 ± 0.040 (2)	8.36 (n=1; no std. dev. calc.)	1.387 ± 0.178** (4)	7.83 ± 1.36* (3)
24 mos	2.973 ± 0.762* (8)	19.73 ± 4.03** (6)	2.667 ± 0.720** (6)	20.05 ± 0.98** (5)
Normalized to Exposure Concentration (mg talc/g control lung per mg talc/m³)				
6 mos	0.069 ± 0.019 (2)	0.078 ± 0.016 (4)	0.087 ± 0.009 (4)	0.075 ± 0.013 (4)
12 mos	0.181 ± 0.022 (4)	0.500 ± 0.081# (4)	0.118 ± 0.028 (4)	0.343 ± 0.077# (4)
18 mos	0.071 ± 0.007 (2)	0.464 (n=1; no std. dev. calc.)	0.231 ± 0.030 (4)	0.435 ± 0.075 (3)
24 mos	0.496 ± 0.127 (8)	1.096 ± 0.224# (6)	0.445 ± 0.120 (6)	1.114 ± 0.055# (5)

(n) number of animals examined for lung talc burden
* significantly different (p≤0.05) from 6 mos group
** significantly different (p≤0.01) from 6 mos group
# significantly different (p≤0.05) from 6 mg/m³ group

Table 8. Lung Talc Burden in Rats (National Toxicology Program (NTP), 1993)

	Male		Female	
Interim Evaluation	**6 mg/m³**	**18 mg/m³**	**6 mg/m³**	**18 mg/m³**
Normalized to Control Lung Weight (mg talc/g control lung)				
6 mos	2.63 ± 0.24 (3)	10.83 ± 0.23 (3)	2.43 ± 0.19 (3)	8.34 ± 0.12 (3)
11 mos	4.38 ± 0.59* (3)	20.96 ± 2.04* (3)	4.71 ± 0.26* (3)	14.16 ± 3.36 (3)
18 mos	7.31 ± 0.71** (3)	27.57 ± 0.91* (3)	7.66 ± 0.34** (2)	24.33 ± 0.63* (3)
24 mos	10.45 ± 1.26** (6)	24.15 ± 3.41* (9)	9.10 ± 0.88** (2)	29.40 ± 2.40** (3)
Normalized to Exposure Concentration (mg talc/g control lung per mg talc/m³)				
6 mos	0.439 ± 0.040 (3)	0.602 ± 0.013# (3)	0.406 ± 0.032 (3)	0.464 ± 0.007# (3)
11 mos	0.731 ± 0.098 (3)	1.165 ± 0.113# (3)	0.785 ± 0.043 (3)	0.787 ± 0.187 (3)
18 mos	1.22 ± 0.12 (3)	1.53 ± 0.05 (3)	1.28 ± 0.06 (2)	1.35 ± ± 0.04 (3)
24 mos	1.74 ± 0.21 (6)	1.34 ± 0.19 (9)	1.52 ± 0.15 (2)	1.63 ± 0.13 (3)

(n) number of animals examined for lung talc burden
* significantly different (p≤0.05) from 6 mos group
** significantly different (p≤0.01) from 6 mos group
# significantly different (p≤0.05) from 6 mg/m³ group

Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
			OVARIAN CANCER			
			PERSONAL USE			
			PROSPECTIVE STUDY			
talc; purity and composition not specified	- 307 registered nurses in 11 states with epithelial ovarian cancer (out of 31,789 subjects of 121,700 total pop. that reported using talc) (Nurses' Health Study)	1982 - 1996	- subjects answered questionnaires every 2 yrs from 1976-1996, subjects were questioned about talc use in 1982 - risk was age-adjusted and multivariate for age, parity, OC use, BMI, tubal ligation history, smoking status, and PMH use - women who did not respond to the questions on talc use in 1982 and who reported a diagnosis of cancer before 1982 were excluded Limitations - question of talc use was ever/never only; did not determine the age at which use began or the duration - this also may have contributed to a higher preva-lence of use compared to other studies - were unable to assess the potential effect of talc use prior to first pregnancy - follow-up period may have been inadequate if latency is >15 yrs - question about tubal ligation was asked as a component of contraceptive use, so not all women may have responded	Ever/never perineal use of talc 58.3%of cases never used perineal talc - 41.7% of cases ever had perineal use of talc (age) (multivariate) Frequency of perineal talc use - 60.6%of cases never used talc on perineum - 14% of cases used talc on perineum <1x/wk (age) (multivariate) - 9.8% of cases used talc on perineum 1-6 x/wk (age) (multivariate) - 15.6% of cases used talc on perineum daily (age) (multivariate) Talc use on sanitary napkins - 78.8%of cases never used talc on sanitary napkins - 11.7% of cases used talc on sanitary napkins (age) (multivariate) Talc use perineally and/or on sanitary napkins - 58.3%of cases did not use talc perineally or on sanitary napkins - 33.6% of cases talc on perineum or sanitary napkins (age) (multivariate) - 8.1% of cases talc on perineum and sanitary napkins (age) (multivariate)	**RR** 1.0 1.05 (0.84-1.32) 1.09 (0.86-1.0) 1.0 1.1 (0.79-1.53) 1.14 (0.81-1.59) 0.95 (0.65-1.4) 0.99 (0.67-1.46) 1.09 (0.79-1.49) 1.12 (0.82-1.55) 1.0 0.89 (0.62-1.29) 0.89 (0.61-1.28) 1.0 1.11 (0.87-1.41) 1.15 (0.9-1.46) 0.89 (0.58-1.35) 0.9 (0.59-1.37)	(Gertig DM *et al*, 2000)
			- the tumors were stratified by histological subtype - risk was adjusted for age or for age, parity, OC use, and tubal ligation, and sometimes for BMI (multivariate)	All serous cancers (185 total) - 54.6% never used talc perineally - 45.4% ever used talc perineally (age) (multivariate) Serous invasive cancers (160 total) - 52.5 % never used talc perineally - 47.5% ever used talc perineally (age) (multivariate) Endometroid cancers (42 total) - 61.9% never used use talc perineally - 38.1% ever used talc perineally (age) (multivariate) Mucinous cancers (50 total) - 60% never used use talc perineally - 40% ever used talc perineally (age) (multivariate)	**RR** 1.0 1.23 (0.02 – 1.64) 1.26 (0.94 – 1.69) 1.0 1.33 (0.98 – 1.82) **1.40 (1.02 – 1.91)** 1.0 0.91 (0.49 – 1.69) 0.91 (0.49 – 1.87) 1.0 0.98 (0.56 – 1.73) 0.93 (0.53 – 1.66)	

Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Study/Diagnosis Yrs	Population/Geographical Area	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
			HOSPITAL-BASED CASES/HOSPITAL-BASED CONTROLS			
talc; purity and composition not specified	1974-1977	-135 women in the Washington, D.C. area with epithelial ovarian cancer (hospital-based) -171 hospital controls	- subjects were asked questions about reproductive and sexual history, medical history, drug use, other exposures, and talc use Limitation - a potential bias is that talc exposure was not a major focus of the study during questioning	Ever/never talc use -45.9% of cases and 35.7% of controls had no exposure to talc -49.7% of cases and 58.5% of controls had exposure to talc Use with diaphragm -18.5% of cases and 24% of controls reported diaphragm use with talc -10.4% of cases and 6.4% of controls reported diaphragm use with no talc Areas of application of talc -57% of cases and 49.1% of controls reported no body talc use -40% of cases and 45.6% of controls reported some body talc use -27.4% of cases and 33.3% of controls reported all-over use of talc -5.2% of cases and 1.8% of controls reported genital use of talc	**RR** 1 0.7 (0.4 - 1.1) 0.8 (0.4 - 1.4) 1.6 (0.7-3.7) 1.0 0.8 (0.5 - 1.2) 0.7 (0.4 - 1.2) 2.5 (0.7 - 10.0)	(Hartge P et al, 1983)
talc; purity and composition not specified	Oct 1978 – Feb 1983	-235 females in London and Oxford, England with epithelial ovarian cancer (from 15 hospitals) -451 age-matched hospital controls	- subjects were asked about talc reproductive and sexual history, contraceptive use, breastfeeding, talc usage, hysterectomy, HRT - all risk estimates were adjusted for age and social class; some were adjusted for parity	Frequency of talc usage never: 37.3% of cases; 39.5% of controls rarely: 2.6% of cases; 3.5% of controls monthly: 3.0% of cases; 5.3% of controls weekly: 24.3% of cases; 17% of controls daily: 30.2% of cases; 30.8% of controls - no consistent trend of increase risk with increasing frequency of talc (χ^2 (trend) = 3.80; p = 0.05)	**RR** 1.0 0.9 (0.3-2.4) 0.7 (0.3-1.8) 2.0 (0.3-3.4; p=0.07) 1.3 (0.8-1.9)	(Booth M et al, 1989)
talc; purity and composition not specified	1981-1985	-77 patient at Johns Hopkins Hospital in Baltimore, MD with epithelial ovarian cancer -46 age-race matched hospital controls	- subjects questioned about presence and length of genital fiber and respiratory fiber exposure (in this study, fiber exposure was defined as exposure to asbestos, talc, and fiberglass), reproductive factors, estrogen use, family history of cancer, and contraceptive use; information on previous abdominal and gynecological operations was ascertained - potential confounders: obesity, socioeconomic status, religion, reproductive status, live births >2, OC use; confounders added dependent on effect on OR	Areas of application of talc -88% of cases and 87% of controls reported genital fiber use -28.9% of cases and 18.6% of controls reported genital bath talc exposure -61.8% of cases and 55.8% of controls reported application of bath talc to body (risk adjusted for # of live births) -50.7% of cases and 54.5% of controls reported cosmetic face powder use (risk adjusted years of education) Use of talc on sanitary napkins or on diaphragm -61.8% of cases and 55.8% of controls reported talc use on sanitary napkins (risk adjusted for highest wt 1 yr prior to diagnosis) -18.9% of cases and 11.4% of controls reported powder on diaphragm (risk adjusted for # of live births and yrs of education)	**OR** 1.0 (0.2-4.0) 1.7 (0.7 - 3.9) 1.6 (0.6 – 2.7) 1.1 (0.4 – 2.7) **4.8 (1.3 – 17.8)** 3.0 (0.8 – 10.8)	(Rosenblatt KA et al, 1992)

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Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
talc; purity and composition not specified	- 499 patients at Roswell Park Cancer Institute, Buffalo, NY, with epithelial ovarian cancer - 755 age-at-diagnosis matched hospital controls - numbers were adjusted based on answers to questionnaires (i.e., if the subject did not respond to talc use or recall the duration of use)	Oct 1982 – Oct 1995	- information on parity, menstrual history, use of exogenous hormones, contraceptive history, talc use, and personal hygiene was obtained and subjects were questioned about medical, social, family, dietary, and occupational histories - risk was adjusted for OC use, smoking history, family history of epithelial ovarian cancer, age at menarche, menopausal status, income, education, geographic location, history of tubal ligation and/or hysterectomy Limitations - ascertainment and recall bias likely - subjects were asked whether condoms or diaphragms were used for contraception, but did not ask about frequency or duration or diaphragm storage in talc	Areas of application of talc -52.2% of cases and 55.1% of controls never used talc -34.0% of cases and 32.2% of controls reported talc use in the genital or thigh area -2.8% of cases and 2.9% of controls reported talc use on sanitary napkins -11.0% of cases and 9.8% of controls reported talc use in genital or thigh area and on sanitary napkins Duration of talc use -56% of cases and 58.4% of controls had no talc use -9.1% of cases and 9.3% of controls used talc for 1-9 yrs -11.4% of cases and 7.6% of controls used talc for 10-19 yrs 23.5% of cases and 24.6% of controls used talc for $\geq$20 yrs	**OR** 1.0 1.0 (0.8 - 1.3) 0.9 (0.4 – 2.0) 1.1 (0.7 – 1.7) 1.0 0.9 (0.6 – 1.5) 1.4 (0.9 – 2.2) 0.9 (0.6 – 1.2)	(Wong C et al, 1999)

HOSPITAL-BASED CASES/POPULATION-BASED CONTROLS

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
talc; purity and composition not specified	- 215 white females in the Greater Boston area with epithelial ovarian cancer (from 12 hospitals) - 215 matched pop. controls	Nov 1978 – Sept 1981	- exposure to talc by way of contraceptive practices, operations, or perineal hygiene was reviewed for each subject and control -risk was adjusted for parity and menopausal status	-42.8% of cases and 28.4% of controls had any perineal exposure as a dusting powder on the perineum or on sanitary napkins; adjusted RR was compared to subjects who with neither exposure -27.9% of cases and 22.3% of controls had used talc for dusting the perineum or sanitary napkins, but not both -14.9% of cases and 6% of controls had exposure through both dusting the perineum and sanitary napkins; RR was compared to subjects with neither exposure	**OR** **1.92 (1.27-2.89**; p<0.003) 1.55 (p=0.06) 3.28 (p<0.001; (1.68-6.42)	(Cramer DW et al, 1982)
talc; purity and composition not specified; often reported as 'baby powder'	- 235 white women in Boston with epithelial ovarian cancer (from 10 hospitals) - 239 age- and residence-matched pop. controls	July 1984- Sept 1987	- subjects were asked questions about demographic and occupational, medical and reproductive, and dietary histories, including use of douches, cigarette smoking, and hygienic practices, including use of douches, type of sanitary protection, and perineal exposure to talc - use of talc on areas other than the perineum were considered non-exposed - risk was adjusted for parity, education, marital status, religion, use of sanitary napkins, douching, age, and wt	Ever/never perineal use of talc -51.5% of cases and 60.7% of controls reported no genital talc application -48.5% of cases and 39.3% of controls reported perineal talc exposure Use on sanitary napkins, underwear, and/or diaphragm -3.8% of cases and 5.0% of controls reported talc use on sanitary napkins and/or underwear -8.5% of cases and 8.8% of controls reported exposure with diaphragm use or from their partner in combination with sanitary napkins and/or underwear -36.2% of cases and 25.5% of controls reported exposure by dusting powder to the perineum in combination with sanitary napkins and/or underwear Frequency of talc application -13.6% of cases and 11.7% of controls reported <5 appl/mo -10.2% of cases and 10.5% of controls reported 5-29 appl/mo -24.7% of cases and 16.7% of controls reported $\geq$30 appl/mo	**OR** 1.0 1.5 (1.0 – 2.1) 1.1 (0.4 – 2.8) 1.2 (0.6 – 2.4) **1.7 (1.1 – 2.7)** 1.5 (0.8 – 2.7) 1.2 (0.6 – 2.2) **1.8 (1.1 – 3.0)**	(Harlow BL et al, 1992)

Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
talc; purity and composition not specified	-767 women from the Delaware Valley area of PA, NJ, and DE with epithelial ovarian cancer (from 39 hospitals) -1367 age- and geography-matched pop. controls	1994-1998		**Duration of use of talc**		(Ness RB *et al.*, 2000)
				-6.0% of cases and 6.3% of controls reported <10 yrs talc use	1.2 (0.5 – 2.6)	
				-20.9% of cases and 16.3% of controls reported 10-29 yrs talc use	1.6 (1.0 – 2.7)	
				-21.7% of cases and 16.3% of controls reported ≥30 yrs talc use	1.6 (1.0 – 2.7)	
				Number of lifetime applications		
				- 8.1% of cases and 7.9% of controls reported <1000 lifetime applications	1.3 (0.7 – 2.7)	
				-24.3% of cases and 19.2% of controls reported 1000-10,000 lifetime applications	1.5 (0.9 – 2.4)	
				-16.2% of cases and 12.1% of controls reported >10,000 lifetime applications	1.8 (1.0 – 3.0)	
				Age at first use of talc		
				-28.1% of cases and 20.9% of controls were <20 yrs old	**1.7 (1.1 – 2.7)**	
				-11.5% of cases and 10.9% of controls were 20-25 yrs old	1.2 (0.6 – 2.2)	
				-8.9% of cases and 7.5% of controls were >25 yrs old	1.6 (0.8 – 3.2)	
				Years since last talc use		
				-20.4% of cases and 11.3% of controls used talc within the last 6 mos	**2.3 (1.3 – 4.0)**	
				-15.3% of cases and 16.3% of controls last used talc 6 mos-10 yrs ago	1.1 (0.7 – 1.9)	
				-12.8% of cases and 11.7% of controls last used talc 10 or more yrs ago	1.4 (0.8 – 2.6)	
			-era of use was examined; restricted to women that were older than 10 yrs in 1960 - same adjustments listed previously were made	**Era of talc use**		
				-12.3% of cases and 12.6% of controls used talc after 1960	1.1 (0.6 – 2.1)	
				-31.9% of cases and 23.9% of controls used talc before 1960	**1.7 (1.1 – 2.7)**	
			-brand of powder used was examined; if more than one brand used, the brand used most frequently and for the longest time was counted - same adjustments listed previously were made	**Brand/type of talc used**		
				-38.7% of cases and 30.1% of controls used brand or generic baby powder	**1.6 (1.1 – 2.5)**	
				- 6.8% of cases and 7.2% of controls used deodorizing or other scented powders	1.2 (0.6 – 2.5)	
			- subjects were asked questions about sexual, menstrual, obstetric, and breast-feeding histories, history of medical condition that may be related to pelvic inflammation, OC use, tubal ligation, hysterectomy, ovarian operations, and talc exposure - risk was adjusted for age, parity, race, familial history of ovarian cancer, OC use, tubal ligation, hysterectomy, and breast-feeding	**Risk based on area of talc application**	**OR**	
				-45.5% of cases and 53.3% of controls did not use talc	1.0	
				-21% of cases and 16% of controls applied talc to the genital/rectal area	**1.5 (1.1-2.0)**	
				-10% of cases and 6.9% of controls applied talc to sanitary napkins	**1.6 (1.1-2.3)**	
				-9% of cases and 7.3% of controls applied talc to underwear	**1.7 (1.2-2.4)**	
				-1.3% of cases and 2.4% of controls applied talc to diaphragm/ cervical cap	0.6 (0.3-1.2)	
			Limitations - low participation rate among cases and controls - potential recall bias - many of the effect sizes were modest	-7.3% of cases and 9.2% of controls reported talc exposure via a male partner	1.0 (0.7-1.4)	
				-43.7% of cases and 37.5% of controls applied talc to feet	**1.4 (1.1-1.6)**	

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Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
				Risk based on length of application to genital/rectal area/feet - 52.3% of cases and 59.9% of controls reported no use - 2.2% of cases and 1.2% of controls reported talc use of <1 yr - 10% of cases and 7.4% of controls reported talc use of 1-4 yrs - 5.2% of cases and 4.3% of controls reported talc use of 5-9 yrs - 30.4% of cases and 27.1% of controls reported talc use of <1 yr	1.0 2.0 (1.0-4.0) **1.6 (1.1-2.3)** 1.2 (0.8-1.9) 1.2 (1.0-1.5)	
talc; purity and composition not specified	- 170 French-Canadian women in Montreal with primary ovarian carcinomas or borderline tumors (from 2 hospitals); - 111 of the cases were sporadic; 58 cases were familial - 170 age- and ethnic group-matched pop. controls	1995-1996	- subjects were asked questions about reproductive factors; familial history of cancer; medical history, including use of hormone replacement therapy, use of OCs, tubal ligation, and hysterectomy; smoking, alcohol, and education; perineal talc use - study was comparing the risk factors between familial and sporadic ovarian cancer	- 10.6% of cases and 4.7% of controls reported perineal use of talc - 9.91% of the sporadic cases and 12.1% of the familial cases reported perineal use of talc	p= 0.064 p= 0.79 (sporadic v. familial)	(Godard B et al., 1998)
	- 153/170 of the cases and 152/170 controls from above - 101 of the cases were sporadic, 51 of the cases were familial		- multivariate analysis was performed with 153 cases and 152 controls	- perineal use of talc by cases vs. controls - perineal talc use by sporadic cases - perineal talc use by familial cases	**RR** 2.49 (0.94-6.58; P=0.066) 2.45 (0.85-7.07; P=0.098) 3.25 (0.83-12.4; P=0.084)	

HOSPITAL-BASED CASES/HOSPITAL- and POPULATION-BASED CONTROLS

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
talcum powder; purity and composition not specified	- 188 women from northern California with primary epithelial cancer (from 7 hospitals) - 280 matched hospital controls - 259 matched pop. controls	Jan 1983 – Dec 1985	- the researchers stated that RR associated with talc use, tubal ligation, and hysterectomy were similar when cases were compared to both control groups; therefore the control groups were combined - risk was adjusted for parity Limitations - failure to interview all eligible ovarian cancer patients and a completely random sample of controls - cofounding by differential talc use among women with characteristics predictive of ovarian cancer (unlikely) - random error in reported talc use	Type of talc exposure - 40% of cases and 43% of controls reported no talc use - 12% of cases and 10% of controls reported talc exposure on the perineum only - 3% of cases and 5% of controls reported talc exposure on sanitary pads only - 5% of cases and 4% of controls reported talc exposure with diaphragm use only - 36% of cases and 31% of controls reported talc exposure by two of the three use types - 1% of cases and 2% of controls reported talc exposure by all three use types	**OR** 1.0 1.45 (0.81-2.6) 0.62 (0.21-1.80) 1.60 (0.63-3.58) 1.36 (0.91-2.04) 0.35 (0.04-2.94)	(Whittemore AS et al., 1988)
			- risk was also examined based on duration of use of talcum powder; talc use after tubal ligation or hysterectomy was excluded - risk was adjusted for parity	Duration of talc use - 55% of cases and 59% of controls did not report yrs of talc use - 18% of cases and 13% of controls reported talc exposure of 1-9 yrs - 27% of cases and 27% of controls reported talc exposure of 10+ yrs - 23% of cases and 19% of controls reported 20+ talc applications/mo - overall trend for 30 uses/mo	1.0 1.60 (1.00-2.57; p=0.05) 1.11 (0.82-1.96; p=0.61) 1.45 (0.94-2.22) 1.30 (0.88-1.92)	

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Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
POPULATION-BASED CASES/POPULATION-BASED CONTROLS						
talc (as baby powder) deodorizing powders that contain other substances in addition to talc	- 116 white women of western Washington state with border-line ovarian tumors (from the Seattle-Puget Sound Cancer Surveillance System) - 158 white age- and residence-matched controls	1980-1985	- subjects were asked questions about reproductive and sexual history, medical history, and perineal exposure to talc - risk was adjusted for age, parity, and use of oral contraceptives

Limitations
- only 30% of potentially eligible cases and controls participated | Types of exposure to talc
-42.2% of cases and 40.5% of controls reported no perineal exposure to powder | **RR** 1 | (Harlow BL & Weiss NS, 1989) |
				-42.2% of cases and 40.5% of controls reported any perineal exposure to powder	1.1 (0.7-2.1)	
				-6.9% of cases and 13.3% of controls reported powder exposure by diaphragm storage only	0.5 (0.2-1.4)	
				-9.5% of cases and 17.1% of controls reported powder exposure by diaphragm storage or by other methods	0.5 (0.2-1.3)	
				-20.7% of cases and 19.0% of controls reported powder exposure following bathing only	1.2 (0.6-2.6)	
				-29.3% of cases and 23.4% of controls reported powder exposure following bathing or by other methods	1.3 (0.8-2.7)	
				-6.0% of cases and 2.5% of controls reported powder exposure by use on sanitary napkins only	2.2 (0.8-19.8)	
				-12.1% of cases and 6.3% of controls reported powder exposure by use on sanitary napkins or by other methods	1.9 (0.9-6.9)	
				-6.0% of cases and 23.4% of controls reported after bathing and on sanitary napkins	2.2 (0.8-18.8)	
			-	Type of powder used (i.e., baby, deodorizing, or cornstarch)
-15.5% of cases and 19.6% of controls reported baby powder only	0.8 (0.4-1.9)	
				-19.0% of cases and 21.5% of controls reported baby powder only or combined use	0.9 (0.5-2.0)	
				-11.2% of cases and 12.0% of controls reported talc, unspecified (no combined use)	1.0 (0.4-2.4)	
				-3.4% of cases and 4.4% of controls reported cornstarch only	0.8 (0.2-3.8)	
				-8.6% of cases and 23.4% of controls reported deodorizing powder only	**3.5 (1.2-28.7)**	
				-12.1% of cases and 4.4% of controls reported deodorizing powder only or combined use	**2.8 (1.1-11.7)**	
				Route of talc exposure and type of powder used
-any powder use after bathing
- 8.6% of cases and 3.8% of controls reported any use of deodorizing powder	3.1 (0.8-10.9)	
				-20.7% of cases and 20.3% of controls reported no use of deodorizing powder	1.1 (0.5-2.4)	
				-any powder use on sanitary napkins
- 6.9% of cases and 23.4% of controls reported any use of deodorizing powder	2.6 (0.9-22.4)	
				-5.2% of cases and 3.8% of controls reported no use of deodorizing powder	1.5 (0.4-6.5)	

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Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
talc-containing dusting powder; purity and composition not specified	- 112 females in Beijing, China with epithelial ovarian cancer (from Beijing Cancer Registry) - 224 age-matched community controls	1984-1986	- subjects were asked questions about menstrual, obstetric, marital, medical, and familial histories - risk was adjusted for education and parity -risk with occupational exposure was also determined Limitations - some ovarian cancer patients may not have been ascertained for the study - high rate of loss due to deaths could reflect on survival and on risk - exclusion of controls with current health problems	Types of talc exposure - 93.8% of cases and 97.8% of controls reported no use of dusting powder - 6.3% of cases and 2.2% of controls reported dusting powder use on the lower abdomen and perineum - number of cases and controls exposed occupationally to talc (occupation was not specified)	RR 1.0 3.9 (0.9-10.6) 0.9 (0.3-2.9)	(Chen Y et al., 1992)
5 categories of powder: talcum, cornstarch, baby, deodorant, and scented body/bath	- 313 white women in western WA (pop.-based) with epithelial ovarian cancer - 422 white age- and geography-matched pop. controls	Jan 1986 – Dec 1988	- subjects were questioned about genital powder exposure, demographic characteristics, reproductive, medical, and smoking histories, and birth control methods - risk was adjusted for age; further adjustment for education, income, marital status, BMI, OC use, or parity did not alter the estimated RRs Limitations - a sizeable number of eligible women, particularly those with ovarian cancer, did not participate - difficult to ascertain whether perineal powder application correctly estimates actual exposure to particles - direct comparison with other studies is limited because of differences in definitions, groupings, and analysis of genital powder use - insufficient information to address influence of condom use on risk	Ever/never genital use of talc - 49.2% of cases and 60.7% of controls reported no lifetime genital powder application - 50.8% of cases and 39.3% of controls reported any lifetime genital powder application Exclusive use of powder - 17.6% of cases and 11.4% of controls reported perineal dusting only - 7.0% of cases and 8.3% of controls reported diaphragm storage in powder only - 3.8% of cases and 2.4% of controls reported powder on sanitary napkins only - 5.8% of cases and 6.6% of controls reported genital deodorant spray only Any perineal dusting and CLE (days) - 30.4% of cases and 20.6% of controls reported any dusting - 6.4% of cases and 5.2% of controls reported ≤2000 days CLE - 7.7% of sasses and 6.2% of controls reported 2001-5000 CLE - 6.7% of cases and 5.2% of controls reported 5001-10,000 CLE - 8.9%of cases and 4.0% of controls reported >10,000 CLE - risk was adjusted for age and other methods of genital powder application	OR 1.0 1.5 (1.1 - 2.0) 1.8 (1.2 – 2.9) 0.8 (0.4 – 1.4) 1.5 (0.6 – 3.6) 1.5 (0.8 – 3.0) 1.8 (0.9 – 3.5) 1.6 (0.9 – 2.9) 1.2 (0.6 – 2.4) 1.8 (0.9 – 3.4)	(Cook LS et al., 1997)

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Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
			- risk was adjusted for age and other methods of genital powder application	Any diaphragm storage in powder CLE (mos)		
				-14.7% of cases and 12.1% of controls reported diaphragm storage in powder	1.0 (0.6 – 1.6)	
				-7.7% of cases and 6.2% of controls reported ≤60 mos CLE	1.1 (0.6 – 1.9)	
				-4.8% of cases and 4.7% of controls reported >60 mos CLE	0.8 (0.4 - 1.7)	
			- risk was adjusted for age and other methods of genital powder application (none/any)	Any powder on sanitary napkins and CLE (mos) and applications		
				-12.1% of cases and 9.5% of controls reported any powder on sanitary napkins	0.9 (0.5 – 1.5)	
				-8.0% of cases and 5.0% of controls reported ≤120 mos CLE	1.3 (0.7 – 2.4)	
				-3.8% of cases and 4.5% of controls reported >120 mos CLE	0.5 (0.2 – 1.1)	
				-7.3% of cases and 4.5% of controls reported ≤1000 lifetime applications	1.3 (0.7 – 2.5)	
				-4.5% of cases and 5.0% of controls reported >1000 lifetime applications	0.6 (0.3 – 1.2)	
			- risk was adjusted for age and other methods of genital powder application	Any genital deodorant spray and CLE (mos) and applications		
				-12.8% of cases and 9.5% of controls reported any genital deodorant spray	**1.9 (1.1 – 3.1)**	
				-7.7% of cases and 7.4% of controls reported ≤12 mos CLE	1.5 (0.9 – 2.8)	
				-4.8% of cases and 2.1% of controls reported >12 mos CLE	**2.7 (1.1 – 6.6;** $p < 0.05$)	
				-9.3% of cases and 8.1% of controls reported ≤500 lifetime applications	1.7 (1.0 – 2.9)	
				-3.2% of cases and 1.4% of controls reported >500 lifetime applications	2.6 (0.9 – 7.6; $p < 0.05$)	
			- risk was adjusted for age	Exclusive use by powder type		
				-5.1% of cases and 3.8% of controls used talcum powder only	1.2 (0.6 – 2.5)	
				-9.9% of cases and 8.5% of controls used baby powder only	1.4 (0.8 – 2.4)	
				-1.6% of cases and 2.6% of controls used cornstarch only	0.9 (0.3 – 2.9)	
				-2.9% of cases and 2.4% of controls used deodorizing powder only	1.0 (0.4 – 2.6)	
				-8.6% of cases and 5.9% of controls used bath/body powder only	1.6 (0.9 – 3.0)	
			- risk was adjusted for age and use of other types of powders (yes/no)	Use of any powder type		
				-10.5% of cases and 5.5% of controls reported any talcum powder	1.6 (0.9 – 2.8)	
				-16.6% of cases and 14.5% of controls reported any baby powder	1.1 (0.7 – 1.8)	
				-2.6% of cases and 3.8% of controls reported any cornstarch	0.8 (0.3 – 2.0)	
				-7.7% of cases and 5.7% of controls reported any deodorizing powder	1.1 (0.6 – 2.0)	
				-16.6% of cases and 10.2% of controls reported any bath/body powder	1.5 (0.9 – 2.4)	

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Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
talc; purity and composition not specified	- 189 women in Greater Athens with epithelial ovarian tumors (2 hospitals) - 200 hospital visitor controls	June 1989- Mar 1991	- the tumors were stratified by histological subtype - risk was adjusted for age - the women were asked about smoking; alcohol and coffee consumption; reproductive history; frequency of use of analgesics, tranquilizers, or hypnotics; hair dyes; talc in the perineal region; hair dyes - multiple regression adjusted for age, yrs of schooling, body wt prior to onset, age at menarche, parity, menopausal status, age at first birth and at menopause, smoking, coffee drinking, alcohol consumption, hair dyeing, talc application, use of analgesics, and tranquilizers/hypnotics, and for mutual confounders Limitations - moderate study size - possibility of selection bias - possibility of information bias	Controls (422 total) 60.7% never used talc perineally 39.3% ever used talc perineally All serous tumors (131 total) -45.8% never used talc perineally -54.2% ever used talc perineally Serous tumors (43 total) -67.4 % never used use talc perineally -32.6% ever used talc perineally Endometroid tumors (36 total) -52.8% never used use talc perineally -47.2% ever used talc perineally Other tumors (103 total); (17 clear cell; 3 undiffentiated; 83 unclassified adenocarcinomas or unspecified carcinomas) -44.7% never used use talc perineally -55.3% ever used talc perineally - 3.1% of cases and 3.5% of controls reported talc application in the perineum - a crude RR, age-adjusted RR, and multiple regression RR were determined	**RR** 1.0 **1.7 (1.1 – 2.5)** 0.7 (0.4 – 1.4) 1.2 (0.6 – 2.3) **1.8 (1.1 – 2.8)** **OR** 0.90 (crude; 0.30-2.74) 0.86 (age-adjusted; 0.27-2.68) 1.05 (multiple regression; 0.28-3.98)	(Tzonou A et al, 1993)
talc; purity and composition not specified, and cornstarch	- 450 women from Toronto and Ontario, Canada with epithelial ovarian cancer (pop.-based) - 564 age-matched pop.-based controls	Nov 1989 – Oct 1992	- subjects were questioned about medical and reproductive histories, menstrual characteristics, pregnancies, hormone and contraceptive use, and talc (and cornstarch) usage, type, and exposure - risk was adjusted for age, OC use, parity, breast-feeding, tubal ligation, hysterectomy, and family history of ovarian or breast cancer	Powder type exposures -44%of cases and 35.6% of controls reported any talc exposure -0.44% of cases and 0.85% of controls reported any cornstarch exposure -0.89%of cases and 1.24% of controls reported cornstarch/talc exposure -11.3% of cases and 8.7% of controls reported talc exposure via sanitary napkins 38.2% of cases and 10.5% of controls reported talc exposure after bathing	**OR** **1.42 (1.08 – 1.86)** 0.31 (0.06 – 1.66) 0.68 (0.18 – 2.33) 1.26 (0.81 – 1.96) 1.31 (1.0 – 1.73)	(Chang S & Risch HA, 1997)

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Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
			- risk was adjusted as above	Frequency (per mo) of after-bath talc use - mean uses/mo after-bath talc was 14.6 for cases and 17.2 for controls		
				- 16.9% of cases and 10.5% of controls reported <10 uses/mo after-bath talc	0.89 (0.74 – 1.07)	
				- 12.8% of cases and 11.3% of controls reported 10-25 uses/mo after-bath talc	**1.84 (1.24 – 2.73)**	
				- 9.1% of cases and 10.6% of controls reported >25 uses/mo after-bath talc	1.13 (0.74 – 1.72)	
					0.95 (0.61 – 1.49)	
			- it was assumed the regular after-bath talc use commenced at age 20 - risk was adjusted as above	Duration of after-bath talc use - mean yrs after-bath talc use was 32.9 yrs for cases and 35.4 yrs for controls	1.09 (0.98 – 1.21)	
				- 13.3% of cases and 9.2% of controls reported <30 yrs after-bath talc use	**1.7 (1.09 – 2.64)**	
				- 15.8% of cases and 11.9% of controls reported 30-40 yrs after-bath talc use	1.44 (0.96 – 2.15)	
				- 9.1% of cases and 11.3% of controls reported >40 yrs after-bath talc use	0.87 (0.54 – 1.38)	
			- risk was adjusted as above	After-bath talc use pre/post 1970 - case mean was 26.4 yrs and control mean was 24.9 yrs after-bath talc use before 1970	1.09 (0.98 – 1.22)	
				- case mean was 6.5 yrs and control mean was 10.4 yrs after-bath talc use after 1970	1.1 (0.89 – 1.35)	
talc; purity and composition not specified	- 200 women in Israel with primary invasive (164) or borderline (36) epithelial ovarian cancer (Israel Cancer Registry) - 408 geography-matched pop. controls	Jan 1990 – Sept 1993	- subjects were asked questions about obstetric and gynecologic history, including infertility and treatment, smoking, education, and talc usage Limitations - no access to medical records to verify information - possibility of recall bias - possibility that results were confounded by a specific cause of infertility	- 89.0% of cases and 94.4% of controls reported never-seldom use of talc - **10.5% of cases and 5.6% of controls reported moderate-a lot use of talc (P= 0.04)**	not given	(Shushan A et al., 1996)
talc; purity and composition not specified	- 824 women in Queensland, New South Wales, and Victoria, Australia with epithelial ovarian cancer (gynecological-oncology registries) - 860 age- and geography-matched pop. controls	Aug 1990 – Dec 1993	- subjects were asked questions about education and ethnicity, and obstetric, marital, occupational, medical, and familial histories, childhood mumps history, and use of talc - risk was adjusted for parity Limitations - potential selection bias	- 56.7% of cases and 52.0% of controls used talc around the abdomen/perineum	<u>OR</u> **1.27 (1.04-1.54)**	(Purdie D et al., 1995)

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Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
talc, baby powder, deodorizing powders; purity and composition not specified	- 563 women in eastern MA and NH with epithelial ovarian cancer (pop.-based) - 523 age-matched pop. controls - (Phase I of the New England Case Control [NECC] study)	May 1992 – March 1997	- subjects were asked questions about demographics, reproductive and menstrual history, medical history, personal habits, and whether talc-, baby-, or deodorizing powders were dusted or sprayed regularly and age at 1st use, type of powder, applications/mo, and total yrs of use -risk was adjusted for age, study center, tubal ligation, BMI, parity, OC use, and family history of breast/ovarian cancer Limitations - possible recall bias - potential bias from confounding	Exposure to talc - 55.4% of cases and 63.9% of controls reported no personal use of talc - 17.6% of cases and 18.0% of controls reported use of talc in non-genital areas - 12.6% of cases and 9.8% of controls reported exposure through dusting of the perineum - 3.6% of cases and 2.3% of controls reported exposure through dusting sanitary napkins - 1.4% of cases and 1.2% of controls reported exposure through dusting underwear - 9.4% of cases and 5.0% of controls reported multiple uses in the genital area	$\underline{OR}$ 1.0 1.08 (0.77–1.50) 1.45 (0.97-2.18) 1.45 (0.68-3.09) 1.21 (0.40-3.64) **2.15 (1.30-3.57)**	(Cramer DW *et al*, 1999)
			- risk adjusted as above	Eve/never genital talc use - 73% of cases and 81.8% of controls reported no genital talc use - 27.0% of cases and 18.2% of controls reported any genital use	1.0 **1.60 (1.18-2.15)**	
			-risk was adjusted for age, study center, tubal ligation, and use of other powders	Type of powder used - 26.4% of cases and 17.6% of controls reported use of talc - 0.2% of cases and 0.6% of controls reported use of cornstarch	**1.69 (1.26-2.27)** 0.31 (0.03-3.01)	
			- subjects with no personal use were asked about use of husband - risk was adjusted as aboveu	No personal use/use of talc by husband - 87.6% of cases and 92% of controls reported no husband talc use - 12.4% of cases and 8.0% of controls reported husbands did use talc	1 .0 1.52 (0.92-2.52)	
			-risk was adjusted for age, study center, tubal ligation, BMI, parity, OC use, and family history of breast/ovarian cancer	Frequency of use per month for total of all uses in the genital area - 11.5% of cases and 5.4% of controls reported ≤30 uses/mo - 10.6% of cases and 9.8% of controls reported 30-39 uses/mo - 9.8% of cases and 2.9% of controls reported 40+ uses/mo	**2.21 (1.37-3.56)** 1.17 (0.78-1.76) 1.57 (0.80-3.10)	
			- risk was adjusted as above	Duration of talc use -9.9% of cases and 5.9% of controls reported <20 yrs talc use -5.8% of cases and 5.0% of controls reported 20-30 yrs talc use -10.6% of cases and 7.1% of controls reported ≥30 yrs talc use - p-value for linear trend, excluding non-genital exposure - p-value for linear trend, including non-genital exposure	**1.86 (1.16-3.00)** 1.33 (0.76-2.30) 1.44 (0.91-2.26) p = 0.477 p = 0.062	
			- same adjustments listed previously were made	Total applications - 9.2% of cases and 5.2% of controls applied talc <3000 x - 6.5% of cases and 5.4% of controls applied talc 3000 – 10,000 x - 6.5% of cases and 3.8% of controls applied talc >10,000 x - p-value for linear trend, excluding non-genital exposure - p-value for linear trend, including non-genital exposure	**1.84 (1.12-3.30)** 1.43 (0.84-2.41) 1.43 (0.92-2.22) 0.164 0.472	

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Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
			- same adjustments listed previously were made	Age at first use of talc - 17.4% of cases and 12.8% of controls were <20 yrs old - 6.5% of cases and 3.4% of controls were 20-25 yrs old - 2.3% of cases and 1.7% of controls were >25 yrs old - p-value for linear trend including non-exposed subjects	**1.46 (1.03-2.07)** **1.87 (1.03-3.39)** 1.54 (0.64-3.72) p=0.504	
			- the tumors were stratified by histological subtype - risk was adjusted for age, BMI, primary relevance with breast or ovarian cancer, parity, OC use, tubal ligation, and study center	Controls (523 total) - 81.8% never used talc perineally - 18.2% ever used talc perineally	**OR** 1.0	
				Serous borderline tumors (86 total) - 73.3% never used talc perineally - 26.7% ever used talc perineally	1.38 (0.82 – 2.31)	
				Serous invasive tumors (229 total) - 68.6 % never use talc perineally - 31.4% ever used talc perineally	**1.70 (1.22 – 2.39)**	
				Mucinous tumors (83 total) - 80.7% never used talc perineally - 19.3% ever used talc perineally	0.79 (0.44 – 1.40)	
				Endometroid/clear cell tumors (130 total) - 76.2% never used use talc perineally - 23.8% ever used talc perineally	1.04 (0.67 – 1.61)	
				Undifferentiated tumors (35 total) - 71.4% never used use talc perineally - 28.6% ever used talc perineally	1.44 (0.67 – 3.08)	
talc; purity and composition not specified	- 668 women in eastern MA and NH with invasive ovarian cancer (pop.-based) - 721 age-matched pop. controls - (Phase 2 of the NECC)	July 1998 – July 2003	- risk for ovarian cancer with talc use was determined - risk was adjusted for age, study center, parity, non-White race, and Jewish religion Limitations - exposure information was collected by self-report, introducing the possibility of misclassification - inability to directly compare anti-MUC1 antibody levels in cases and controls to calculate an OR	Talc use - 47.8% of cases and 47.6% of controls reported no talc use - 32.0% of cases and 28.2% of controls reported genital use of talc - 20.2% of cases and 24.1% of controls reported body use of talc only	**OR** 1.0 1.16 (0.90 – 1.49; P=0.25) 0.87 (0.66 - 1.15; P=0.33)	(Cramer DW et al., 2005)

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Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
talc; purity and composition not specified	-210 women with ovarian cancer -600 birth-, DNA type-,and menopausal status-matched controls (these are subjects included in the Nurses' Health Study that provided blood or buccal samples)	1989-2004	- examined whether an association between genital talc exposure and ovarian cancer risk is modified by variants of the *NAT2* and *GSTM1* genes and the *GSTT1* gene - subjects were asked about application of talcum, baby or deodorizing powder to the perineal area or sanitary napkins - risk with regular talc use and frequency of genital talc use was determined -risk was adjusted for the matching factors, duration of oral contraceptive use, parity, tubal ligation, BMI, and duration of PMH use Limitations - inability to detect interactions with certain combinations of genes and for specific histologic subtypes - loss of some detail due to the use of common exposure and covariate definitions (particularly for the NECC)	total epithelial cancer (210 cases; 600 controls) - 40% of cases and 39% of controls reported any history of genital talc use - 70.8% of cases and 76% of controls reported no regular genital talc use (1x/wk or more) - 29.2% of cases and 24% of controls reported regular genital talc use Frequency of genital talc use - 61.5% of cases and 64.6% of controls reported no frequency of genital talc use - 9.2% of cases and 11.4% of control reported use <1 x/wk - 11.3% of cases and 11.2% of controls reported use 1-6 x/wk - 18% of cases and 13% of controls reported daily genital talc use - P_{trend} for frequency of genital talc use	**OR** p= 0.79 1.0 1.24 (0.83 – 1.83; p = 0.15) 1.0 0.98 (0.54 – 1.79) 1.01 (0.57 – 1.79) 1.44 (0.88 – 2.37; p = 0.08) 0.18	(Gates MA *et al.*, 2008)
	-1175 women from MA and NH with epithelial ovarian cancer -1202 age- and state-matched pop. controls - (pooled data from subjects in Phase 1 and Phase 2 of the NECC that provided a blood specimen)	May 1992 – July 2003		serous invasive ovarian cancer (93 cases; 263 controls) - 68.2% of cases and 73.8% of controls reported no regular genital talc use - 31.8% of cases and 26.3% of controls reported regular genital talc use Frequency of genital talc use - 61.4% of cases and 62.9% of controls reported no frequency of genital talc use - 6.8% of cases and 10.8% of control reported use <1 x/wk - 13.6% of cases and 10.4% of controls reported use 1-6 x/wk - 18.2% of cases and 15.8% of controls reported daily genital talc use - P_{trend} for frequency of genital talc use	1.0 1.48 (0.82-2.68) 1.0 0.79 (0.29-2.11) 1.64 (0.71-3.79) 1.34(0.65-2.76) 0.29	
			- subjects were asked about use of talcum, baby or deodorizing powder, type of use of the powder, frequency of use, number of years of use, brand used -risk was adjusted for the matching factors, duration of OC use, parity, tubal ligation, BMI, and duration of PMH use - risk with regular talc use and frequency of genital talc use was determined - risk was adjusted for age, study center, duration of OC use, parity, tubal ligation, BMI, duration of PMH use	total epithelial cancer (1175 cases; 1202 controls) - 29% of cases and 24% of controls reported any history of genital talc use - 73.2% of cases and 79.7% of controls reported no regular genital talc use (1x/wk or more) - 26.8% of cases and 20.3% of controls reported regular genital talc use Frequency of genital talc use - 70.9% of cases and 76.3% of controls reported no frequency of genital talc use - 2.3% of cases and 3.4% of control reported use <1 x/wk - 10.5% of cases and 8.0% of controls reported use 1-6 x/wk - 16.3% of cases and 12.3% of controls reported daily genital talc use - P_{trend} for frequency of genital talc use	**p = 0.003** 1.0 **1.40 (1.15 – 1.70; p < 0.001)** 1.0 0.72 (0.43 – 1.19) 1.33 (1.00 – 1.79) **1.41 (1.10 – 1.79; p=0.006)** **0.002**	

Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
				serous invasive ovarian cancer (450 cases; 1202 controls)		
				- 69.0% of cases and 79.7% of controls reported no regular genital talc use	1.0	
				- 31.0% of cases and 20.3% of controls reported genital talc use	**1.62 (1.26-2.09)**	
				- 66.6% of cases and 76.3% of controls reported no frequency of genital talc use	1.0	
				- 2.4% of cases and 3.4% of control reported use <1 x/wk	0.65 (0.32-1.33)	
				- 12.5% of cases and 8.0% of controls reported use 1-6 x/wk	**1.56 (1.08-2.26)**	
				- 18.5% of cases and 12.3% of controls reported daily use	**1.61 (1.18-2.20)**	
				- P_{trend} for frequency of genital talc use	**< 0.001**	
	- pooled analysis of the NECC study (Phase 1 and Phase 2 combined) and the 210 cases and 600 controls from the Nurses' Health Study (presented above)		- the researchers analyzed the interactions between talc use and genes in detoxification pathways	total epithelial cancer		
				- no regular genital talc use (1x/wk or more)	1.0	
				- any reported regular genital talc use	1.36 (1.13 – 1.63)	
				Frequency of genital talc use		
				- no frequency of genital talc use	1.0	
				- reported use <1 x/wk	0.82 (0.55 – 1.20)	
				- reported use 1-6 x/wk	1.26 (0.97 – 1.63)	
				- reported daily genital talc use	**1.41 (1.14 – 1.76)**	
				- P_{trend} for frequency of genital talc use	**<0.001**	
				serous invasive ovarian cancer		
				- reported no regular genital talc use	1.0	
				- reported any genital talc use	**1.60 (1.26 – 2.02)**	
				- no frequency of genital talc use	1.0	
				- 2 reported use <1 x/wk	0.70 (0.39 – 1.24)	
				- reported use 1-6 x/wk	**1.12 – 2.21**	
				- reported daily use	**1.56 (1.17 – 2.08)**	
				- P_{trend} for frequency of genital talc use	**<0.001**	
				- there was no clear evidence of an interaction with *GSTM1* alone or *NAT2*		

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Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/Geographical Area	Study/Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
talc; purity and composition not specified	"average risk" women from the 3 phases without hysterectomy or family history of cancer - 1098 women with invasive ovarian cancer (pop.-based) - 1363 age-matched pop. controls that were >40 yrs old (includes women from NECC phases 1 and 2, and the 897 Phase 3 cases and 857 Phase3 controls)	1992-2008 (all 3 phases) (Phase 3: 2003-2008)	- Phase 1(Cramer DW et al., 1999) and Phase 2(Cramer DW et al., 2005) described previously - reviewed relative risk for "average risk" women (excluded women at high risk for breast or ovarian cancer) Limitations - use of case-control data to develop the scoring system because of: - potential for recall bias - potential for selection bias - the calculation of only RR and not absolute risk	Long-term use of talc - 84.9% of cases and 88.8% of controls reported no long-term (10+ yr) talc use - 15.1% of cases and 11.2% of controls reported long-term talc use	OR 1.0 1.42 (1.12 – 1.81; P = 0.004)	(Vitonis AF et al., 2011)
talc; purity and composition not specified	- 609 women from Los Angeles county with ovarian cancer (pop. based) - 688 race/ethnicity- and age-matched controls	1998-2002	- subjects were asked questions about medical, gynecological, reproductive, and lifestyle histories, family history of breast or ovarian cancer, OC use; tubal ligation or hysterectomy; use of NSAIDs, and talc use - risk was adjusted for race, age, education, tubal ligation, cancer history, menopausal status, OC use, parity	Use of talc - 60% of cases and 68.2% of controls never used talc - 40% of cases and 31.8% of controls ever used talc - 18.5% of case and 15% of control talc users used talc in non-perineal area - 21.5% of case and 16.9% of control talc users used talc in perineal area Frequency and duration of talc use - 5.8% of cases and 4.5% of controls used talc for ≤20 yrs and ≤10x/mo - 3.8% of cases and 4.4% of controls used talc for ≤20 yrs and >10- ≤30x/mo - 3.5% of cases and 3.1% of controls used talc for ≤20 yrs and ≥30x/mo - 7.4% of cases and 7.1% of controls used talc for >20 yrs and ≤10x/mo - 8.4% of cases and 6.3% of controls used talc for >20 yrs and >10- ≤30x/mo - 11.1% of cases and 6.5% of controls used talc for≥20 yrs and ≥30x/mo Total number of talc uses - 8.1% of cases and 7.6% of controls used talc ≤5200 x - 7.6% of cases and 6.8% of controls used talc >5200- ≤15,600 x - 10.4% of cases and 8.9% of controls used talc >15,600-≤52,000 x - 13.9% of cases and 8.6% of controls used talc >52,000 x	RR 1.0 1.48 (1.15 – 1.91) 1.43 (1.03 – 1.98) 1.53 (1.13 – 2.09) 1.36 (0.79 – 2.32) 1.16 (0.63 – 2.12) 1.23 (0.63 – 2.41) 1.27 (0.80 – 2.01) 1.57 (0.99 – 2.50) 2.08 (1.34 – 3.23) 1.2 (0.77 – 1.88) 1.38 (0.87 – 2.20) 1.34 (0.89 – 2.02) 1.99 (1.34 – 2.96)	(Wu AH et al., 2009)

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Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
			- examined risk based on total number of talc uses	**Before 1975**		
				- 4.0% of cases and 5.1% of controls used talc ≤200 x	0.84 (0.47 – 1.51)	
				- 4.8% of cases and 4.2% of controls used talc >200-≤15,600 x	1.41 (0.79 – 2.53)	
				- 8.1% of cases and 6.5% of controls used talc >15,600-≤52,000 x	1.45 (0.91 – 2.31)	
				- 13.6% of cases and 8.4% of controls used talc >52,000 x	**1.93 (1.29 – 2.88)**	
				After 1975		
				- 4.1% of cases and 2.5% of controls used talc ≤200 x	1.95 (0.98 – 3.89)	
				- 2.8% of cases and 2.6% of controls used talc >200-≤15,600 x	1.17 (0.56 – 2.48)	
				- 2.6% of cases and 2.5% of controls used talc >15,600	0.98 (0.45 – 2.13)	
talc; purity and composition not specified	- 83 African-American and 550 white women from 48 counties of NC with epithelial ovarian cancer	1999-2008	- examined risk factors in African-American vs. white women, including use of talc	**African-American women**	**OR**	(Moorman OG et al, 2009)
			-risk was adjusted for age	- 54.2% of cases and 56.0%of controls reported no talc use	1.0	
				- 45.8% of cases and 44.0% of controls reported any talc use	1.19 (0.68 – 2.09)	
	- 134 African-American and 533 white age-, race/ethnicity-, and geographical region-matched controls		**Limitations**	**White women**		
			- relatively small sample size of African-American women	- 59.6% of cases and 61.0%of controls reported no talc use	1.0	
			- modest sample size precluded conducting analyses within subgroups	- 40.4% of cases and 39.0% of controls reported any talc use	1.04 (0.82 – 1.33)	
			- participation bias			
talc; purity and composition not specified	- 256 women from 22 central CA counties with epithelial ovarian cancer (pop.-based)	2000-2001	- subjects were asked questions on menstrual, repro-ductive, gynecological, surgical, and family cancer histories, use of exogenous hormones	**Ever/never use of talc**	**OR**	(Mills PK et al, 2004)
				- 57.4% of cases and 62.9% of controls never used talc	1.0	
			- examined risk with talc use based on frequency, duration, and cumulative use and timing of use	- 42.6% of cases and 37.1% of controls ever used talc	**1.37 (1.02 – 1.85)**	
	- 1122 age- and ethnicity-matched controls		- numbers were adjusted based on available data	**Frequency of use**		
			- risk was adjusted for age, race/ethnicity, OC use, and breastfeeding	- 13.4% of cases and 12.5% of controls used talc rarely to several times/mo	1.34 (0.87 – 2.08)	
				- 12.4% of cases and 13.2%of controls used talc 1-3x/wk	1.16 (0.74 – 1.81)	
				- 16.5% of cases and 11.1% of controls used talc 4-7x/wk	**1.74 (1.14 – 2.64)**	
			Limitations	- P trend	**0.015**	
			- relatively small sample size	**Duration of use**		
			- low response fraction	- 7.4% of cases and 9.2% of controls used talc for ≤3 yrs	1.01 (0.58 – 1.76)	
			- possible recall bias	- 13.2% of cases and 9.1% of controls used talc for 4-12 yrs	**1.86 (1.16 – 2.98)**	
			- inability to exclude use during non-ovulatory periods or and post-tubal ligation or hysterectomy	- 11.9% of cases and 9.4% of controls used talc for 13-30 yrs	1.45 (0.90 – 2.32)	
			- inability to differentiate among formulations used	- 8.6% of cases and 8.1% of controls used talc for >30 yrs	1.22 (0.72 – 2.08)	
				- P trend	**0.045**	
				Cumulative use (frequency x duration)		
				- 7.4% of cases and 8.8% of controls were in the 1st quartile (lowest exposure)	1.03 (0.59 – 1.80)	
				- 11.5% of cases and 8.8% of controls were in 2nd quartile	**1.81 (1.10 – 2.97)**	
				- 14.0% of cases and 9.9% of controls were in 3rd quartile	**1.74 (1.11 – 2.73)**	
				- 8.2% of cases and 8.1%of controls were in 4th quartile (highest exposure)	1.06 (0.62 – 1.83)	
				- P trend	0.051	

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Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
talc; purity and composition not specified	- 1576 women from Australia with epithelial ovarian cancer - 1509 age- and state-of-residence-matched pop. controls	Jan 2002 – Sept 2005	- subjects were asked questions about medical and surgical and family cancer histories, lifestyle habits, reproductive factors, hysterectomy/tubal ligation, and talc use - risk was adjusted for age, education, parity, and OC use Limitations - low response rate for controls, which could result in selection bias - medical histories were self-reported	**Year of first use** - 21.5% of cases and 19.4% of controls before /during 1975 - 19.4% of cases and 15.0% of controls after 1975 **Age at first use** - 12.4% of cases and 16.0% of controls were <20 yrs old - 10.7% of cases and 5.8% of controls were 20-24 yrs old - 17.8% of cases and 12.6% of controls were ≥25 yrs old **First use before or after first birth** - 18.8% of cases and 23.8% of controls prior to first birth - 22.0% of cases and 10.6% of controls after first birth **Yrs since last use** - 13.2% of cases and 12.5% of controls are current users - 11.2% of cases and 5.8% of controls used talc 1-2 yrs ago - 8.3% of cases and 7.8% of controls used talc 3-20 yrs ago - 8.3% of cases and 8.3% of controls used talc >20 yrs ago - 54% of cases and 57% of controls reported never using talc in the perineal region - 46% of cases and 43% of controls reported ever using talc in the perineal region **Duration of use (with no ligation/hysterectomy)** - 13% of cases and 13% of controls reported 0-10 yrs talc use - 14% of cases and 15% of controls reported >10-25 yrs talc use - 19% of cases and 16% of cases reported >25 yrs talc use - P_{trend}	1.22 (0.84 – 1.77) **1.92 (1.27 – 2.91)** 0.95 (0.61 – 1.48) **2.41 (1.43 – 4.09)** **1.80 (1.19 – 2.73)** 0.98 (0.64 – 1.48) **2.51 (1.63 – 3.87)** 1.27 (0.81 – 1.98) **2.40 (1.43 – 4.05)** 1.57 (0.90 – 2.73) 1.13 (0.66 – 1.94) <u>OR</u> 1.0 **1.17 (1.01 – 1.36)** 1.13 (0.90 – 1.41) 1.08 (0.87 – 1.34) **1.29 (1.04 – 1.58)** **0.021**	(Merritt et al., 2008)
talc; purity and composition not specified	- 230 women with serous ovarian tumors and 133 women with benign mucinous tumors in Australia - 752 pop. controls	2002 - 2005	- examined the association between use of talc and the risk of benign mucinous and serous ovarian tumors- - risk was adjusted for age, state of residence, education, parity, hormonal contraceptive use, hysterectomy, and smoking status - **OR for each factor examined is presented in the order mucinous, serous, combined**	- 56% of mucinous cases, 55% of serous cases, and 56% of controls reported no talc use in the perineal region - 44% of mucinous cases, 45% of serous cases, and 44% of controls reported talc use in the perineal region **Amount of talc used in the perineal region** - 11% of mucinous cases, 6% of serous cases, and 10% of controls reported minimal talc use in the perineal region - 14% of mucinous cases, 9% of serous cases, and 11% of controls reported moderate talc use in the perineal region - 18% of mucinous cases, 27% of serous cases, and 21% of controls reported substantial talc use in the perineal region	<u>OR</u> 1.0 1.19 (0.80 – 1.76) 1.04 (0.75 – 1.43) 1.10 (0.84 – 1.45) 1.02 (0.53 – 1.98) 0.70 (0.37 – 1.30) 0.85 (0.52 – 1.38) 1.57 (0.87 – 2.84) 0.85 (0.49 – 1.48) 1.05 (0.68 – 1.64) 0.98 (0.58 – 1.66) 1.21 (0.82 – 1.79) 1.16 (0.83 – 1.62)	(Jordan et al., 2007)

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Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
				P_{trend} for:		
				mucinous tumors	0.9	
				serous tumors	0.2	
				combined	0.3	
dusting powder, many contain talc	- 812 women from 13 counties in western WA state with epithelial ovarian cancer (pop.-based) - 1313 age-matched pop. controls	Jan 2002 – Dec 2005	- subjects were asked questions about lifestyle, medical, reproductive, and contraceptive histories, use of contraceptive and menopausal hormone preparations, and genital powder exposure - risk was adjusted for age, year of diagnosis, residence, parity, and hormonal contraception - subjects were asked to report the types of powder(s) used after bathing, including talcum, baby, cornstarch, deodorant, body/bath, and other or unknown	- 86.2% of cases and 88.5% of control reported never using powder after bathing	**OR** 1.0	(Rosenblatt KA *et al.*, 2011)
				- 13.8% of cases and 11.5% of controls reported use of powder after bathing	1.27 (0.97 – 1.66)	
				- 93.2% of cases and 91.7% of controls did not use powder on sanitary napkins	1.0	
				- 6.8% of cases and 8.3% of controls used powder on sanitary napkins	0.82 (0.58 – 1.16)	
				- 77.7% of cases and 72.6% of controls (that were diaphragm users) did not use powder on diaphragms	1.0	
				- 22.3% of cases and 27.4% of controls (that were diaphragm users) used powder on diaphragms	0.72 (0.48 – 1.10)	
				- 89.6% of cases and 90.5% of controls did not use vaginal deodorant spray	1.0	
				- 10.4% of cases and 9.5% of controls used vaginal deodorant spray	1.15 (0.85 – 1.56)	
			- risk was evaluated based on duration, frequency, and timing of use - risk was adjusted as above	- 86.2% of cases and 88.5% of controls never used powder	1.0	
				Duration of use		
				- 4.1% of cases and 2.9% of controls used powder for 1-9.9 yrs	1.39 (0.85 – 2.28)	
				- 3.6% of cases and 2.7% of controls used powder for 10-19.9 yrs	1.46 (0.87 – 2.45)	
				- 3.7% of cases and 3.0% of controls used powder for 20-34.9 yrs	1.28 (0.78 – 2.10)	
				- 2.3% of cases and 2.9% of controls used powder 35+ yrs	0.91 (0.51 – 1.62)	
				Lifetime number of applications		
				- 3.2% of cases and 2.7% of controls reported 1-1599 applications of powder	1.21 (0.71 – 2.06)	
				- 5.6% of cases and 2.8% of controls reported 1600-4799 applications of powder	**2.08 (1.32 – 3.27)**	
				- 2.5% of cases and 3.0% of controls reported 4800-9999 applications of powder	0.87 (0.50 – 1.53)	
				- 2.2% of cases and 2.8% of controls reported 10,000+ applications of powder	0.87 (0.48 – 1.57)	
				Age at first use		
				- 1.5% of cases and 2.1% of controls were <15 yrs old	0.74 (0.37 – 1.50)	
				- 3.3% of cases and 2.7% of controls were 15-20 yrs old	1.20 (0.71 – 2.03)	
				- 3.9% of cases and 3.3% of controls were 20-30 yrs old	1.25 (0.77 – 2.03)	
				- 5.1% of cases and 3.4% of controls were 30+ yrs old	**1.69 (1.08 – 2.64)**	

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Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
talc; purity and composition not specified	- 902 women from Western PA, Eastern OH, and Western NY in the HOPE study with primary epithelial ovarian, peritoneal, or Fallopian tube cancer - 1802 age group- and geography-matched controls	2003 - 2008	- subjects were asked about reproductive, gynecological, and medical histories, lifestyle, family medical history, whether they ever sought medical attention for fertility issues, use of fertility drugs - risk was adjusted for race, education, geographical site, BMI, family breast and ovarian cancer history, tubal ligation, OC use, number of live births, breast-feeding, age at menarche, menopausal status, perineal talc use, and HRT use Limitation - inability to identify infertile women that never sought medical attention - reliance on self-reported fertility drug use	<u>Time since first use</u> - 5.2% of cases and 3.1% of controls reported ≤25 yrs - 4.7% of cases and 3.1% of controls reported 25-38 yrs - 2.0% of cases and 2.6% of controls reported 38-45 yrs - 2.0% of cases and 2.7% of controls reported 45+ yrs <u>Age at last use</u> - 3.1% of cases and 2.5% of controls were <35 yrs old - 4.3% of cases and 3.0% of controls were 35-50 yrs old - 3.1% of cases and 2.7% of controls were 50-60 yrs old - 3.2% of cases and 3.3% of controls were 60+ yrs old <u>Time since last use</u> - 6.4% of cases and 5.3% of controls are current users - 3.2% of cases and 2.0% of controls reported ≤12 yrs - 1.7% of cases and 2.16% of controls reported 13-23 yrs - 2.3% of cases and 2.1% of controls reported 24+ yrs <u>Calendar year of first use</u> - 2.3% of cases and 3.0% of controls reported ≤1959 - 3.0% of cases and 2.9% of controls reported 1960-1969 - 3.2% of cases and 2.9% of controls reported 1970-1979 - 5.3% of cases and 2.7% of controls reported 1980+ <u>Ever/never use of talc</u> - 72.4% of cases and 79.1% of controls reported never using talc in the perineal region - 27.6% of cases and 20.9% of controls reported ever using talc in the perineal region	**1.77 (1.12 – 2.78)** 1.46 (0.91 – 2.32) 0.87 (0.47 – 1.61) 0.82 (0.44 – 1.52) 1.14 (0.66 – 1.97) 1.42 (0.88 – 2.31) 1.25 (0.73 – 2.13) 1.21 (0.72 – 2.05) 1.30 (0.89 – 1.91) 1.74 (0.98 – 3.10) 0.85 (0.44 – 1.66) 1.13 (0.61 – 2.08) 0.86 (0.48 – 1.53) 1.10 (0.65 – 1.89) 1.12 (0.66 – 1.89) **2.03 (1.28 – 3.24)** <u>OR</u> 1.0 **1.40 (1.16 – 1.69)**	*(Kurta ML et al, 2012)*

EFFECT OF TUBAL LIGATION OR HYSTERECTOMY ON RISK

HOSPITAL-BASED CASES/HOSPITAL-BASED CONTROLS

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
talc; purity and composition not specified	- 211/499 patients at Roswell Park Cancer Institute with epithelial ovarian cancer had tubal ligation or hysterectomy - 261/755 age at diagnosis-matched hospital controls had tubal ligation or hysterectomy	Oct 1982 – Oct 1995	- described previously	- 48.2% of cases and 42% of controls used talc and did not have tubal ligation or hysterectomy - 47.4% of cases and 49.8% of controls used talc and had tubal ligation - 52% of cases and 60% of controls used talc and had a hysterectomy	<u>OR</u> 1.2 (0.8 – 1.6) 0.8 (0.5 – 1.2) 0.9 (0.4 – 2.2)	*(Wong C et al, 1999)*

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Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
talcum powder; purity and composition not specified	-135 cases had undergone tubal ligation or hysterectomy within 5 yrs of the diagnosis			- risk excluding these cases	0.9 (0.4 – 2.2)	(Whittemore AS et al., 1988)
HOSPITAL-BASED CASES/HOSPITAL- and POPULATION-BASED CONTROLS						
	-188 women from northern California with primary epithelial cancer (from 7 hospitals) -280 matched hospital controls -259 matched pop. controls	Jan 1983 – Dec 1985	- described previously	-48% of cases and 54% of controls did not use talc	**OR** 1.0	
				-52% of cases and 46% of controls used talc	1.37 (0.97-1.96)	
				-37% of cases and 34% of controls did not use talc and had no ligation or hysterectomy	1.0	
				-38% of cases and 28% of controls used talc and had no ligation or hysterectomy	1.33 (0.58-2.01)	
				-11% of cases and 20% of controls did not use talc and had ligation or hysterectomy	*0.50 (0.29 – 0.88; p<0.01)*	
POPULATION-BASED CASES/POPULATION-BASED CONTROLS						
talc; purity and composition not specified	-450 women in the Boston area with epithelial ovarian cancer -454 pop. matched controls (study group combined (Cramer DW et al., 1982) and (Harlow BL et al., 1992)	Nov 1978 – Sept 1987	- described previously	-86.6% of cases and 87.7% of controls had no ligation or hysterectomy were talc users	**OR** 1	(Cramer DW & Xu, 1999)
				-13.4% of cases and 12.3% of controls had tubal ligation or hysterectomy and were talc users	1.1 (0.6-2.1)	
				-90.0% of cases and 84% of controls had no ligation or hysterectomy were non-talc users	1	
				-10% of cases and 16% of controls had tubal ligation or hysterectomy and were non-talc users	*0.6 (0.4-1.0; P=0.04)*	
talc; purity and composition not specified	-307 registered nurses in 11 states with epithelial ovarian (Nurses' Health Study; described previously)	1982 - 1996	-described previously	- risk of ever talc users that had tubal ligation compared to never talc users	**RR** 0.97 (0.71-1.32)	(Gertig DM et al., 2000)
				- risk for ever talc use when excluding those with history of tubal ligation or hysterectomy	1.15 (0.89-1.49)	
talc; purity and composition not specified	-450 women from Toronto and Ontario, Canada with epithelial ovarian cancer (pop.-based) -564 age-matched pop.-based controls	Nov 1989 – Oct 1992	- study was described previously - risk with yrs of after-bath talc use and tubal ligation/hysterectomy was examined - risk was adjusted as described previously	case mean was 28.4 yrs and control mean was 26.9 yrs of after-bath talc use before ligation/hysterectomy	**OR** 1.11 (0.99 – 1.24)	(Chang S & Risch A, 1997)
				- case mean was 4.5 yrs and control mean was 8.5 yrs of after-bath talc use after ligation/hysterectomy	1.03 (0.82 – 1.29)	
talc; purity and composition not specified	-256 women from 22 central CA counties with epithelial ovarian cancer (pop.-based) -1122 age- and ethnicity-matched controls	2000-2001	- study was described previously - risk of talc use and hysterectomy or tubal ligation was examined - risk was adjusted as described previously	Tubal Ligation -57.4% of cases and 65.8% of controls did not have tubal ligation and never used talc	**OR** 1.0	(Mills PK et al., 2004)
				-42.6% of cases and 34.2% of controls did not have tubal ligation and ever used talc	**1.54 (1.10 – 2.16)**	
				-56.9% of cases and 54.9% of controls did have tubal ligation and never used talc	1.0	
				-43.1% of cases and 45.1% of controls did have tubal ligation and ever used talc	0.88 (0.46 – 1.68)	

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Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
talc; purity and composition not specified	-1576 women from Australia with epithelial ovarian cancer -1509 age- and state of residence-matched pop. controls	Jan 2002 – Sept 2005	- study was described previously - risk was examined with number of years talc use post-hysterectomy or tubal ligation	Hysterectomy -59.5% of cases and 63.7% of controls did not have a hysterectomy and never used talc -40.5% of cases and 36.3% of controls did not a hysterectomy and ever used talc -50.0% of cases and 58.8% of controls did have a hysterectomy and never used talc -50.0% of cases and 41.2% of controls did have a hysterectomy and ever used talc -88% cases and 88% controls reported no talc use post-surgery -3% of cases and 3% of controls reported 0-10 yrs talc use -6% of cases and 6% of controls reported >10-25 yrs talc use -3% of cases and 3% of controls reported >25 yrs talc use -trend	1.0 1.33 (0.95 – 1.87) 1.0 1.79 (0.91 – 3.52) **OR** 1.0 1.08 (0.71 – 1.62) 1.14 (0.82 – 1.57) 1.00 (0.64 – 1.51) P = 0.61	(Merritt MA *et al.*, 2008)

OCCUPATIONAL EXPOSURE AND RISK

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
talc used as a coating agent for paper; purity and composition not specified; workers may also have been exposed to asbestos and/or other dusts	-46 female pulp and paper workers from 10 mills in Norway with epithelial ovarian cancer -179 age-matched controls identified by incidence density sampling	1953 – 1999 (mostly from 1980+)	-risk estimates specific to mill, work department, agent, and time period - indicators of occupational exposure included duration of employment, time since 1st exposure to diagnosis, and year of 1st exposure - subjects were asked about occupational history, possible household asbestos exposure, fertility pattern, age at menarche and menopause, OC use, family cancer history, and other personal factors Limitations - there were many missing values for the question on hygienic talc use	-50% of cases and 52% of controls reported never being exposed to talc -50% of cases and 48% of controls reported ever being exposed to talc	**OR** 1.0 1.10 (0.56 – 2.18)	(Langseth H & Kjærheim K, 2004)
talc; purity and composition not specified	-275 women in the Washington, D.C. area with epithelial ovarian cancer (hospital-based) -316 hospital age- and race-matched controls	1978-1981	- RR of ovarian cancer was determined according to length of occupational exposure to talc within various occupations - exposure = # of yrs in the job assigned probabilities of definite, probable, and possible exposure - risk was adjusted for employment, race, age, parity, and gynecologic surgery Limitation - no information was available on individual exposure characteristics, leading to the assumption that it was homogenous within job title	-95.7% of cases and 90.2% of controls were not exposed -1.8% of cases and 3.5% of controls were exposed for <5 yrs -0.7% of cases and 2.5% of controls were exposed for 5-9 yrs -1.8% of cases and 3.8% of controls were exposed for 10+ yrs	**RR** 1.0 0.5 (0.1 – 1.4) 0.3 (0.1 – 1.4) 0.5 (0.2 – 1.5)	(Hartge & Stewart, 1994)

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Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
			ENDOMETRIAL CANCER			
talc; purity and composition not specified	- 599 women from the Nurses' Health Study with invasive en-dometrial adenocarcinoma	1982-2004	- described previously - risk was assessed among all women - risk was adjusted for age, parity, age at last birth, menarche, and menopause, OC and PMH use, BMI, smoking, diabetes, menopausal status, and family history of uterine cancer Limitations - single assessment of talc use (ever/never) - did not assess duration of talc use	Use of talc - 55.8% of cases reported never using talc perineally - 44.2% of cases reported ever using talc perineally - 66.3% of cases reported no regular perineal use of talc (1+/wk) - 33.7% of cases reported regular perineal use of talc	<u>IRR</u> 1.0 1.13 (0.96 – 1.33) 1.0 1.17 (0.99 – 1.40)	(Karageorgi S *et al.*, 2010)
			- risk assessed in premenopausal women (70 cases [11.7% of all women] were premenopausal) - risk was adjusted for age, parity, age at last birth, age at menarche, OC use, BMI, smoking, diabetes, and family history of uterine cancer	Talc use in premenopausal women - 67.1% of cases reported never using talc perineally - 32.9% of cases reported ever using talc perineally - 75.7% of cases reported no regular perineal use of talc (1+/wk) - 24.3% of cases reported regular perineal use of talc	1.0 0.69 (0.40 – 1.19) 1.0 0.77 (0.42 – 1.39)	
			- risk was assessed among post-menopausal women (529 cases [88.3% of all women] were post-meno-pausal) - risk estimate was multivariate (as for all women) or adjusted by age	Talc use in post-menopausal women - 54.3% of cases reported never using talc perineally - 45.7% of cases reported ever using talc perineally - 65% of cases reported no regular perineal use of talc (1+/wk) - 35% of cases reported regular perineal use of talc	<u>Multivariate</u> 1.0 **1.21 (1.02 – 1.44)** 1.0 **1.24 (1.03 – 1.48)**	
				as above	<u>Age-Adjusted</u> 1.0 **1.38 (1.16 – 1.64)** 1.0 **1.40 ((1.17 – 1.68)**	
			- risk in post-menopausal women based on frequency of use and application to sanitary napkins -risk was adjusted multivariate (as above) or by age	Frequency of Use 10.8% of cases reported perineal use of talc <1x/wk 16.4% of cases reported perineal use of talc 1-6x/wk 18.5% of cases reported daily use of talc	<u>Multivariate</u> 1.09 (0.81 – 1.45) 1.28 (1.00 – 1.63) 1.24 (0.98 – 1.56)	
				as above	<u>Age-Adjusted</u> 1.22 (0.91 – 1.62) **1.40 (1.10 – 1.79)** **1.49 (1.18 – 1.87)**	
				Sanitary napkin talc use - 85.7% of cases never used talc on sanitary napkins - 14.3% of controls used talc on sanitary napkins	<u>Multivariate</u> 1.0 0.98 (0.75 – 1.27)	
				as above	<u>Age-Adjusted</u> 1.0 1.04 (0.80 – 1.35)	

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Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
talc; purity and composition not specified	- 1399 women in Australia with primary endometrial cancer (pop. based) - 740 controls	July 2005-Dec 2007	- subjects were asked about medical, hormonal, and reproductive histories, other potential risk factors, and talc use - risk was adjusted for age, age at menarche, parity, pregnancies, OC use, hormone replacement therapy, BMI, and smoking status Limitation - non-participation, in that those who did not partici-pate may have more advanced disease - non-differential misclassification of talc use - residual confounding may have distorted the results	Use of talc - 40.7% of cases and 41.5% of controls never used talc - 59.3% of cases and 58.5% of controls ever perineal talc use - 71.9% of cases and 70.4% of controls reported ever upper body use Frequency of any perineal talc use - 5.1% of cases and 7.1% of controls reported infrequent use - 9.1% of cases and 8.5% of controls reported use a few times/mo - 11% of cases and 7.1% of controls reported use a few times/wk - 33.3% of cases and 35% of controls reported daily use - P_{trend} (including non-talc users)	$\underline{OR}$ 1.0 0.88 (0.68 – 1.14) 0.9 (0.71 – 1.14) 0.68 (0.40 – 1.15) 0.88 (0.56 – 1.41) 1.32 (0.82 – 1.11) 0.82 (0.61 – 1.14) 0.44	(Neill AS *et al.*, 2012)
				Duration of any perineal talc use - 19% of cases and 16% of controls reported 1-20 yrs use - 15.6% of cases and 11.2% of controls reported 21-40 yrs use - 18.2% of cases and 18.8% of controls reported 41-60 yrs use - 5% of cases and 11.2% of controls reported 61-80 yrs use - P_{trend} (including non-talc users)	1.21 (0.84 – 1.75) 1.1 (0.73 – 1.65) 0.82 (0.57 – 1.17) 0.25 (0.15 – 0.43) *<0.001*	
				Frequency of any upper body talc use - 4.4% of cases and 6.6% of controls reported infrequent use - 6.9% of cases and 9.1% of controls reported use a few times/mo - 15.4% of cases and 10.1% of controls reported use a few times/wk - 45.1% of cases and 44.3% of controls reported daily use - trend (including non-talc users)	0.57 (0.35 – 0.93) 0.58 (0.38 – 0.89) **1.45 (1.01 – 2.09)** 0.9 (0.70 – 1.16)	
				Duration of any upper body talc use - 20.7% of cases and 19.4% of controls reported 1-20 yrs use - 16.9% of cases and 12.8% of controls reported 21-40 yrs use - 23.6% of cases and 22.6% of controls reported 41-60 yrs use - 9.3% of cases and 14% of controls re ported 61-80 yrs use -P_{trend} (including non-talc users)	1.16 (0.85 – 1.58) 1.12 (0.79 – 1.59) 0.86 (0.64 – 1.17) 0.41 (0.28 – 0.61) *0.001*	
			- risk was evaluated using a "composite" variable that multiplied frequency of talc use by years of use to assess lifetime exposure -resulting values were categorized as low (<5 yrs); moderate (5-20 yrs); high (20-40 yrs); very high use (40+ yrs)	Perineal talc use - 16.6% of cases and 15.6% of controls had low lifetime use - 12% of cases and 11.4% of controls had moderate lifetime use - 11.2% of cases and 8.6% of controls had high lifetime use - 17.2% of cases and 20.9% of controls had very high lifetime use - P_{trend} (including non-talc users)	0.95 (0.65 – 1.37) 1.0 (0.66 – 1.54) 1.01 (0.64 – 1.60) 0.67 (0.47 – 0.96) 0.07	
				Upper body talc use - 13.5% of cases and 17% of controls had low lifetime use - 14.7% of cases and 13% of controls had moderate lifetime use - 16.5% of cases and 12.6% of controls had high lifetime use - 25.8% of cases and 25.9% of controls had very high lifetime use - P_{trend} (including non-talc users)	0.72 (0.52 – 1.01) 1.25 (0.87 – 1.78) 1.07 (0.75 – 1.52) 0.8 (0.59 – 1.07) 0.49	

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Abbreviations: BMI = body mass index; C.I. = confidence interval; CLE = cumulative lifetime exposure; HOPE = Hormone and Ovarian Cancer Prediction; HRT = hormone replacement therapy; IRR = incidence rate ratios; NECC – New England Case Control; NSAID = non-steroidal anti-inflammatory drug; OC = oral contraceptive; OR = odds ratio; PMH = postmenopausal hormone; pop. = population; RR = relative risk

Bolded text was used to highlight statistically significant increases
Italicized text was used to highlight statistically significant decreases

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Table 10. Summary of case-control studies evaluating ovarian cancer risk for "ever" use of talc in the perineal area

# Case subject	# Control subjects	Study Years	P/H cases	OR or RR	95% C.I.	Reference
HOSPITAL-BASED CASES						
135	171	1974-1977	H	0.7	0.4 – 1.1	(Hartge P *et al.*, 1983)
215	215	1978-1981	H	**1.92**	**1.27 – 2.89**	(Cramer DW *et al.*, 1982)
77	46	1981-1985	H	1.7	0.7 - 3.9	(Rosenblatt KA *et al.*, 1992)
499	755	1982-1995	H	1.0	0.8 – 1.3	(Wong C *et al.*, 1999)
235	239	1984-1987	H	1.5	1.0 – 2.1	(Harlow BL *et al.*, 1992)
189	200	1989-1991	H	1.05	0.28 – 3.98	(Tzonou A *et al.*, 1993)
767	1367	1994-1998	H	**1.5**	**1.1 – 2.0**	(Ness RB *et al.*, 2000)
153	101	1995-1996	H	2.49	0.94 – 6.58	(Godard B *et al.*, 1998)
POPULATION-BASED CASES						
116	158	1980-1985	P	1.1	0.7 – 2.1	(Harlow BL & Weiss NS, 1989)
112	224	1984-1986	P	3.9	0.9 – 10.6	(Chen Y *et al.*, 1992)
313	422	1986-1988	P	**1.5**	**1.1 – 2.0**	(Cook LS *et al.*, 1997)
450	564	1989-1992	P	**1.42**	**1.08 – 1.86**	(Chang S & Risch HA, 1997)
824	860	1990-1993	P	**1.27**	**1.04 – 1.54**	(Purdie D *et al.*, 1995)
563	523	1992-1997	P	**1.60**	**1.18 – 2.15**	(Cramer DW *et al.*, 1999)
668	721	1998-2003	P	1.16	0.90 – 1.49	(Cramer DW *et al.*, 2005)
609	688	1998-2002	P	**1.48**	**1.15 – 1.91**	(Wu AH *et al.*, 2009)
83	134	1998-2008	P	1.19	0.68 – 2.09	(Moorman OG *et al.*, 2009)
550	553	1998-2008	P	1.04	0.82 – 1.33	(Moorman OG *et al.*, 2009)
256	1122	2000-2001	P	**1.37**	**1.02 – 1.85**	(Mills PK *et al.*, 2004)
1576	1509	2002-2005	P	**1.17**	**1.01 – 1.36**	(Merritt MA *et al.*, 2008)
363	752	2002-2005	P	1.10	0.84 – 1.45	(Jordan SJ *et al.*, 2007)
902	1802	2003-2008	P	**1.40**	**1.16 – 1.69**	(Kurta ML *et al.*, 2012)

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CHARTS

Chart 1. Odds ratio and confidence intervals in case-control studies evaluating ovarian cancer risk for "ever" use of talc in the perineal area

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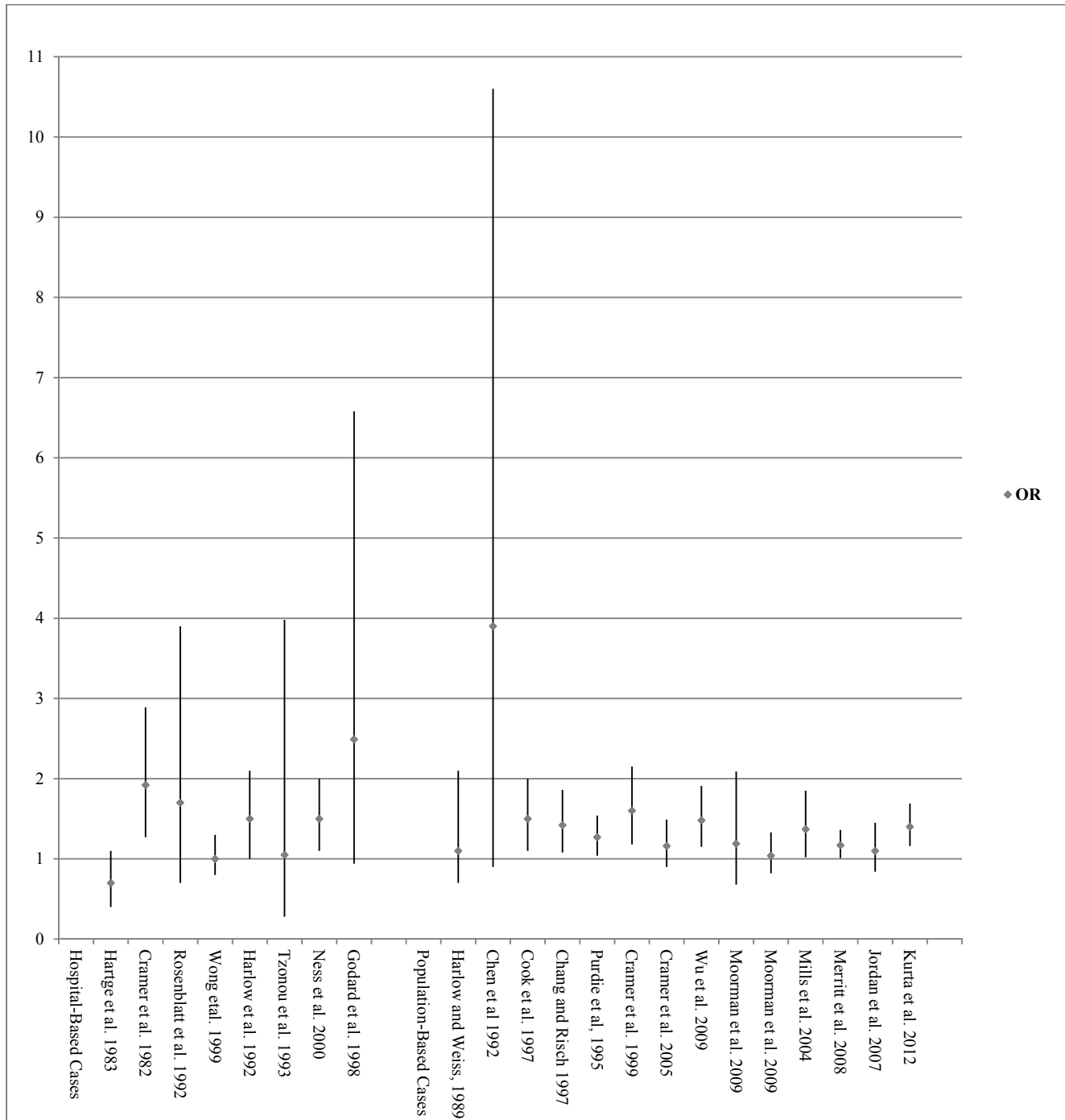
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TALC	9	01B - Baby Lotions, Oils, Powders, and Creams
TALC	17	02A - Bath Oils, Tablets, and Salts
TALC	1	02C - Bath Capsules
TALC	43	03A - Eyebrow Pencil
TALC	101	03B - Eyeliner
TALC	869	03C - Eye Shadow
TALC	13	03D - Eye Lotion
TALC	79	03F - Mascara
TALC	61	03G - Other Eye Makeup Preparations
TALC	3	04B - Perfumes
TALC	104	04C - Powders (dusting and talcum, excluding aftershave talc)
TALC	3	04D - Sachets
TALC	10	04E - Other Fragrance Preparation
TALC	1	05A - Hair Conditioner
TALC	2	05G - Tonics, Dressings, and Other Hair Grooming Aids
TALC	1	05I - Other Hair Preparations
TALC	1	06H - Other Hair Coloring Preparation
TALC	290	07A - Blushers (all types)
TALC	500	07B - Face Powders
TALC	201	07C - Foundations
TALC	3	07D - Leg and Body Paints
TALC	54	07E - Lipstick
TALC	44	07F - Makeup Bases
TALC	13	07G - Rouges
TALC	11	07H - Makeup Fixatives
TALC	102	07I - Other Makeup Preparations
TALC	5	08A - Basecoats and Undercoats
TALC	1	08B - Cuticle Softeners
TALC	7	08E - Nail Polish and Enamel
TALC	1	08G - Other Manicuring Preparations
TALC	1	09A - Dentifrices
TALC	51	10A - Bath Soaps and Detergents
TALC	18	10B - Deodorants (underarm)
TALC	29	10E - Other Personal Cleanliness Products
TALC	1	11A - Aftershave Lotion
TALC	3	11C - Mens Talcum
TALC	2	11G - Other Shaving Preparation Products
TALC	37	12A - Cleansing
TALC	4	12B - Depilatories
TALC	32	12C - Face and Neck (exc shave)
TALC	18	12D - Body and Hand (exc shave)
TALC	9	12E - Foot Powders and Sprays
TALC	54	12F - Moisturizing
TALC	7	12G - Night
TALC	28	12H - Paste Masks (mud packs)
TALC	2	12I - Skin Fresheners
TALC	25	12J - Other Skin Care Preps
TALC	1	13A - Suntan Gels, Creams, and Liquids
TALC	5	13B - Indoor Tanning Preparations

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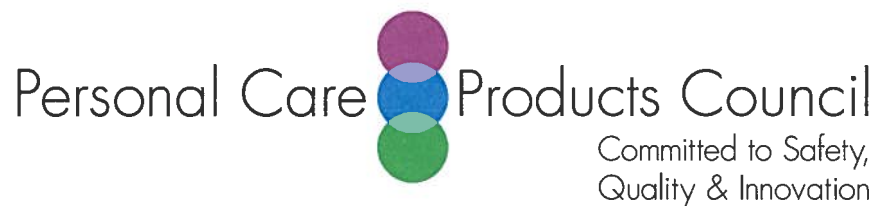
Memorandum

TO: F. Alan Andersen, Ph.D.
              Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: John Bailey, Ph.D.
              Industry Liaison to the CIR Expert Panel

DATE: January 21, 2010

SUBJECT: Updated Concentration of Use Talc

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Concentration of Use - Talc

Product Category	Concentration of Use
Baby shampoos	7%
Baby lotions, oils powders and creams	99%
Bath oils tablets and salts	1-88%
Bubble baths	0.4-2%
Other bath preparations	0.001%
Eyebrow pencil	0.01-79%
Eyeliner	0.1-90%
Eye shadow	20-100%
Eye lotion	2%
Mascara	1-50%
Other eye makeup preparations	2-6%
Perfumes	2%
Powders (dusting and talcum)	15-99%
Sachets	9%
Other fragrance preparations	3-9%
Hair conditioners	0.4%
Rinses (noncoloring)	0.05%
Shampoos (noncoloring)	0.04%
Tonics, dressings and other hair grooming aids	10%
Hair dyes and colors (all types requiring caution statement and patch test)	0.4-13%
Other hair coloring preparations	6%
Blushers (all types)	48-94%
Face powders	20-100%
Foundations	7-99%

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Leg and body paints	0.09-83%
Lipstick	3-74%
Makeup bases	7-53%
Makeup fixatives	10%
Other makeup preparations	0.8-85%
Basecoats and undercoats (manicuring preparations)	1-7%
Cuticle softeners	0.004-18%
Nail creams and lotions	2%
Nail polish and enamel	0.002-11%
Other manicuring preparations	35%
Other oral hygiene products	11%
Bath soaps and detergents	0.001-70%
Deodorants (underarm)	2-75%
Other personal cleanliness products	0.03-20%
Aftershave lotions	14%
Men's talcum	96%
Shaving soaps (cakes, sticks etc.)	0.04%
Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0005-0.005%
Face and neck creams, lotions and powders	0.03-70%
Body and hand creams, lotions and powders	0.1-84%
Foot powders and sprays	0.9-97%
Moisturizing creams, lotions and powders	3-5%
Night creams, lotions and powders	3%
Paste masks (mud packs)	0.2-18%
Skin fresheners	0.002-0.2%
Other skin care preparations	0.03-20%

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Suntan gels, creams and liquids	15-41%
Indoor tanning preparations	74%
Other suntan preparations	3%

Information collected in 2009

Table prepared December 15, 2009

Updated January 21, 2010 (basecoats and undercoats increased to 7%)
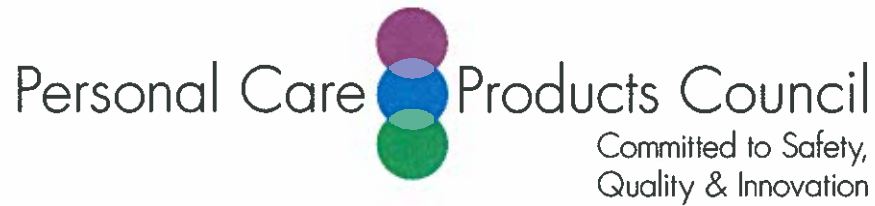
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Personal Care Products Council
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Quality & Innovation

Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: August 2, 2012

SUBJECT: Concentration of Use by FDA Product Category: Talc Use in Spray Products

Concentration of Use by FDA Product Category
Talc Use in Spray Products*

Product Category	Spray	Not Spray
Foundations	1-6% (aerosol)	12-76%
Leg and body paints	2% (aerosol)	Not reported
Makeup bases	35% (aerosol)	36%
Deodorants	1-30% (aerosol)	6-85%
Face and neck products	0.4%	40%
Body and hand products	0.3%	96%

*A survey was completed to assess the use of Talc in spray products. Companies were asked whether or not they use Talc in spray products. If the answer was yes, the companies were asked to provide the maximum use concentration of Talc in the spray product and in products that are not sprays in the same FDA product category.

Information collected in 2012
Table prepared August 2, 2012

Personal Care Products Council
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Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: October 15, 2012

SUBJECT: Comments on the Scientific Literature Review on Talc

Key Issues

p. 22 - The hamster inhalation carcinogenicity study, which is described for the first time in the section analyzing ovarian cancer risk, also needs to be presented in the Carcinogenicity section under Inhalation exposure (p.11-14).

p.22-23 - Please remove reference 156 (from 1978) from this report. On p. 23 it states: "The effects of instillation of B[a]P alone were not investigated in this study, but the researchers noted that B[a]P does not initiate respiratory tumors. Therefore, it appears that talc had a co-carcinogenic effect in inducing respiratory tumors in hamsters when instilled intratracheally with B[a]P."

This statement by the authors (ref 156; from 1978) is very dated and does not capture the current understanding of B[a]P toxicity, and used as currently written in a modern assessment is very misleading. B[a]P is an IARC 1 human carcinogen with several adverse intratracheal administration studies cited in the IARC monograph (attached). The lack of a B[a]P-only intratracheal dose group in this study (ref 156) is a serious design flaw. The text as written implicates talc is a causative factor, while the totality of the talc inhalation literature demonstrates that Talc is not an inhalation carcinogen while B[a]P is a carcinogen. The authors conclusion would only be relevant, were there:
1.   a B[a]P-only intratracheal dose group in the study, and
2.   there were no tumors in the B[a]P-only dose group;
3.   yet the IARC monograph clearly shows that B[a]P is a carcinogen by intratracheal administration

Due to the design flaw and its implications to the conclusions made by the original authors, the text discussing this reference should be removed from the CIR report, as this 1978 conclusion is incorrect given the current knowledge regarding B[a]P.

p.28-29, Table 2 - The only concentrations that should be included in the spray row are those from the 2012 survey of the spray use of Talc. A footnote should be added to the spray product row to explain how the second survey was completed. Because Talc clogs nozzles of spray products, it

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would be very difficult to have a spray product containing 74% or 75% Talc, and impossible to have a spray product containing 97% Talc. If all the FDA product categories are presented in the use table, it would be better to provide the categories grouped as FDA designed them, rather than the exposure categories for which there are always exceptions.

References 16 and 19 - Please do not use the On-Line as the reference for Talc specifications. Although CIR staff can access the On-Line for this information, the public cannot use this Council member-only resource.

Additional Comments

Report cover - If the date on an SLR does not agree with the date the SLR was placed on the CIR website, the SLR report should state that the comment period is 60 days from the posting date. For example, the SLR on Talc is dated August 15, 2012 although the report was posted on August 21. Therefore, the 60 day comment period does not end until October 21.

p.1 - In the first sentence under the Definition and Structure heading, please delete the word "pure" from the following statement: "as a mineral, the pure talc corresponding to the chemical formula...". The word "pure" is not necessary when referring to the chemical formula.

p.2 - In the Analytical Methods section, please include the method used by FDA in its recent Talc survey.

p.7 - Please correct the description of the doses used in the rat LD_{50} study. It currently says "50, 100, 500, 100, 2000 or 3000 mg/kg" - the second "100" should be "1000".

p.8, p.32, Table 4 - The text says the oral study was 6 days in duration, while Table 4 states it was 5 days. Which is correct?

p.8 - In the text, please indicate that the baby powder used in the inhalation study in hamsters was 95% Talc.

p.8, p.24 - In reference to the statement "Application of talc on damaged skin....", please clarify what reference 57 means by damaged skin. The information cited to reference 58 suggests that this means skin with open wounds, which is not relevant for cosmetic use of Talc. The term "damaged skin"needs to be clarified because this term as used in the original PEG report was misinterpreted by some as any type of damage including conditions, such as sunburn, in which the skin barrier was intact.

p.9 - Please give some indication of the type of workers included in "Studies examining radiological, lung-function, and clinical (e.g., wheezing, coughing, bronchitis) parameters..."

p.9 - In the Respirable Particles During Use section, "form" needs to be corrected to "from"

p.10 - In the first sentence of the Reproductive and Developmental Toxicity section, please change "not a reproductive toxicant" to "not a developmental toxicant". This sentence refers to studies in which the animals were treated only during gestation. Many aspects of reproduction are not examined in this type of study.

p.14 - If Zazenski et al. (1995) (reference 11) provided a value for "human exposure to respirable Talc particles during normal product use" please include it in the CIR report. What did they mean by "normal product use"?

p.15 - In the first paragraph under the heading Particulate Migration in the Genital Tract, please provide an explanation as to why the studies on non-Talc particles are relevant to talc.

2

p.15 - Was the same material (bone black) studied in both reference 99 and 101? The description of reference 101 suggests that just carbon particles from bone black were studied. Did they really identify "carbon particles" or bone black particles? Bone black, also called CI 77267 is defined as a mixture of carbon, calcium phosphate and calcium carbonate. It would be helpful to describe the material studied.

p.15 - Please revise the following sentence so that India ink is the subject of "was transferred". "In a study using India ink, it was found that injection of 0.2 ml India ink into the uterine cavity 15 min - 24 hr prior to abdominal surgery was transferred to the Fallopian tubes on 27/50 women in the proliferative phase and in 23/35 women in the secretory phase of the menstrual cycle."

p.18 - As many papers are being cited (including papers in which the authors analyze the ovarian cancer epidemiology studies), the heading "CIR Analysis of Ovarian Cancer Risk in the Epidemiological Studies" should be changed to "Analysis of Ovarian Cancer Risk in the Epidemiological Studies".

p.19 - Please add a reference to the following sentence: "A meta-analysis of the association between talc-dusted diaphragm use and ovarian cancer risk yielded a summary odds ratio (OR) of 1.03 (95% CI: 0.80-1.37)."

p.22 - Please provide some indication of dose used in the rat ovarian injection study (reference 52).

p.23 - Please delete "BP was not defined". As suggested later in the paragraph, BP stands for British Pharmacopeia. The 2008 edition of the British Pharmacopeia can be found in John Krowka's office.

p.23-24 - In the Summary, whenever "baby powder" is used, please indicate the talc content, or whether or not it is known if the material tested was actually Talc.

p.25 - In the Summary, the hamster inhalation carcinogenicity study also needs to be mentioned.

p.30, Table 3 - What species served as the source of PMNs used in reference 168?

p.33, Table 4 - The protocol and description of the results for reference 174 do not appear to be consistent. The Dose Duration column appears to indicate that some rats were exposed for 3 months and 6 months, but the results only discuss animals exposed for 10 days and 1 year.

p.34, Table 4 - Please clarify what was done in reference 177. Do all the results represent measurements in lung lavage fluid?

p.36, Table 5 - In the description of methods for reference 62, please indicate the number of subjects in each exposure subgroup. Please make the following changes in the Findings row: change "observed vs. exposed" to "observed vs. expected"; and change "al (SMR = 0.77)l" to "all (SMR = 0.77)".

p.37, Table 5 - Please state whether or not reference 63 controlled for smoking status.

p.38, Table 5 - In the description of reference 68 it says that both US mortality rates and Vermont mortality rates were used. In the Findings section, it is not clear what source was used to determine the expected number of deaths provided.

p.39, Table 5 - It is not clear if the first row on p.39 is a continuation of reference 67 or a new study as the reference is missing. If this is just a study of mortality, it would be helpful to add "mortality" after "Nested case-control for respiratory disease" and "Nested case control for lung cancer".

p.42, Table 5 - Under findings FEV_1 (ml) is given as "-6.58 (13.81-0.65)"; as -6.58 is not in the confidence interval this is not correct, perhaps it should be "-13.81".

3

p.43, Table 5 - In reference 76, were the symptoms that were assessed self-reported (assessed by questionnaire)? If so, please change "the prevalence of symptoms (as %) according to cumulative exposure were determined" to "the prevalence of self-reported symptoms (as %) according to cumulative exposure were determined" (or indicate symptoms as diagnosed by a medical professional).

p.46, Table 6 - The Procedure entry for reference 13 indicates that they had samples to represent the baby and mother's exposure, but only one Respirable Amount is provided. Does 0.10 mg/min/m^3 represent just the baby's exposure? What was the estimate of the mother's exposure?

p.46-47, Table 6, Reference 31 - In the Other Results section of reference 31, it is not clear what is meant by "respirable talc accumulated during 4 samples" followed by air concentrations. This occurs once on p.46 and once on p.47.

p.49-72, Table 9 - Many case control studies of ovarian cancer look at the association of ovarian cancer and multiple endpoints in addition to Talc exposure. In studies in which multiple endpoints were examined, it would be helpful to provide the association with the highest OR or RR.

p.54, Table 9 - Under Types of exposure to talc (reference 182), please delete the word "only" in the following group descriptions: "by diaphragm storage only or by other methods"; "exposure following bathing only or by other methods"; "by use on sanitary napkins only or by other methods".

p.55, Table 9, Reference 132 - Either more details should be added about the types of powders used in this study, or the lack of details about the types of powders used should be added as a limitation for this study.

p.59, Table 9 - The first OR for Frequency of use per month for total of all uses in the genital area needs to be corrected. It currently says ".21 (1.37-3.56)" as .21 is not within the range of the 95% CI this cannot be correct.

p.66-67, Table 9, Reference 193 - In the descriptions of other studies states are abbreviated. Therefore, "Washington state" should be changed to "WA" in the description of this study. In the first part of the findings the exposures are described as "powder" in the second part "talc" is stated, or neither powder nor talc is stated. Were they really able to distinguish among persons that used talc and persons that used other types of powders?

p.68, Table 9, Reference 126 - Did they really distinguish between Talc and the use of other powders in this study?

p.69, Table 9, Reference 197 - What types of occupations resulted in talc exposure in reference 197?

4

Personal Care Products Council
Committed to Safety,
Quality & Innovation

Memorandum

TO: F. Alan Andersen, Ph.D.
             Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
             Industry Liaison to the CIR Expert Panel

DATE: October 15, 2012

SUBJECT: Comments on the Scientific Literature Review on Talc

Anonymous. 2012. Letter to Dr. F. Alan Andersen concerning the Scientific Literature Review on
     Talc as Used in Cosmetics with attachments.

October 12, 2012

Dr. F. Alan Andersen
Director
Cosmetic Ingredient Review
1101 17th Street N.W., Suite 412
Washington, D.C. 20036-4702

Dear Dr. Andersen:

We write regarding the Cosmetic Ingredient Review's ("CIR's") August 15, 2012 "Talc as Used in Cosmetics" Scientific Literature Review ("the Review"). As a preliminary matter, we would like to commend CIR for its thoughtful and meaningful analysis of the varied and complex issues regarding cosmetic talc addressed by the Review. We also greatly appreciate CIR's invitation to all interested parties to submit additional information concerning these issues.

In response to that invitation, we write to provide the CIR with information and documents concerning: (1) a 1986 United States Food and Drug Administration ("FDA") response to a citizen's petition requesting an asbestos warning on cosmetic talc products; and (2) the disavowed and discredited claims of asbestos contamination in the articles cited at footnotes 9 and 147 of the Review.

I.   1986 FDA Denial of Petition Requesting Asbestos Warning on Cosmetic Talc

The Review provides a useful chronology of important regulatory studies and actions concerning the use of talc in cosmetic. We respectfully recommend expanding this chronology to include an important FDA ruling relating to talc used in cosmetics and whether any warning labels should be required. More specifically, the Review describes the FDA's 1979 response to a 1978 request by the Public Citizen Health Research Group for the elimination of talc in all drugs and cosmetics. (Review at 4.) The Review does not, however, include the FDA's 1986 response to a 1983 petition that again addressed the safety of cosmetic talc products.

In 1983, the FDA received a citizen's petition "requesting that cosmetic talc be labeled with an asbestos warning statement." (July 1986 Letter from J.W. Swanson, Acting Associate Commissioner for Regulatory Affairs of the FDA to Mr. Phillippe Douillet, Re: Docket No. 83P-0404 ("1986 FDA Response"), attached hereto as Exhibit A, at 1.) The FDA determined—after conducting a thorough risk assessment—that there was "no need to require a warning label on cosmetic talc" and, in fact, that "the risk from a worst-case estimate of exposure to asbestos from cosmetic talc would be less than the risk from environmental background levels of exposure to asbestos (non-occupational exposure) over a lifetime." (*Id.* at 2.) The FDA accordingly denied the petition in 1986. (*Id.* at 3.) We enclose a copy of the FDA's 1986 response, including attachments thereto.

Dr. F. Alan Andersen
October 12, 2012
Page 2

II. Discredited and Disavowed Claims of Asbestos Contamination in 1968 and 1976 Articles Cited in the Review

At page 21, the Review states: "Thirty or more years ago, cosmetic talc samples often contained substantial amounts of asbestos fibers, which clearly represent a carcinogenic risk," citing (1) "Cralley LJ, Key MM, Groth DH, Lainhart WS, and Ligo RM. Fibrous and mineral content of cosmetic talcum products. *Am.Ind.Hyg.Assoc J.* 1968;29:(4):350-354" ("1968 Cralley Article"); and (2) "Rohl AN, Langer AM, Selikoff IJ, Tordini A, and Klimentidis R. Consumer talcums and powders: Mineral and chemical characterization. *Journal of Toxicology and Environmental Health.* 1976;2:255-284" ("1976 Rohl & Langer Study"). Because the claims of asbestos contamination in talc products in those articles, however, have been disavowed and/or discredited, we respectfully request that the language quoted above be modified as follows:

> Thirty or more years ago, questions arose whether certain cosmetic talc samples contained substantial amounts of asbestos fibers, which, if true, clearly represented a carcinogenic risk. Both the FDA and IARC reviewed such claims and could not substantiate them.

A. 1968 Cralley Article

In 1971, Dr. Lewis Cralley, the lead author of the 1968 Cralley Article, reported at a 1971 FDA meeting that asbestos was never actually found in the talc samples studied. The minutes from that FDA meeting state that Dr. Cralley: "Reviewed his published study of fibers in talc and stated emphatically that *he could detect only talc by X-rays. His reference to the probable presence of asbestos fiber in these talcs was, in fact, only a 'probability'* based on the known geology of talc deposits." (Aug. 11, 1971 Memo re: FDA Meeting – Asbestos in Cosmetic Talcs, Aug. 3, 1971, attached hereto as Exhibit B, at 2 (emphasis added).) Indeed, the 1968 Cralley Article explicitly states that "the fibrous material [detected in the talc samples] was predominantly talc but *probably* contained minor amounts of tremolite, anthophyllite, and chrysotile as these are often present in fibrous talc mineral deposits." (1968 Cralley Article, attached hereto as Exhibit C, at 353 (emphasis added).)

B. 1976 Rohl & Langer Study

In a response to the 1976 Rohl & Langer Study, the Chief Mineralogist of the Colorado School of Mines Research Institute, Jerome B. Krause, demonstrated why "[t]he analytical methods described by [Rohl and Langer in their 1976 article] for identification and quantification of tremolite, anthophyllite, and serpentine are invalid" and "the results reported are without analytical basis and the conclusions drawn are invalid and misleading." (Jerome B. Krause, *"Mineralogical Characterization of Cosmetic Talc Products,"* 2 J. Toxicology & Envtl. Health 1223, 1223, 1226 (1977), attached hereto as Exhibit D.) Volume 93 of the World Health Organization International Agency for Research on Cancer ("IARC") Monographs on the Evaluation of Carcinogenic Risks to Humans: Carbon Black, Titanium Dioxide and Talc,

Dr. F. Alan Andersen
October 12, 2012
Page 3

credited Krause's criticisms in this 1977 paper, and further emphasized that: "Rohl *et al.* (1976) stated that their methodology did not distinguish between asbestos and non-asbestiform mineral fragments." (Exhibit E at 303-04.) The 1986 FDA response to the 1983 citizen's petition requesting an asbestos warning on talc products, discussed above, credited a similar paper by Krause, "*Misidentification of Asbestos in Talc*" (an attachment to the 1986 FDA Letter, Exhibit A hereto), in emphasizing the "questionable reliability" of studies reporting asbestos contamination in cosmetic talc products in the 1970s. (1986 FDA Letter, Exhibit A hereto, at 1.)

The FDA itself commissioned a study of approximately 200 talc samples by "internationally-recognized expert on mineralogical chemistry," Professor Seymour Z. Lewin of New York University, the results of which were published in 1973. (July 31, 1973 Memorandum from Dr. Alfred Weissler, Acting Dir., Div. of Color Tech., to Dr. Robert M. Schaffner, Dir., Office of Tech., FDA, *Summary and Comments on Prof. Lewin's Analytical Results for Asbestos in Talc* (July 31, 1973) ("Weissler Memo"), attached hereto as Exhibit F.) Dr. Lewin concluded that "[m]ost of the commercial talcs tested are free of any detectable amount of any of the asbestiform minerals," (July 10, 1973 Memorandum from S. Z. Lewin, New York University, to Dr. George Thompson, FDA, *Determination of Asbestos Contents of Commercial Talcum Powders* at 3, attached to Weissler Memo, Exhibit F hereto), and, unlike Drs. Rohl and Langer, found no asbestiform or non-asbestiform anthophyllite—which can often be confused with talc—in any of the samples studied. (Weissler Memo, Exhibit F hereto, ¶ 3.)

Indeed, Dr. Langer has admitted that his work during the timeframe of the 1976 Rohl & Langer Study was based on misunderstandings about the complex nature of amphibole minerals at that time. (*See* A. M. Langer & R. P. Nolan, *Distinguishing Asbestiform Tremolite from Non-Asbestiform Tremolite* (1989)), attached hereto as Exhibit G, at 3 ("[S]ince that time, 1975, more data have become available on the nature of these minerals, more detailed than existed thirteen years ago.").)

We respectfully submit, therefore, that neither the 1968 Cralley article nor the 1976 Rohl & Langer Study should be credited to the extent they claimed that "cosmetic talc samples often contained substantial amounts of asbestos fibers." At most, these articles alleged asbestos contamination in certain talc samples without a reliable scientific basis or regulatory confirmation.

We hope that CIR finds this information helpful.

Exhibit A

JUL 11 1986

1986 JUL 21 PM 3: 00

Phillippe Douillet
One Holyoke Lane
Stony Brook, New York 11790

Re: Docket No. 83P-0404

Dear Mr. Douillet:

This responds to your November 8, 1983, petition requesting that cosmetic talc be labeled with an asbestos warning statement, information on asbestos particle size, and the proportion of talc impurities in the product.

You assert that, because the mining of talc almost invariably includes the mining of asbestos as well, cosmetic talc may contain significant amounts of asbestos particles that present an inhalation hazard to humans. Also, you cite references to substantiate that significant amounts of asbestos have been found in commercial talc samples, that asbestos inhalation is hazardous to humans, and that asbestos contaminants in talc will produce toxicological responses when inhaled.

FDA recognizes that asbestos inhalation over extended periods is hazardous to humans. The agency is also aware that some cosmetic talc produced in the 1960s and early 1970s did contain asbestiform minerals. However, your petition has not persuaded us that the cosmetic talc that is presently being produced contains significant amounts of asbestiform minerals.

During the early 1970s, FDA became concerned about the possibility that cosmetic talc did contain significant amounts of this material. The agency received several reports about such contamination. However, at that time, the analytical procedures for determining asbestos in talc were not fully developed, and most of the analytical work was conducted without scientific agreement as to which methods were well-suited for the identification of asbestiform minerals in talc. Consequently, FDA considered all analytical results to be of questionable reliability. This assessment proved to be correct because many questions were subsequently raised about results reported in the literature in the early 1970s (see enclosed copy of National Bureau of Standards Special Publication 506 entitled "Misidentification of Asbestos in Talc"). Because of the questionable nature of the analytical results, the agency was not able to assess reliably the levels of asbestiform minerals in cosmetic talc then in the marketplace.

83P-0404

PDN1

Mr. Phillippe Douillet - Page 2

Under these circumstances, FDA decided that the most appropriate actions that it could take to protect the public health would be to make the reports public and to request assistance from the affected industry in developing acceptable analytical procedures. This approach apparently has led to considerable improvement in the quality of this talc.

After FDA took these actions, many cosmetic manufacturers began to analyze their talc for asbestiform minerals as part of their quality control programs, and talc suppliers began to sell higher purity talcs to the cosmetic industry. By 1976, asbestos analytical methodology was sufficiently developed that the Cosmetic, Toiletry, and Fragrance Association (CTFA) could issue a specification (copy enclosed) for cosmetic talc. This specification required that such talc be free of fibrous amphibole (e.g., asbestos in the form of asbestiform tremolite) using a CTFA method of analysis that is capable of detecting 0.5 percent of amphibole asbestos. This specification contributed to the continued improvement of cosmetic talc quality.

In addition, FDA surveillance activities that were conducted in the latter portion of the 1970s showed that the quality of cosmetic talc had significantly improved, and that even when asbestos was present, the levels were so low that no health hazard existed. Our scientists recently reviewed data from these surveillance activities and concluded that the risk from a worst-case estimate of exposure to asbestos from cosmetic talc would be less than the risk from environmental background levels of exposure to asbestos (non-occupational exposure) over a lifetime.

Consequently, we find that there is no basis at this time for the agency to conclude that there is a health hazard attributable to asbestos in cosmetic talc. Without evidence of such a hazard, the agency concludes that there is no need to require a warning label on cosmetic talc.

FDA should also point out that, in reviewing your petition, we found several problems with the information on which you relied. The publication "Asbestiform Impurities in Commercial Talcum Powders," which you cite in your petition, appears to contain a number of significant errors that lead us to question the accuracy of the findings that were reported. For your information, we have enclosed a copy of a June 8, 1973, rebuttal of this publication that was written by the Chief Minerologist of the Colorado School of Mines Research Institute in Golden, Colorado. Also, your petition's 1978 book reference to the Mt. Sinai School of Medicine findings is too old to reflect present contamination levels. Further, we are not convinced that the Mt. Sinai findings pertained to cosmetic talc. Your reference states that common commercial talcs were analyzed, but it does not specify whether these commercial talcs were industrial grade or cosmetic talc.

Mr. Phillippe Douillet - Page 3

For all of these reasons, your petition is denied. This denial is without prejudice to the future filing of a petition on this matter, accompanied by all relevant data in support of the petition.

Sincerely yours,

H. J. W. Swanson

Acting Associate Commissioner
for Regulatory Affairs

Enclosures

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cc:  HFC-1
     HFC-200  (#G-86-182)
     HFC-220  (Rogers/file)
     HFF-1
     HFF-100
     HFF-152
     HFF-300
     HFF-302
     HFF-310
     HFF-440
     GCF-1  (Horton/Derfler)
     HFA-224
     HFA-305
Prepared:JRTaylor:5/15/86
Initialled:JRTaylor:5/15/86, 6/5/86
           EJCampbell:5/15/86, 6/5/86
           HJEiermann:5/16/86, 6/9/86
           JAWerninger:5/19/86
           WGFlamm:5/29/86, 6/9/86
           IRLake:5/29/86, 6/12/86
           RJLenahan:5/29/86, 6/10/86
           LBBrock:6/10/86
           RWGill:6/12/86
F/T:JRTaylor:sag:6/4/86
Concurred:EBrisson:6/27/86
Retype:RLSpencer:cdk:6/27/86:disk.26 (#1.32)
Revised:PSDerfler:7/3/86
Retype:RLSpencer:cdk:7/7/86
Concurred:PDerfler:7/8/86
Revised:Concurred:LHorton:7:9/86
F/T:RLSpencer:bka:7/10/86
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COSMETIC TALC

CTFA Adopted Name:
TALC

DEFINITION: Cosmetic Talc is an essentially white. odorless. fine powder. ground from naturally occurring rock ore. It consists typically of 90% hydrated magnesium silicate. having the ideal formula $Mg_6[Si_8O_{20}]\cdot(OH)_4$. with the remainder consisting of naturally associated minerals such as calcite, chlorite. oolomite, kaolin and magnesite. and containing no detectable fibrous, asbestos minerals.

TEST	SPECIFICATION	METHOD
Color	As specified by the buyer and showing no change after heating	Heat 1 to 2 g at 200°C for 5 minutes
Odor	As specified by the buyer	
Identification	Positive:	
	1. Close match to CTFA Spectrum—IR with no indication of foreign materials	CTFA G 3-1
	OR	
	2. (Alternate) Close match to X-ray Powder Diffraction File No. 19-770, published by ASTM, showing the most intense reflections at d values about 9.35, 1.53 and 4.59 Å	ASTM D 934-74
Slip	As specified by the buyer	
Lustre	Do.	
Water-Soluble Iron	Passes test	USP XIX, page 487
Screen Test	100% through 100 mesh 98% minimum through 200 mesh Finer grades: as specified by the buyer	CTFA C 6-1
Water Soluble Substances	0.1% maximum	USP XIX, page 487 See test for "Reaction and Soluble Substances"
Acid Soluble Substances	As specified by the buyer 6.0% maximum	CTFA E 32-1
Loss of Ignition	5.0% maximum	USP XIX, page 487
Arsenic (as As)	3 ppm maximum	CTFA F 1-1, Parts I-A and II
Lead (as Pb)	20 ppm maximum	CTFA F 2-1, Parts I-A and II
Fibrous Amphibole . . . . (Asbestiform Tremolite et al)	None detected	CTFA J 4-1
Free Crystalline Silica . . . . (Quartz)	As specified by the buyer	CTFA J 5-1 (DTA) Alternate: CTFA J 6-1 (X-ray)

. . . . . .

COLORADO SCHOOL OF MINES RESEARCH INSTITUTE

P.O. Box 112

GOLDEN, COLORADO 80401

TO   W. H. Ashton

FROM   W. T. Caneer

DATE   June 8, 1973

PROJECT NO.   C10704

SUBJECT   Meeting with Bowling Green State University Geological Staff

A paper entitled "Asbestosform Impurities in Commercial Talcum Powders," published in the January 1972 issue of The Compass of Sigma Gamma Epsilon (Vol. 49, No. 2) stated that 18 commercial talcum powders examined contained from 4% to 46% asbestiform minerals. The average asbestiform content was 18%. The data in this paper has subsequently been quoted and has been a source of inquiry by interested individuals both in and outside of government agencies. The amount of asbestiform minerals reported is so large that the data could initiate costly FDA hearings on the matter. Since our general observations at the Research Institute relative to asbestiform minerals in talc are at such a large variance to those reported in the paper, an investigation of the paper was undertaken. To date we have reviewed the paper and have discussed the data with the authors. The people involved in the investigation were W. T. Caneer and Dr. Jerry Krause of the Research Institute and Dr. Maynard Slaughter of the Colorado School of Mines.

REVIEW OF THE PAPER

A review of the paper suggested that a number of errors are present. Some of these apparent errors may be illustrated by the following table which appeared in the paper:

Table I

Qualitative Mineral Analyses by X-ray Diffraction

Sample Number	Talc	Asbestosform Minerals (Serp.	Trem-Act.	Anth.)	Carbonates	Anhydrite	Clay (Mica)	Misc. Mins.*
1	x	x	x			x	x	x
2	x	x				x	x	x
3	x	x				x	x	x
4	x	x	x	x	x	x	x	x
5	x	x	x			x	x	x
6	x	x		x	x	x	x	x
7	x	x				x	x	x
8	x	x	x	x	x	x	x	x
9	x	x					x	x
10	x	x				x	x	x
11	x		x		x	x	x	x
12	x				x	x	x	x.
13	x		x	x	x		x	x
14	x	x			x	x	x	x
15	x	x	x			x	x	x
16	x		x					x
17	x		x	x		x	x	x
18	x	x		x		x	x	x

*Additives and inert minerals and compounds.

According to this table, asbestiform minerals were identified by X-ray diffraction. By the method of X-ray diffraction used, one could only expect to identify mineral groups to which asbestiform minerals belong. Numerous common non-asbestiform minerals also occur in these groups.

A differentiation is shown for tremolite-actinolite and anthophyllite. It is not likely that these minerals could be differentiated by the X-ray methods used.

The mineral anhydrite ($CaSO_4$) is also reported by X-ray diffraction for all except three of the samples. We have never found anhydrite in any talc samples examined at the Research Institute. Furthermore, from the standpoint of geological occurrences and rock genesis, one would not expect to find anhydrite associated with talc. With these factors in mind, a study was made to determine how one may possibly make an identification of anhydrite in talc.

It soon became apparent that a talc k-beta diffraction peak was being inter-
preted as belonging to anhydrite. A filter is used to screen out k-beta
radiation in X-ray diffraction analysis. However, the filter is not 100%
efficient and some of the k-beta passes through the filter and can lead to
erroneous interpretation.

The table also shows serpentine as one of the asbestiform minerals identified
by X-ray diffraction for most of the samples. This is usually based on the
occurrence of a 7-angstrom peak. However, chlorite also gives a 7-angstrom
peak and chlorite is a common constituent of talc. A differentiation of the two
minerals can usually be made based on other diffraction peaks. Since chlorite ·
is a common constituent of talc and none was reported for the 18 samples, it
is likely that chlorite was misidentified as serpentine.

Table II was presented in the paper and shows quantitative mineral analyses
by petrographic microscopic techniques.

Table II

Quantitative Mineral Analyses by Petrographic Microscope
(Volume Percent)

Sample Number	Percent Talc Flakes	Percent Carbonate Grains	Percent Asbestosform Minerals
1	73	5	22
2	92	*trace	8
3	**79	trace	21
4	57	20	23
5	82	trace to 1	18
6	72	13	15
7	89	5	6
8	61	5	34
9	80	4	16
10	92	4	4
11	86	trace	14
12	76	20	4
13	48	6	46
14	90	4	6
15	74	4	22
16	80	trace	20
17	70	6	24
18	76	trace	24

*Less than 1 percent.   **Includes muscovite.

memo to W. H. Ashton   Page 4   June 8, 1973

It is perhaps significant that no anhydrite was observed by microscopic
techniques even though it was reported in 15 of the 18 samples by X-ray
diffraction. It is perhaps also significant that no specific asbestiform
minerals were reported in Table II -- only a total percent of asbestiform
minerals. This led us to suspect that any grain with a high length to thick-
ness ratio observed under the microscope would be classified as asbesti-
form. This could lead to the misidentification of the edges of talc plates
and of talc shards as asbestiform minerals.

DISCUSSIONS WITH THE AUTHORS

Of the three authors, two were graduate students (Snider and Pfeiffer) at
the time the paper was written. J. Mancuso is on the Geology Department
staff and acted as advisor for the research and the paper. Snider is pres-
ently with the Michigan Geological Survey in Mt. Pleasant, Michigan, and
Pfeiffer is a geologist for Texaco in Midland, Texas. We discussed the
paper with Mancuso in Bowling Green and held telephone conversations with
Snider and Pfeiffer. We made it clear to these people that the data presented
in their paper could lead to very serious charges against the products. They
readily agreed that their data could easily have errors, and if so it would
save them much possible embarrassment at a later date by correcting their
errors now.

Apparently the paper was submitted for publication to fill an issue of the
journal which was being devoted entirely to the Bowling Green Geology Depart-
ment. Apparently a Dr. I. I. Oster (a fruit fly expert in the Biology Depart-
ment) told them that he had been conducting experiments related to the
injection of talc products into mice for the purpose of determining the effects
of the injections upon the mice. He requested that the Geology Department
make mineralogical determinations of the asbestiform minerals in the talc
products. None of the three authors had had any previous experience with talc
mineralogy, but they decided that it would be a suitable subject for a paper.
Our discussions yielded the following significant results.

1. All three authors readily admitted that they did a "rush-job." About 2
    weeks was spent in gathering data for the paper.

2. They agreed that asbestiform minerals cannot be identified by X-ray dif-
    fraction. X-ray diffraction is capable only of identification of a mineral
    group which contains both asbestiform and non-asbestiform minerals.

3. They admitted that they did not adequately check the "talc edge effect"
    which could lead to the misidentification of talc plate edges as asbestiform
    minerals by microscopic analysis.

4. They did not take into account the possible presence of chlorite in the talc and could have well misidentified chlorite as serpentine (which of course includes chrysotile).

5. Relative to the identification of anhydrite, they admitted that they probably misidentified a k-beta talc peak.

6. They counted only 100 grains for their quantitative microscopic analyses. Though their data is presented in terms of volume percent they neither measured the size of the grains counted nor considered the difference in the volume of a fiber as opposed to a plate. We pointed out that the statistics involved are totally unacceptable.

7. They admitted that they probably made many errors in conducting the project and seem anxious to rectify them before there is a possible accounting with the FDA or some other agency.

8. The following list identifies the talc products examined in the Bowling Green Study.

Sample No.	Brand Name	Quoted % Asbestiform Minerals
1	Mennen Talc Powder	22
2	J & J Baby Powder	8
3	Corn Silk	21
4	Estee Lauder	23
5	Cuticura (South Africa)	18
6	Coty-Muquist de Boio	15
7	April Showers (N.Y.)	6
8	Remington Shave Talc	34
9	Cashmere Bouquet	16
10	Imprevu	4
11	Avons Sachete Occur	14
12	Heaven's Scent	4
13	Excalibur Spray (Avon)	46
14	Loves Fresh Lemon	6
15	Mennens Baby Magic	22
16	Ammens Medicated Powder (ZnO)	20
17	ZBT Baby Powder	24
18	Cuticura (U.S.A.)	24

9. About a year ago Howard Jack, who was with the American Geological Institute at the time, requested and got the list of various brands of talc examined in the Bowling Green study. His motivation is unknown to us. We have determined that Jack is now apparently with some governmental agency and we are trying to determine his interest in the samples.

We asked to see their X-ray diffraction patterns and also requested splits of the samples. They could not locate the diffraction patterns and found only two samples (Nos. 8 and 13) while we were there. They are still trying to locate the others and said that they would send them to us when and if they find them.

They spent an inadequate amount of time and have admitted to making errors relative to the identification and amount of asbestiform minerals. They apparently will not stand behind the data presented in the paper if they are pressed to do so. ' I also believe that they will retract the data after we present them our data and after they have had time to do some checking on their own.

/nkr

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date   June 6, 1985

From   QRAC (Quantitative Risk Assessment Committee)

Subject   Asbestos in Talc

To   W. Gary Flamm, Ph.D.
Director, Office of Toxicological Sciences (HFF-100)

Using Linda Taylor's report [1] and other information on asbestos and talc, we conclude that the added human risk of lung cancer and mesothelioma from possible asbestos in talc is less than 10^{-8} lifetime risk and quite possibly orders of magnitude less. We have used, as our population at risk, infants that may be routinely dusted with talcum powder for an estimated period of 2 years.

Infant Dose and Worker Exposure:

Based upon one experimental 2 yr. exposure scenario for talcum powder dusting, babies would apparently inhale no more than about 6.5×10^3 asbestiform fibers per year (4.95 talc fibers/cc x 1000cc/1 x .58 1/min. breathing rate x 43.8 min/wk powdering x 52 wk/yr. x .1% asbestos in talc). The asbestiform fibers are difficult to detect, poorly defined in shape, and of a highly variable subtype. We assume .1% tremolite or anthophyllite asbestos in talc based on 1977 FDA measurements and other recent samples [1, 10, 11]. To be called asbestiform fibers, the fibrous silicates must be greater than 5 um. and have length/width ratio greater than 3. These inherent detection and geometrical measurement limitations for asbestos in talc make comparisons with worker exposure to a different type (mainly amosite, crocidolite and chrysotile) and shape of asbestos highly problematical [5]. In fact there is a

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general consensus that current talc mines are virtually free of asbestos (offending mines have gradually been abandoned) and that any residual silicates in talc are so finely and smoothly ground as to represent virtually no risk to humans whatsoever even where an occasional fiber just barely satisfies the technical definition for asbestiform fibers. However, this consensus belief would require better geometric measurements than currently exist for both current commercial talc fibers and for workplace asbestos fibers during the past 50 years. Nevertheless, baby exposure in fibers per year is crudely estimated at about 0.3×10^{-6} times that of worker exposure in several well known epidemiological studies (e.g., Selikoff study: 15 f/ml in workplace x 12,000 ml/min breathing rate x 60 min/hr x 8 hr/day x 5 days/wk x 50 wks./yr. = 2.16×10^{10} f/yr. vs 6.5×10^{3} f/yr for baby) [1].

A complicating factor, however, is that human cancer risk from these studies seems to follow different time-dose response patterns for the two main cancer endpoints (lung cancer and mesothelioma). Although several human epidemiological studies exist which could be utilized for quantitative risk assessment purposes, it is most illustrative to consider the largest of these occupational studies, namely, that of Selikoff, et. al. [7,8] in which 17,800 insulation workers were exposed to a mixed variety of asbestos fibers (mainly amosite and chrysotile) for about 25 years on average. Through 1976, 2,271 deaths (12.7% of total) had occurred.

Lung Cancer:

Lung cancer rates were about 4.6 times average (486 observed/106 expected). Since this nearly 360% excess lung tumor

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rate seems to apply to nonsmokers alone as well as smokers and
nonsmokers combined [6], then, assuming hypothetically that one can
extend excess relative risks to very low asbestos exposures, one
would expect to see an excess lifetime lung tumor rate among asbes-
tos exposed nonsmokers of about 1.8% (360% x the normal lifetime
nonsmoker lung tumor rate of about .5% - integrating 1979 survival
rates against Garfinkel's 1960-1972 nonsmoker age-specific lung
tumor rates [12, 13]). Excess lung cancer rates appear to be
proportional to dose and duration of exposure, but not to some high
power of time-since-first-asbestos exposure [6]. Thus, excess
lifetime lung cancer risk for talc exposed babies who will never
smoke would appear to be approximately the product of 1) an excess
1.8% lifetime risk for nonsmoking asbestos exposed workers, 2) a
baby/worker yearly exposure ratio of 0.3×10^{-6}, and 3) a
baby/worker exposure duration ratio of 2 yrs/25 yrs. This product
yields a value of $.4 \times 10^{-9}$ added lifetime risk for lung tumors.
Similarly, averaging eventual smokers in with the lifelong
nonsmokers assumed above, the average added lifetime lung cancer
risk for the talc exposed baby will be at worst about 10 times
higher or about $.4 \times 10^{-8}$. We note that current (1979) lifetime
total respiratory cancer rates are about 5% and have nearly doubled
since 1960, possibly reflecting rapidly changing smoking patterns
during and after World War II, primarily among women. However,
decreased tar levels in cigarettes and decreased per capita use of
cigarettes since about 1965 should result in a gradual leveling off
or decline in the total respiratory and/or lung cancer rate of the
general population [14].

Mesothelima:

The estimation of lifetime risk of mesothelioma is somewhat more difficult since the mesothelioma response data appears quite nonlinear in time since first exposure. We have investigated four different methods of mathematically modelling the nonlinear mesothelioma data. They all indicate an upper bound on lifetime risk for talc powdered infants of about 10^{-8} risk and quite possibly a much lower upper bound if the conservative assumptions upon which they were based do not hold. These four methods consisted of mathematically treating mesothelioma as 1) a nonincidental tumor with no time lag between tumor initiation and death, 2) a nonincidental tumor with a 10 year time lag between tumor initiation and clinical observation, 3) an incidental tumor, and 4) treating asbestos as a first stage intervener in an Armitage-Doll multistage carcinogenic process [9].

In fact methods 1-3 yielded virtually identical risks (.5-.75 x 10^{-8} risk). While method 4 yielded a risk 2-3 times higher (1.5 x 10^{-8} risk), it could easily have yielded a risk up to several orders of magnitude lower than 10^{-8} if we had simply assumed asbestos intervenes at a later stage of the carcinogenic process in this hypothetical Armitage-Doll multistage model. There was general concurrence among these four methods, and it suffices to briefly summarize Method 1.

Method 1: based upon fitting $bt^{3.1}$ (nonincidental analysis) to a

1922-1946 cohort of the Selikoff, et. al. data.

A reasonably simple way to estimate the median life (ML) risk to median survival age 77 (in 1979) for humans exposed 2 yrs. to talcum

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powder during infancy is given by the product of the following terms:

(a) (77 yrs. since first exposure for infants/37 yrs. since first exposure for 1922-46 cohort as of $1978^+)^{3.1}$ = 9.70.

(b) (2 yr. infant exposure duration/34 yrs. approx. worker exposure duration for 1922-1946 worker cohort) = .059.

(c) (infant/worker) yearly exposure ratio = 0.3×10^{-6}.

(d) 1922-1946 cohort cumulative mesothelioma response of 3.75% (180 mesotheliomas/4,800 cohort members).

This product yields a median life risk of R_{ML} = 0.64×10^{-8}.

Tumors other than Lung and Mesothelioma: (Selikoff study)

Although significant tumor increases were observed at other sites in the workers (e.g., esophagus, stomach and colon), their risk is dominated by that of the lung (less than 10^{-9} or 10^{-8} risk, depending upon whether or not the baby becomes a smoker) and by mesothelioma risk (less than 10^{-8} risk).

Other Comments on Total Cancer Risk:

These estimates of added lifetime human cancer risk are 2 orders of magnitude below those implied in Linda Taylor's memo 1) due to the fact that the more recent detection studies suggest .1% or less asbestos in talc on average rather than the 1% assumed by Dr. Taylor: and 2) due to a 10 fold conversion error going from fibers/cc in the air to fibers inhaled/yr by the infant.

Although mothers may receive an exposure for each infant powdered, their added lifetime risk from talc should be relatively smaller than the infant's since their mouths and noses are considerably further from the densest portion of the talc cloud than is the case for the captive infant during the daily powdering period (the inverse square law for exposure may apply).

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Finally, the risks implied by the Selikoff study are generally on the high side of those implied by the other smaller epidemiological studies and we see little value in repeating calculations here for those studies (see reference 6 for details).

Ovarian Talc Study:

For completeness, a discussion is presented on a human epidemiological study purporting to show an association between talc use (talcum powder used for genital dusting on the perineum or on sanitary napkins) and ovarian cancer.

The Cramer et.al. study [2], which purported to show a significantly increased relative risk for ovarian cancer associated with talc use, 1) appears to have been misinterpreted statistically, 2) was uncorrected for several likely biasing factors and 3) appears to have been strongly contradicted by another study showing a reduced relative risk as significant in the negative direction as the Cramer study was in the positive direction.

The Cramer study's most prominent analysis (Mantel-Haenszel) was adjusted for only 2 factors and gave a relative risk (RR) of around 1.92 (p less than .003) and 95% confidence limits of 1.27 to 2.89 for 215 cases (talc users for genital or sanitary napkin dusting) vs 215 controls. Cramer's more comprehensively adjusted but seemingly de-emphasized multivariate regression analysis for 9 possible simultaneously confounding variables yielded a smaller and much less significant relative risk of 1.61 (p=.03), with 95% confidence limits of 1.04-2.49. It should be noted that the crude relative risk with no adjustments whatsoever was 1.89. In any case, if the authors had limited their logistic regression analysis as they subsequently did for their Mantel-Haenszel analysis, to those 121 cases where the first chosen control did not refuse to participate

(refusal bias), then the resulting p-value can be predicted through extrapolation of the other reported analyses to be greater than .05 and perhaps greater than .1. Unfortunately, the authors did not report this analysis. Instead they selectively chose to point out only that the relative risk of those exposed to talc both as a genital dusting powder and through sanitary napkins declined from a relative risk of 3.28 (p less than .001) to 2.44 (p less than .05) when the potentially biasing control refusals were eliminated from analysis. Apparently the authors felt it unnecessary to report those p-values that were greater than .05.

Since there were twice as many singles among the cases (21%) as among the controls (11%), the life style of singles might easily have biased the original overall relative risk of 1.92 [3]. However, the multivariate logistic analysis (RR=1.61) using all of the original 215 cases and 215 controls clearly adjusted for marital status along with such variables as religion, educational level, ponderal index, age at menarche, exact parity, oral contraceptive or menopausal hormone use, and smoking. The partially adjusted Mantel-Haenszel analysis (RR=1.92) only adjusted for menopausal status and crude parity.

Furthermore, it is generally assumed that any real positive cancer effect will show an increased risk with increased dose. Cramer only reported one subanalysis where he crudely considered dose response. He divided the small group of talc-dusted diaphragm users into those using diaphragms less than 5 years and into those using diaphragms more than five years. However, rather than showing an increased relative risk with increased dose (increased length of usage), the relative risk actually decreased noticeably

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though not in a "statistically significant" fashion from 1.82 to
1.23 as diaphragm use increased from less than 5 years to more than
5 years.

In addition to the above interpretations of Cramer's own
results, several potentially biasing factors could not be adjusted
for by the logistic analysis. First, a possible positive correlation
between talc use and ovarian disease etiology due to patient-perceived
hygenic or cosmetic reasons would bias the relative risk upwards
[4]. Second, a recall bias among hospital cases relative to
community controls is quite plausible since cases may have greater
incentive as well as opportunity to recall whether they should
classify themselves as talc users [3]. Talc users from the
community may well be modest in either participating as controls
(the refusal bias already discussed) or in subsequently admitting
talc use as a control subject. The recall bias might be expected
to be even greater - as was possibly observed - for estimation of
the relative risk for those using talc both on sanitary napkins and
as a dusting powder (RF=3.28, p less than .001; or RR=2.44, p less
than 0.05, after the refusal bias is eliminated) than for those
engaged in only a single type of use.

Finally a talc and ovarian cancer study by Hartge, et. al.
[4], appears to strongly contradict the reportedly positive Cramer
study. Overall 135 cases and 171 control women matched by age, race
and hospital were questioned on talc use. The estimated relative
risk of ovarian cancer by talc users was reported to be 0.7 (95%
confidence interval of 0.4 to 1.1). Adjustments for race, age, and
gravidity (pregnancy) had no effect upon the estimate. No subanalyses

resulted in relative risks significantly greater than 1. It would
appear that no refusal bias was operative in the Hartge study since
none was reported. Also it would appear that recall bias was non-
existent since there appeared to be no recall bias on the use or
nonuse of douching.

SUMMARY

In summary, any hypothetical systemic added lifetime cancer risk
(e.g., mesothelioma and lung cancer) to humans due to asbestos fibers in
talc (principally for babies subject to 2 years of talc dusting) appears
to be less than 10^{-8} added lifetime risk and possibly several orders of
magnitude lower risk still, depending upon assumptions and uncertainties
alluded to above, especially those regarding geometrical shape of any
possible asbestos fibers in talc, and limits of detection for asbestos
in talc. In addition, there appears to be no association between
customary human talc use per se and ovarian cancer.

Robert Brown

Robert Brown

ATTACHMENT:

Signature Page

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SIGNATURE PAGE

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DEPARTMENT OF HEALTH & HUMAN SERVICES

⬤

Public Health Service

Lorina

Memorandum

Date	May 21, 1985
From	Robert Brown BRAB, Division of Mathematics (HFF-118)
Subject	Four methods of quantitating mesothelioma risk based on the Selikoff, et. al., insulation workers asbestos study. Technical support for QRAC's asbestos risk assessment.
To	QRAC

In fig. 1 we have plotted on a log-log scale Selikoff's original mesothelioma incidence data vs. years since first exposure to asbestos. Incidence is defined as number of mesotheliomas/man-years exposure. The data do not seem to fit a single straight line. Uncertainties of exposure in the early part of the century and the general decline in intensity of asbestos exposure after World War II are possible sources of error. For these reasons, as well as general lack of fit of both recent data and distant past data, Peto recommended use of a more homogeneous subset of workers for quantitative purposes, namely those workers first exposed between 1922 and 1946 [8]. It can be inferred from Selikoff's report that this subset consists of about 4800 workers.

Peto reports 180 mesotheliomas (3.75%) among this subgroup out of a total of 236 mesotheliomas for all 17,800 workers followed from 1967 until about 1978 or 1979. Note that Selikoff only reported 175 mesotheliomas total; however, his reported follow-up period was also shorter (1967-1976).

Plotting Peto's homogeneous 1922-46 cohort subset, we see that $bt^{3.1}$ nicely fits the data (expressed as a straight line on log-log paper with a slope of 3.1). We also see that $b(t-10)^{2.1}$ nicely fits the data (with a different value for the constant b) and may be a reasonable

way of looking at mesotheliomas since the time lag from mesothelioma
induction to death is not zero. The time of mesothelioma induction is
not even a well defined concept and may be intimately entertwined with
the concept of stage definition in, for example, a multistage cancer
process. Nevertheless, both these model fits assume mesothelioma to be
a nonincidental tumor (i.e., a life table where incidence is the ratio
#tumor bearers/#survivors, re-expressed in man-years, per time interval).
If we assume mesothelioma annual incidence to be better approximated by
a prevalence or incidental definition, (#tumor bearers/#dead in interval),
then $bt^{1.64}$ seems to be a rough though not very tight fit to the original
Selikoff data. Peto's reported 1922-1946 data set does not easily allow
determination of a prevalence fit. However, since the prevalence
denominator is defined in terms of deaths per time interval rather than
the much larger number of survivors to date, the first 2,271 deaths
(12.7% of 17,800 workers) reported by Selikoff are very heavily weighted
with the 1922-1946 cohort used exclusively in the two nonincidental
curve fits above. Therefore comparisons of slightly different cohort
subsets may still be useful. We estimate that the average time since
first exposure for the Peto subset (1922-1946 first exposure) is about
37 years (Peto's 1978[+] follow-up) or 35 years (Selikoff's 1976
follow-up). This compares to 25 years average time since first exposure
usually reported for all 17,800 workers. We also make the assumption
that workers ceased exposure on average 3 years before death.

Method 1: based upon fitting $bt^{3.1}$ (nonincidental analysis) to a 1922-1946 cohort of the Selikoff, et. al. data.

A reasonably simple way to estimate the median life (ML) risk to median survival age 77 (in 1979) for humans exposed 2 yrs. to talcum powder during infancy is given by the product of the following terms:

(a) (77 yrs. since first exposure for infants/37 yrs. since first exposure for 1922-46 cohort as of $1978^+)^{3.1}$ = 9.70.

(b) (2 yr. infant exposure duration/34 yrs. approx. worker exposure duration for 1922-1946 worker cohort) = .059.

(c) (infant/worker) yearly exposure ratio = 0.3×10^{-6}.

(d) 1922-1946 cohort cumulative mesothelioma response of 3.75% (180 mesotheliomas/4,800 cohort members).

This product yields a median life risk of $R_{ML} = 0.64 \times 10^{-8}$.

Method 2: based upon $b(t-10)^{2.1}$ (delayed observation or time lagged nonincidental analysis).

Note that to estimate real mesothelioma incidence (time of mesothelioma induction – the last stage of the multistage cancer process) at age x, the worker must be assumed to have been autopsied or surgically inspected at some average age, say x+10. Thus, assumming the worker stops exposure 3 years before death, the component relative and absolute risk factors for incidence at age 77 now are the following:

(a) ((87 yrs.-10 yrs.)/(37 yrs.-10 yrs.)$^{2.1}$ = 9.03.

(b) (2 yr. infant exposure duration/(37-10) yr. worker exposure duration) = .074.

(c) (infant/worker) exposure rate ratio = 0.3×10^{-6}.

(d) 3.75% mesothelioma response in 1922-1946 cohort

Thus $R_{ML} = 0.75 \times 10^{-8}$.

Method 3: based upon $bt^{1.64}$ (prevalence or incidental analysis):

The relative and absolute risk product factors are:

(a) (77 yrs. since first exposure for infant/35 yrs. since first exposure for the 2,271 deaths to 1976)$^{1.64}$ = 3.64.

(b) (2 yr. infant exposure/34 yr. ave. worker exposure duration for 2,271 deaths to 1976) = .059.

(c) (infant/worker) exposure rate ratio = 0.3×10^{-6}.

(d) 7.7% mesothelioma cumulative prevalence to 1976 (175 mesotheliomas/2,271 deaths).

Thus $R_{ML} = 0.50 \times 10^{-8}$.

Method 4: based upon $bt^{3.1}$ (nonincidental analysis) and a first stage effect in a generalized multistage process.

We assume that bt^{k-1} fits the time-response data of a nonincidental tumor and is consistent with a first-stage-only effect in a generalized multistage process (with K stages), where biological time t starts at age of first exposure and continues until death [9]. Although this is not precisely true for the 1922-46 asbestos worker cohort, it appears to be approximately true. Moreover the time lag from cessation of exposure to end of followup (1976 or 1978[+]) is assumed to be small compared to total duration of exposure (i.e., exposure duration is a large fraction of time since first exposure). However, the exposure duration for infants is very small compared to median lifespan. Thus, while we fit worker yearly incidence data to bt^{k-1} we should extrapolate yearly incidence (I) for exposed infants using the expression $I = b(t^{K-1} - (t-d)^{K-1})$ for a K stage multistage process with duration of exposure d and time since first exposure t [9].

Now K-1 = 3.1 from Fig. 1 and b can be written as the product of a constant K_m and f where f is the time adjusted yearly dose of asbestos fibers in ml-yrs. K_m is a constant dependent upon the type and dimensions of the asbestos. Since f = 3.43 f/ml-yr. (15 ave. f/ml in workplace (1922-1946) x 8 hrs./24 hrs. x 5 days/7 days x 50 wks/52 wks) for the Selikoff study, K_m can be computed from the plot of $I = K_m f t^{3.1}$ in Fig. 1. At t = 20 yrs, I = 5.6 x 10^{-4}, implying that the $\ln K_m$ = ln (5.6 x 10^{-4})-ln(3.43)-3.1(ln 20) = -7.49-1.23-9.29=-18.01.

Thus K_m = 1.51 x 10^{-8} (same as Peto obtains). Continuing, I = $K_m f(t^{K-1}-(t-d)^{K-1}) = K_m f t^{K-1}(1-(1-d/t)^{K-1})$ which roughly = $K_m f t^{K-1}(d/t)(K-1)$ for d much less than t (using Taylor expansions). Thus yearly incidence is approximately $I = K_m fd(K-1)t^{K-2}$. Integrating (without correcting for decreasing survival) over a total of T years yields a cumulative incidence of about $I_c = K_m fdT^{K-1}$. If d = 2 yrs. infant exposure duration, T = 77 yrs., K-1 = 3.1, f = 3.43 f/ml-yr. for worker x 0.3 x 10^{-6} (infant/worker exposure ratio) = 1.03 x 10^{-6} f/ml-yr., and K_m = 1.51 x 10^{-8}, then I_c = 2.2x10^{-8}.

However, this figure assumes no mortality from competing causes of death and does not even adjust for the effect of previous mesothelioma related deaths. Factoring in a standard population age-specific mortality or corresponding survival function into the above integral would yield a median life risk of about 75% of 2.2x10^{-8} or R_{ML} = 1.6x10^{-8}. This correction for survival can vary depending upon the limits of integration and what functional forms are under the integral, but for median life risk estimates the correction ranges from 1.0 down to .5 at worst. We also note that integrating I out to 100 yrs. of life with

respect to a standard mortality curve should yield approximately the same risk as cumulative incidence to median age 77 yrs. without any mortality adjustments. These approximately cancelling effects of two mathematical refinements may support the utility of using the median lifespan in simple calculations.

Comments on the 4 Mesothelioma extrapolation methods:

First and most importantly, it should be noted that the first 3 methods yield virtually identical median lifespan risks for babies exposed to talc for 2 years ($.5-.75 \times 10^{-8}$). Thus many of the debates over the "correct model" appear somewhat superfluous. In particular heated debates over whether mesothelioma rates follow given high or low powers of time appear to be superfluous since the power of time is compensatingly related to other poorly defined and difficult to measure conceptual model parameters (e.g., tumor stage initiation and consequent time lag to clinical detection or death, and context of tumor observation (incidental or nonincidental)). Furthermore, small perturbations of the rough estimates of worker exposure or the power of time (K) have only a small effect on the overall risk.

All the above models appear to be reasonable summary descriptors of the observable data and result in simple extrapolatory tools for the given problem of inferring median lifetime risk from infant exposure. One can always make method 4 computationally more difficult if one avoids use of the approximations.

A second observation is that the rough mutual agreement of the results of the 4 extrapolation methods does not necessarily imply that

the obtained excess median life risk is accurate even if the infant and worker exposure were to the same type and dimension of asbestos fiber. For example, none of the four models take into account the possibility that accumulated dose rather than yearly dose rate might more accurately reflect the biological burden of asbestos due, for example, to its ability to reside in vivo in the lung, pleural or peritoneal lining for years without being excreted (although encystment may be possible). Note also that we did not define dose on a mg/kg body weight basis. Although, we prefer such s definition for routine compounds that are ingested and metabolized, we strongly suspect that routine approach to be inappropriate for asbestos. In addition, all 4 methods assume linearity in response vs. dose at all dose levels. However, we have virtually no reliable dose response data from any of the epidemiological studies.

Furthermore, some investigators have suggested that the nonconstant accumulated asbestos dose may be as conceptually consistent with a late stage multistage carcinogenic process as the more usually defined yearly asbestos dose rate appears to be consistent with a first stage Armitage-Doll multistage process [9]. Although the theory and computations are more complicated for nonconstant exposures, it does appear that median life risks from infant exposure to asbestos affecting only a late stage in the carcinogenic process will generally result in much smaller risks than those calculated above for a first-stage-only effect in the carcinogenic process.

Our third observation which we have just hinted at is that method 4 above (the first-stage-only effect in a multistage model) may be just another way of implementing method 1, but just slightly more computationally difficult and having a slightly higher risk, partially because it substitutes a theoretical risk integration against the current (1979) U.S. population's standard survival function for the implicitly observable but poorer asbestos worker's cumulative survival of an earlier era in a more toxic environment. For example, the method 4 risk is about 2.6 times greater than the average risk of methods 1-3. There are probably other reasons for this 2.6 fold increase in risk over methods 1-3. However, since even partial intervention of asbestos fibers at later stages of the carcinogenic process in the Armitage-Doll multistage model imply lower overall risks, we prefer the simpler methods 1-3 at this moment to the more complicated multistage models whose proper application with respect to the stage or stages affected is still very much in doubt.

In general, we do not put a lot of faith in mechanical use of sophisticated but unverifiable models, but we will occasionally refer to them as in method 4 where we can suggest implicit and perhaps elucidative connections to apparently more humble and simpler procedures.

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Summary:

All four mathematical methods of modelling the nonlinear mesothelioma response data from the Selikoff study indicate a lifetime added human risk to infants exposed 2 years to talc powdering of at most about 10^{-8} risk, and quite probably far less risk, if for example, asbestos intervenes in the carcinogenic process at a later stage than the first stage which was assumed in method 4 for the Armitage-Doll multistage process.

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K·E LOGARITHMIC 1 · 5 CYCLES **Fig 1** 46 7520
KEUFFEL & ESSER CO. MADE IN U.S.A.

Selikoff Asbestos Study (17,800 workers on asbestos union.
Mesotheliomas   roles as of Jan.1, 1967)

Original data   Peto's Homogeneous Subset
(1911-1967 First exposure)   (1922-1946 first exposure)
(1967-1976 follow up)   + expanded follow up ' for about 1978'

Nonincidental
Assumption
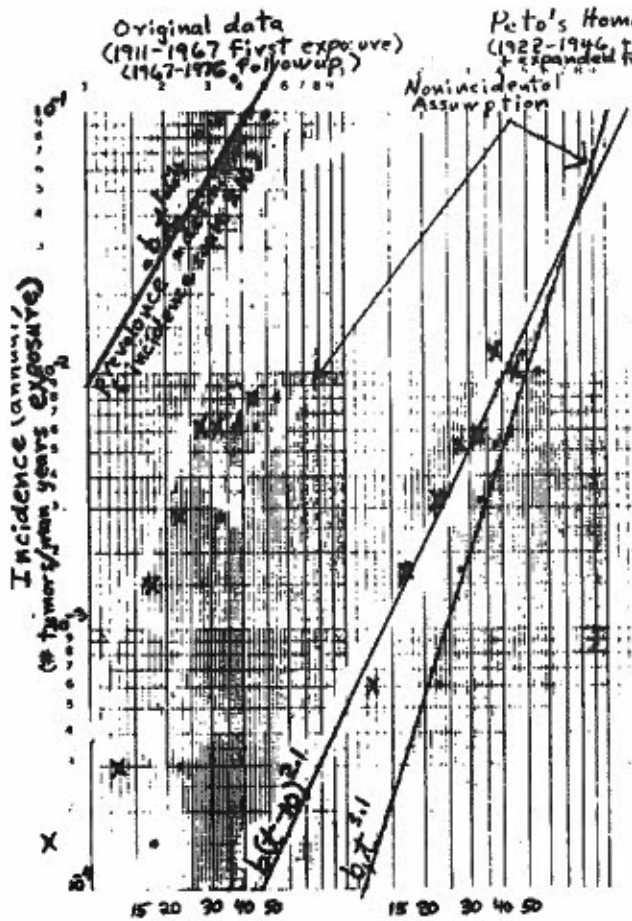
Selikoff's Original Data (1911-1967 first exposure)

Time Since First Exposure	#Mesotheliomas / #person yrs at risk (Incidence)	#Mesotheliomas / #deaths
0-14 years	0 /85,396 (0.0)	0 /136 (.0)
15-19	5/34,066 (.00015)	5/189 (.026)
20-24	9/31,263 (.00029)	9/320 (.028)
25-29	32/20,657 (.0015)	32/388 (.082)
30-34	32/11,598 (.0028)	32/340 (.094)
35-39	34/5,408 (.0063)	34/253 (.134)
40-44	20/3,140 (.0063)	20/203 (.098)
45	43/6,345 (.005)	43/458 (.097)
	175/2,873 (.00105)	175/2,287 (.077)

Peto's 1922-1946 Homogeneous Subset

15-19	3/6,739 (.0004)
20-24	28/12,515 (.0017)
25-29	47/14,771 (.0053)
30-34	44/7,256 (.0063)
35-39	25/7,591 (.0067)
40-44	28/2,328 (.012)
45-49	9/872 (.010)
50+	18/49,581 2 (.0037)

Incidence (annual)
(# tumors/pers. years exposure)

15 20 30 40 50   15 20 30 40 50

• no time lag
X 10 yr. time lag

Years since first exposure

November 15, 1984

Food Additives Evaluation Branch (HFF-156)

Request for Quantitative Analysis of Risk from Potential Exposure to Asbestos from Cosmetic Talc Use.

Quantitative Risk Assessment Committee
Attention: Ronald Lorentzen, Ph.D. (HFF-100)

CITIZEN'S PETITION 83P-0404   Philip Douillet
                                               1 Holyoke Lane
                                               Stony Brook, N.Y. 11790

Mr. Philip Douillet has submitted a petition requesting certain mandatory labeling on cosmetic talcs to warn consumers of asbestos hazards associated with such products.

BACKGROUND

Cosmetic talc is used as a face powder and body powder by both adults and children to lubricate the skin and prevent chafing and discomfort caused by moisture and heat. The normal use of cosmetic talc in infants has not been reported to be harmful[1], although the accidental aspiration of excessive amounts in infants has been reported to cause serious but reversible acute respiratory disease in some instances and death in isolated cases.[2-5]

As discussed below, talc, a hydrous magnesium silicate, occurs fairly commonly in nature. Table 1 lists the minerals that are commonly found in talc deposits.

FDA STATUS

There are no regulations concerning the use of talc as an ingredient in cosmetic products. Under current law, the burden of proof that a cosmetic may be harmful in that it contains a harmful substance rests with FDA. FDA must have data or other information demonstrating that a product contains a poisonous or deleterious substance that is harmful under customary conditions of use before any action can be taken either to restrict or prohibit the use of an ingredient or product.

TABLE I

	Mineral	Ideal formula
Carbonates	Calcite	$CaCO_3$
	Dolomite	$CaMg(CO_3)_2$
	Magnesite	$MgCO_3$
Amphiboles	Tremolite	$Ca_2Mg_5Si_8O_{22}(OH)_2$
	Anthophylite	$(FeMg)_7Si_8O_{22}(OH)_2$
Serpentine	Antigorite	$Mg_3Si_2O_5(OH)_4$
	Chrysotile (uncommon)	$Mg_3Si_2O_5(OH)_4$
	Lizardite (uncommon)	$Mg_3Si_2O_5(OH)_4$
Others	Quartz	SiO_2
	Mica, e.g. Phlogopite	$K_2(Mg,Fe)_6[Si_6Al_2O_{20}](OH)_4$
	Chlorite, e.g. Penninite	$(Mg,Al,Fe)_{12}[Si,Al)_8O_{20}](OH)_{16}$

IDENTITY

Talc

Talc as a pure chemical compound is defined as hydrous magnesium silicate, $Mg_3Si_4O_{10}(OH)_2$, and consists of a brucite sheet containing magnesium ions sandwiched between silica sheets that are held together by relatively weak forces. A variety of elements such as nickel and iron may be included in the talc particle lattice but are so bound within the particle that they are not free to exert any biological action[6]. Talc can be tubular, granular, fibrous, or platy, but it is usually crystalline, flexible, and soft. Talc is a member of the family of silicate minerals that have a similar atomic structure and occur widely in a large number of different varieties. These silicate minerals are derived from metamorphic alteration of mineral rocks that sometimes include the amphibole and serpentine groups of asbestos after their exposure to specific temperatures, pressures, and circulating liquid solutions. Talc may be formed also by the thermal metamorphism of silicon dolomites.

The purity and physical form of any sample of talc dust as well as the other minerals that are associated with it are, therefore, directly related to the source of the talc and to the minerals found in the ore body from which it is mined. Talc commonly contains chlorites and carbonates, the former being sheet silicate minerals containing magnesium, aluminum, and iron. The carbonate mineral components of talc are mainly magnesite, dolomite, and calcite. Quartz (free silica), iron oxides, sulphides, and various silicates can also be associated with talc.

Since serpentine is one of the minerals from which talc has evolved, it can be associated with talc and is sometimes a contaminant of talc dust. Tremolite, a member of the amphibole group of asbestos, and chrysotile or antigorite of the serpentine group, are the commonest asbestos contaminants of industrial talc dust, although (according to Pooley, F.D., 1975) chrysotile has never been reported to be present in the high-grade talc used in health and cosmetic talc. As talc dusts are obtained from different sources, the amount and specific form of talc, as well as the amount and nature of mineral contaminants, will be different for each dust.

The U.S. Department of the Interior, in a letter dated February 24, 1984,[7] indicated that, with regard to talc deposits and whether any were asbestos free, talc deposits can contain the mineral tremolite. However, even for those deposits that do contain tremolite, it was stated that it is important to understand the distinction between non-fibrous (non-asbestiform) tremolite, which may be common to some talc deposits, and fibrous, asbestiform, tremolite, which is a very rare

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form for that mineral. Similarly, actinolite and anthophyllite only very rarely have fibrous forms. Therefore, the presence of tremolite, actinolite, or anthophyllite in a talc deposit does not necessarily indicate the presence of asbestos, because they usually are not fibrous. Additionally, it was stated in the letter that the minerals crocidolite and amosite do not form in the same geological environment as talc; therefore, it is extremely unlikely that they would be found in any talc deposits. However, it is possible that chrysotile might occur in rocks in or around some talc deposits, but it would probably be in only very minor amounts.

As to what percentage of talc deposits might contain 0.5% or greater of asbestos, this would have to be evaluated for individual deposits. It is also stated that asbestos cannot be formed by shearing during mining. If asbestos minerals are not present to begin with, they will not be formed by mechanical means during mining or crushing operations. This last point is disputed by others.

Asbestos

Asbestos is not one mineral but a generic term used to describe a family of naturally occurring fibrous hydrated silicates divided on the basis of mineralogical features into two groups: serpentines and amphiboles. The important property of asbestos as compared to non-asbestiform varieties of silicates is the presence of mineralogically long, thin fibers that can be easily separated. According to some definitions, there are as many as thirty varieties of asbestos, but only six are of commercial importance. These, together with their chemical composition, are shown in Figure 2.1.

The word "asbestos" is derived from the Greek word meaning "inextinguishable", and the origin of its name reflects one of its principle characteristics: fire resistance. But asbestos has many other qualities that enhance its commercial utility, among them tensile strength, durability, flexibility, and resistance to heat, wear, and corrosion. As an aside, because of its many uses (insulation material, as a fire retardant, linings for brakes and clutch facings, reinforcing agent in cement and pipes, as filters, etc.) and its natural occurrence, it is not surprising that asbestos is found in ambient air, in drinking water, and in foods.

The mineralogical classification of what is and what is not asbestos is complex, and as a result, many definitions of asbestos have appeared in the scientific literature. One definition of the term, asbestos, was published in the Federal Register in 1975 by the U.S. Occupational Safety and Health Administration (October 9, 1975, pp. 47652, 47760). According to this definition, asbestos is considered to include the naturally occurring minerals chrysotile, amosite, crocidolite,

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Figure 2.1

Principal Varieties of Asbestos

Asbestos

Serpentine   Amphiboles

Chrysotile
White Asbestos
$Mg_3 (Si_2O_5)(OH)_4$

Anthophyllite
$Mg, Fe)_7 (Si_8O_{22})(OH)_2$

Tremolite
$Ca_2Mg_5 (Si_8O_{22})(OH)_2$

Crocidolite
Blue Asbestos
$Na_2Fe_3Fe_2 (Si_8O_{22})(OH)_2$

Actinolite
$Ca_2 (Mg, Fe)_5 Si_8O_{22} (OH)_2$

Amosite
$(Fe, Mg)_7 Si_8O_{22} (OH)_2$
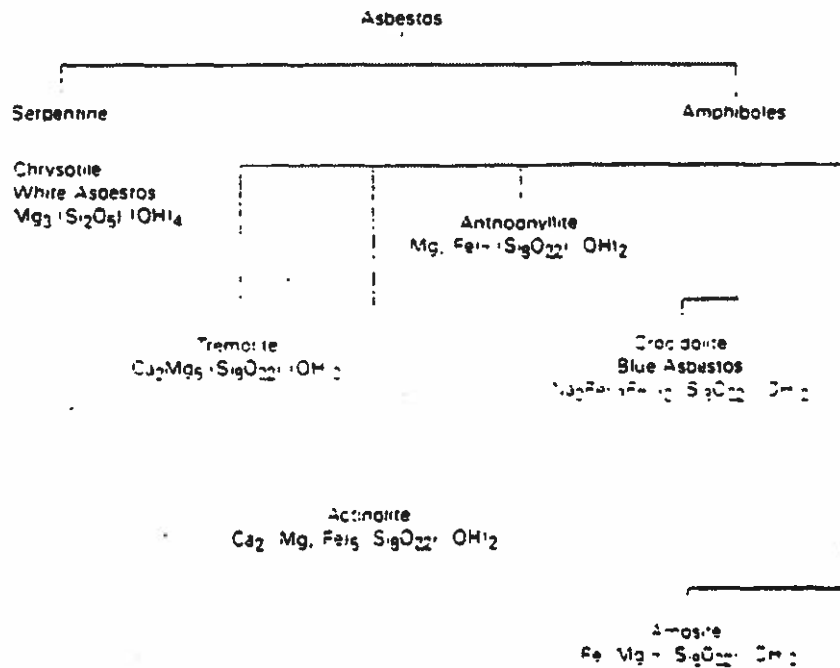
SOURCE   Dr. Eric J. Chatfield. "The Problems of Measurement of Asbestos." in Ontario.
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          Asbestos, Second Public Meeting, Friday, December 12, 1980.* reported by Lydia
          Dotto (Toronto: Royal Commission on Asbestos 1981) Appendix A Figure 1
          p 2

tremolite, actinolite, and anthophyllite, if the individual crystals or fragments are greater than 5 micrometers in diameter, and have a length to diameter ratio of 3 or greater.

Each of these six minerals included in OSHA's asbestos standard occurs in both an asbestiform and a non-asbestiform variety. Three of the six minerals have been given different names for each of their two forms. Chrysotile in its non-asbestiform variety is called antigorite. Crocidolite is called riebeckite. Amosite is called cummingtonite-grunerite. The other three minerals--because they occur in their asbestiform varieties so rarely in nature--are each called by only one name, regardless of their form. Tremolite, anthophyllite, and actinolite are labeled asbestos by OSHA in both their forms. According to mineralogists, this is incorrect, and it is poor science.

HEALTH EFFECTS

Evaluation of potential health effects from exposure to talc contaminated with asbestos and from other nonoccupational exposures to asbestiform fibers depends primarily on the results of epidemiological studies of occupational groups exposed to asbestos. Most of the data come from cohort studies (see Appendix I) of workers exposed to asbestos of various types and in a variety of industries and occupations. Much information has been obtained from these studies. However, they also suffer from limitations common to many epidemiological studies and from some additional problems related to determining dose (exposure) and response (health end point, such as death from a specific cause). Despite the limitations of individual studies, when all the studies are considered, exposure to asbestos increases the risk of developing lung cancer, mesothelioma, asbestosis, and possibly other cancers.

To quantify health risks from an exposure, it is necessary to obtain dose-response data, but exposure measurements are particularly difficult to obtain. Because of the long latency period for asbestos-associated diseases, investigators have found it necessary to try to reconstruct past exposures. Techniques of measurement vary from place to place and over time[8,9]. For example, fiber counts obtained by light microscope in various industrial settings may need to be multiplied by a factor varying from 2 to 8 to obtain a true count of fibers longer than 5 um.

Typically, a cumulative dose measurement is used. This does not take into account the time lapsed since last exposure nor does it distinguish between short exposures of high intensity and long exposures to low dust concentrations. In addition, a cumulative dose measurement does not change when exposure ceases. Variability in these exposure-related factors affects mortality responses in occupational cohorts. In some studies, exposure surrogates, such as type of job and duration of employment, are used to estimate exposure. These estimates may be less precise than actual measurements.

Figure 2.4

Principal Asbestos-Related Diseases and
Conditions and Their Sites in the Human Body

Carcinoma
of Larynx

Carcinoma
of Bronchus

Thickening
of Pleura

Asbestosis

Carcinoma
of Stomach

Mesothelioma

Carcinoma
of Colon
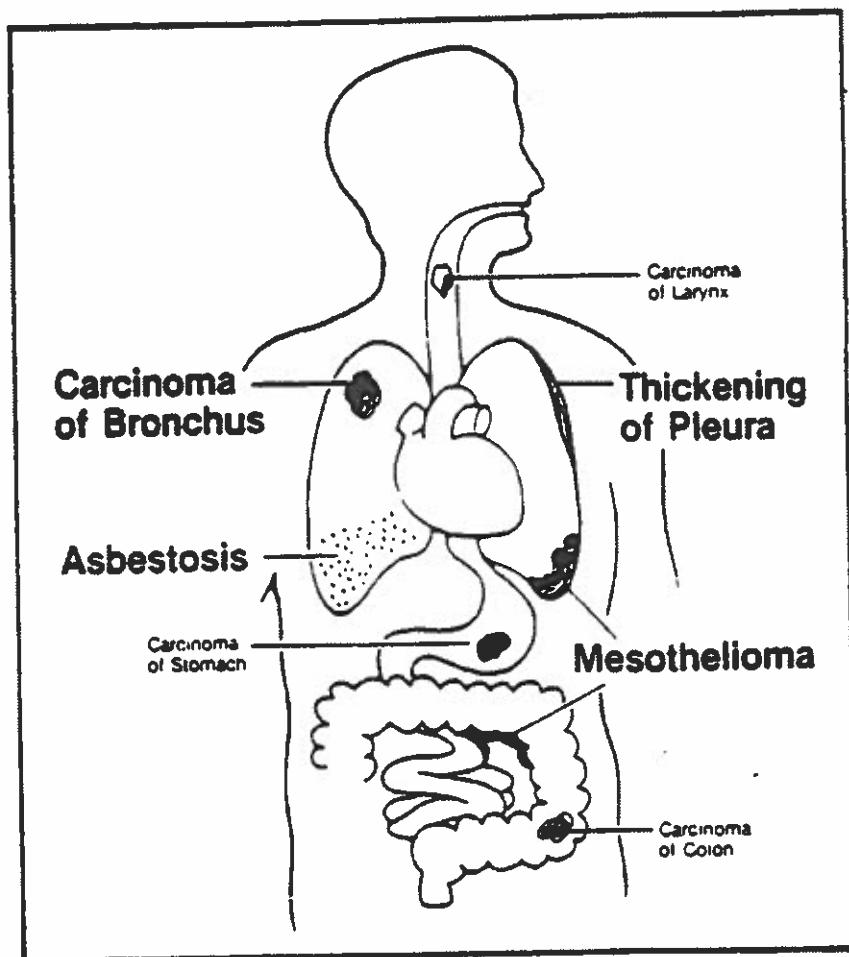
SOURCE. Illustration by Mr Jerry Farrell Audio-Visual Centre McMaster University consultative assistance ov Dr David C F Muir Director Occupational Health Program Health Sciences Centre McMaster University, Hamilton Ontario

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There may also be variability in reporting causes of death, ascertainment of deaths, and diagnostic accuracy of the reported cause of death. Inaccuracies are particularly likely for mesothelioma and asbestosis[10].

Methodological differences are a major source of variation in comparing studies[11]. For example, the results obtained will depend on the criteria for selecting the cohort, the choice of comparison groups, the influence of other environmental factors that may introduce competing disease risks, and the records available.

In addition, heterogeneity in the time at which onset of exposure begins can introduce additional distortion in the observed relative risks[12], especially because the types of exposure experienced by some workers in the distant past may differ from exposures experienced only more recently. Weiss also discussed how the results of lung cancer studies can be affected if persons who left a job are not included in the study cohort. He found that the exclusion of these workers could affect the relative risk by a factor of 2 to 3.

An additional difficulty is encountered when comparing dose-response results from mortality and morbidity studies, particularly if the morbidity studies are confined to active workers, which is usually the case. A bias is introduced in studies of active workers, since those with severe disease have probably already left employment. However, asbestosis generally progresses after cessation of dust exposures[13;14].

Numerous follow-up studies of asbestos-related mortality have been conducted on cohorts with varying intensity and duration of exposure, type of exposure, type of work, time and duration of follow-up periods, differences in the completeness of the cohort, completeness of mortality ascertainment, availability of smoking histories, geographic area of analysis. Because of the variations noted, it is not surprising that the standardized mortality ratios (SMRs) and dose-response results differ greatly among studies. In general, however, the same major diseases--lung cancer, mesothelioma, and asbestosis--have been observed, although not all investigators conducting these studies have reported or detected excesses of all three of these diseases.

Talc

The health effects of talc have been studied only in relation to occupational exposures[15-25]. Data available on the health hazards associated with occupational exposure to talc are not extensive. Exposure to talc itself in high concentrations has been shown to produce excess mortality, mainly due to respiratory diseases.

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Workers from different geographic regions containing talc with or without fibers have been studied to determine if any adverse health effects are associated with the asbestiform fiber content of talc. Adverse effects have been found in some studies among workers exposed to talc both with and without fibers. These studies are discussed in the following paragraphs.

Epidemiological studies on workers exposed to talc containing fibers have demonstrated adverse effects on pulmonary function. In a study of 121 New York miners and millers exposed to talc containing tremolite and anthophyllite fibers, pulmonary function was found to be significantly decreased.[26] Reductions in forced vital capacity (FVC) and 1-second forced expiratory volume (FEV_1) were associated with employment duration and the amount of fiber present. Increased pleural thickening and calcification were detected in talc workers with 15 or more years of employment[26].

A mortality study of 398 New York miners exposed to talc containing fibers has demonstrated excess mortality from nonmalignant respiratory disease, excluding influenza, bronchitis, or pneumonia (5 observed/1.3 expected)[27]. An excess in lung cancer with an average latency of 20 years was also observed (9 observed/3.3 expected). Additional studies have had conflicting results. Some investigators have found no significant increases in lung cancer and nonmalignant respiratory disease[28], whereas others have reported significant increases in lung cancer, attributed to the silica content of talc.[29,30]

Morbidity and mortality studies have also been conducted on workers exposed to talc with low or undetectable levels of fibers. A study on the respiratory function of 103 Vermont talc workers indicated that there was a reduction in pulmonary function in smokers[31]. After adjusting for smoking, the effect of the exposure to talc was not statistically significant, although there was evidence of an exposure-related effect in workers with an annual dust exposure of approximately 1.5 mg/m^3. Exposure to talc dust was also associated with small opacities seen on chest radiographs.

Gamble et al.[26] conducted a cross-sectional study of 299 workers from Montana, Texas, and North Carolina who were exposed to talc containing low levels of silica and fiber. There was no significant difference in lung function, respiratory symptoms, or pneumoconiosis between workers and controls, although there was a significant increase in bilateral pleural thickening among the workers. Results of pulmonary pathology studies also have provided evidence of fibrosis in workers exposed to talc that does not contain fibers[33].

A mortality study of 392 Vermont workers exposed to talc not containing fibers showed that there were excess deaths from nonmalignant

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respiratory disease, excluding influenza and pneumonia, among millers (11 observed/1.79 expected)[34]. This excess mortality was associated with small opacities seen on chest radiographs. An excess of respiratory cancer mortality among miners was also noted (5 observed/1.15 expected) but was attributed to exposures other than talc.

In a recent case-control study[37], increased risk of ovarian cancer was shown for women who regularly used talc either (or both) as a dusting powder on the perineum or on sanitary napkins compared to women who did not engage in either practice (See Table 4). No data with regard to asbestos contamination of the talc were provided. Studies of female asbestos workers are presented in Appendix I.

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Table 4: Relative Risks (RR) for Common Epithelial Ovarian Cancers Associated with Talc Exposure in Perineal Hygiene

| | No perineal exposure | Any perineal exposure | Types of Perineal Exposure | | |
			As dusting powder but not on napkins	On napkins but not as dusting powder	Both on napkins and as dusting powder
Cases (Total = 215)	123(57.2%)	92(42.8%)	43(20.0%)	17(7.9%)	32(14.9%)
Controls (Total = 215)	154(71.6%)	61(28.4%)	34(15.8%)	14(6.5%)	13(6.0%)
Crude rr	1	1.89	1.58	1.52	3.08
Adjusted RR*	-	1.92	1.55		3.28
95% confidence limits	-	(1.27-2.89)	(0.98-2.47)		(1.68-6.42)

*Adjusted for parity and menopausal status

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Note: A study (reviewed in Appendix II) of mesothelioma incidence in domestic dogs concluded that there was an association between the incidence of mesothelioma and asbestos exposure; the source of exposure of the dogs was from the use of flea powders and/or the owners asbestos-related occupations (hobbies).

Additionally, an animal inhalation study (reviewed in Appendix II) with talc (Italian 00000 grade) did not indicate talc to be carcinogenic.

Asbestos

Asbestos associated diseases generally have been related to occupational exposures, such as those experienced by some miners, insulators, and factory workers (see Appendix I). Recently, however, there has been concern that exposures to asbestos and related fibers may present a health hazard to the general public.

Because asbestos and other asbestiform fibers appear to be ubiquitous, virtually everybody is exposed to some extent. During autopsy, asbestos fibers have been detected in the lungs of most urban residents studied. Reported concentrations of asbestos in urban air are shown in Table 7-6. Exposure to the general public is of concern because the population involved is large and includes unhealthy persons. Also, exposure may begin in childhood (as with baby powder application), leaving a longer time for the development of adverse effects. Additionally, asbestos may enhance the carcinogenic effects of other materials. There is little information about the health effects of most nonoccupational exposures to asbestos (see NAS report, Ref. 100). Although babies have been powdered with talc powder for many years, there is no evidence that this has resulted in an increase in asbestos-related disease.

Three principal diseases are related to exposure to one or more of the commercial asbestos minerals. These are: (1) lung cancer, which includes cancer of the trachea, bronchus, and the lung proper; (2) mesothelioma, a cancer of the pleural and peritoneal membranes that invest the lung and abdominal cavities, respectively; and (3) asbestosis, a diffuse interstitial fibrosis of the lung tissue often leading after long exposure to severe loss of lung function and respiratory failure. These diseases are not equally prevalent in the various groups of asbestos workers that have been studied; the amount and type of disease depend on the duration of exposure, on the intensity of exposure, and possibly on the type or types of asbestos to which the individual was exposed. Only lung cancer and mesothelioma will be considered here. Asbestos appears to act principally as a late stage carcinogen (promoting agent) that multiplies the underlying risk of lung cancer that occurs in the absence of asbestos exposure. The nature of the dose-response relationship for asbestos-related diseases is discussed below.

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TABLE 7-6. Summary of Environmental Asbestos Exposure Samples[a]

Sample Sets	No. of Samples	Measured Concentration (ng/m^3)		Equivalent Concentration (fibers/cm^3)[b]		Reference
		Median	90th Percentile	Median	90th Percentile	
1. Paris air	161	0.7	3.2	0.00002	0.00011	Sebastien et al., 1980
2. Paris (outdoor control)	19	0.7	5.2	0.00002	0.00017	Sebastien et al., 1980
3. Outdoor control samples, for U.S. schools	31	0.9	9.8	0.00003	0.00033	Constant et al., 1982
4. Air of 48 U.S. cities	187	1.6	6.8	0.00005	0.00023	Nicholson, 1971
5. Air of U.S. cities	127	2.3	7.8	0.00008	0.00026	U.S. Environmental Protection Agency, 1974
6. Air of five U.S. cities (outdoor control sample)	34	6.7	31.9	0.00022	0.00106	Nicholson et al., 1975, 1976
7. New York City air	22	13.7	42.9	0.00046	0.00143	Nicholson et al., 1971
8. Air 0.5 mile (0.8 km) from asbestos spraying	17	22.5	82.6	0.00075	0.00275	Nicholson et al., 1971
9. Air in U.S. schoolrooms without asbestos	31	16.3	72.7	0.00054	0.00242	Constant et al., 1982
10. Air in Paris buildings with asbestos surfaces	135	1.8	32.2	0.00006	0.00107	Sebastien et al., 1980
11. Air in U.S. buildings with cementitious asbestos	28	7.9	19.1	0.00026	0.00064	Nicholson et al., 1975, 1976
12. Air in U.S. buildings with friable asbestos	54	19.2	96.2	0.00064	0.00321	Nicholson et al., 1975, 1976
13. Air in U.S. schoolrooms with asbestos surfaces	54	62.5	550	0.00208	0.01833	Constant et al., 1982
14. Air in U.S. schools with damaged asbestos surfacing materials	27	121.5	465	0.00405	0.01550	Nicholson et al., 1978

[a]Adapted from Nicholson, 1983.
[b]Based on conversion factor of 30 ug/m^3 = 1 fiber/cm^3.

(1) Lung Cancer

Most epidemiological studies (reviewed in Appendix II) of asbestos
workers that have demonstrated an excess lung cancer risk associated
with the inhalation of asbestos have produced results consistent not
only with a linear relationship between cumulative dose and mortality,
but also consistent with the absence of a threshold. In all of these
studies, there appears to be a progressive and proportional increase in
the SMR (standard mortality ratio) for lung cancer with increasing dose
and no evidence of a threshold level. This evidence cannot be accepted
without some qualification, however. All of the studies have the
intractable difficulty of separating out the effects of cumulative dose
from duration of exposure.

Persons exposed to asbestos nonoccupationally can be at increased risk
of contracting these asbestos-associated cancers. In one of the first
studies linking asbestos exposure and mesothelioma, the disease was
found among residents of an asbestos mining area in South Africa. These
subjects had presumably inhaled the material in the surrounding air.[42]
In another study, persons living in households with asbestos factory
workers in New Jersey were reported to be at increased risk of
asbestos-associated disease.[43]

There is debate about the carcinogenic risk at low exposure levels of
asbestos because lung cancer risks at low doses over a working lifetime
have not been estimated to date by observation but rather by
extrapolation from observed risks at higher exposure levels.[44]
Accordingly, there is no direct evidence of the existence or absence of
a threshold for lung cancer. It may arguably be the case that with
further inquiry and better information the scientific community will be
able to demonstrate that there is a dose level for asbestos for which
the body's defense mechanisms are effective, or that asbestos acts
differently at lower rather than higher doses, thus demonstrating a
threshold level for the induction of cancer. At the present time, that
information does not appear to exist. Since a threshold dose level for
asbestos-related lung cancer has not been established, many
investigators conclude that it is prudent to assume that there is none
and that any dose may induce lung cancer.[45] A linear non-threshold
model is less likely to underestimate the risk at low doses than any
other plausible model.

(2) Malignant mesotheliomas are rare cancers that appear as thick,
diffuse masses inside any of the serous membranes (mesothelia) that line
body cavities. Epidemiologic research has shown that exposure to
asbestos can produce mesothelioma at two sites: the pleura (the serous
membrane that surrounds the lungs and lines the thorax) and the
peritoneum (the serous membrane that surrounds the abdominal organs and
lines the abdominal and pelvic cavities).

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The status of pleural and peritoneal mesothelioma as marker diseases for asbestos exposure stems from the fact that these diseases seldom occur in people who have not been exposed to asbestos in excess of normal ambient levels.

The nature of the dose-response relationship for mesothelioma has been less firmly established than that for either lung cancer or asbestosis. Indeed, it has been suggested that very trivial doses of asbestos are capable of inducing the disease and that as a result there is no dose-response relationship for mesothelioma at all.[46] That mesothelioma is associated with low levels of exposure for brief periods of time appears to be based upon isolated anecdotal case reports and upon more systematic case-series reports of mesothelioma arising from non-occupational household or neighborhood exposures.[47,48] Newhouse et al.[48] reported nine cases of mesothelioma in family contacts of asbestos workers and eleven cases among individuals whose only identified asbestos exposure was associated with living within one-half mile of an asbestos factory. In these cases of non-occupational exposure, pleural mesotheliomas predominated over peritoneal mesothelioma. The evidence is not inconsistent with the existence of a dose-response relationship for mesothelioma. Although deaths from mesothelioma have been reported after what appear to have been brief (for gas mask workers) or low (for family contact and neighborhood cases) exposures, the Ontario Commission[49] concluded that the evidence suggests that the actual exposures approached or were equivalent to corresponding occupational exposures; it further agreed with the IARC[50] conclusion that there is no evidence of risk of mesothelioma to the general population.

There is a time interval between the initial exposure to asbestos and the clinical manifestation of the diseases it causes. The latency period for cancer is thought to be long; rarely less than 10 years and often more than 20 years. Mesothelioma appears to have the widest range of latency--again, they rarely occur less than 10 years from the time of first exposure to asbestos, but they can occur as many as 40 years or more from the onset of exposure.[51] It has been suggested that the death rates from mesothelioma appear to rise at an exponential rate from the time since first exposure; death rate appears to rise at a rate between the third and fourth power of time since first exposure;[52,54] other work suggests the fifth power of time.[55] What the data demonstrate is that the incidence of mesothelioma rises rapidly the longer the time period since a person is first exposed to asbestos. As a result, the age at which a person is first exposed to asbestos becomes a very significant factor in determining the overall risk of contacting mesothelioma.

While the mesothelioma incidence rates appear to be independent of the age at which exposure first took place, the practical result is that the risk of contacting mesothelioma is greater the earlier in life one is first exposed. (This is important to keep in mind when considering baby

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powder exposure.) The magnitude of the risk will still depend on the amount and duration of exposure (and, possibly, fiber type); and where that exposure is minimal, the risk, albeit greater for exposures earlier rather than later in life, will also be minimal.

The disease rate of lung cancer among persons exposed to asbestos appears to be quite unlike that of mesothelioma. Rather than being time-dependent, lung cancer rates appear to be age-dependent.[56] The majority of lung cancer deaths, both in smokers and non-smokers, occur after age 50 and over half occur after age 60, irrespective of the time of first exposure. This suggests that the risk of contracting lung cancer is much greater in older groups than in younger groups. Asbestos exposure appears to have the effect of multiplying the risk of lung cancer that exists apart from that exposure; and the risk of lung cancer contributed to by asbestos exposure appears to be virtually independent of the age when that exposure took place and will be simply proportional to cumulative dose.

The consistency of an increased cancer risk at extrathoracic sites and its magnitude are less for cancer at other sites than for lung cancer. Nevertheless, many studies document significant cancer risks at various GI sites. Cancer of the kidney has also been found to be significantly elevated. Among female workers, ovarian cancer has been found in excess (Appendix I, #16). While no other specific sites have been shown to be elevated at the 0.05 level of significance, the category of "all cancers other than lung, GI tract, or mesothelial" is significantly elevated.

Several epidemiological investigations reported in the literature provide data on exposure levels of asbestos related to mortality and specific cause of death, while most do not provide exposure data. Those with relevant data are reviewed in Appendix I (see Summary table). In these investigations, different epidemiological approaches were used, various definitions of the study groups were adopted, observations took place over different periods of time, types of controls varied, time interval from first exposure was unknown, some workers exposed to more than one type of fiber, etc.

Several studies are briefly described below:

Mining and Milling

Chrysotile. Three cohorts occupationally exposed to chrysotile asbestos during mining and milling operations had a moderately increased risk for lung cancer (SMRs from 1.0 to 2.6). In the largest investigation, McDonald et al. (1980)[57] studied all employees who had worked for at least 1 month in Quebec mines. From 1950 to 1975, 3,291 deaths occurred among the 9,850 male employees successfully traced and followed for 20 years or more after initial employment. An increase in lung cancer

mortality was observed (SMR = 1.3, 230 observed vs. 184 expected), and
the risk increased with duration of employment (SMR = 1.0 for < 1 year
to 1.6 for ≥ 20 years) and level of exposure (SMR = 0.9 for < 30
mppcf(yr) to 2.3 for ≥ 300 mppcf(yr). Eleven cases of mesothelioma were
observed.

Anthophyllite. Male and female employees of anthophyllite asbestos
mines in Finland were studied by Meurman et al. (1974, 1979),[58,59] who
reported a two-fold increase in lung cancer mortality (44 observed vs.
22.4 expected) and no mesotheliomas among the 1,045 persons successfully
traced. All lung cancer deaths occurred among the male employees, and
the risk was associated with estimated intensity of exposure (SMR = 1.4
vs. 3.3 for low and heavy exposures, respectively). Lung cancer risk
among nonsmoking asbestos-exposed employees was 1.4 compared to a
relative risk of 17.0 for the asbestos-exposed employees who smoked.

Crocidolite. For exposure associated with crocidolite mining in Western
Australia, there was a similar increase in risk of lung cancer (SMR =
1.6, 60 observed vs. 38.2 expected) and a strong association with
mesothelioma.[60] Twenty-six cases of pleural mesothelioma were observed
among the 526 deaths, and the mesothelioma risk increased with increased
duration and intensity of exposure. Follow-up period was relatively
short.

No increases in gastrointestinal cancer were observed for any of the
mining and milling cohorts reviewed.

Manufacturing

Chrysotile. Most asbestos exposures associated with manufacturing
processes involve mixed fiber types, but Dement et al. (1982,
1983a,b)[9,61,62] examined the risks associated with exposure to
chrysotile asbestos in textile factory workers. They observed a marked
increase in lung cancer mortality (SMR = 3.2, 35 observed/11.1
expected), and the risk was strongly correlated with exposure level.
There was also one peritoneal mesothelioma. Increased risks for both
lung cancer and nonmalignant respiratory disease were observed at
exposure levels lower than those reported in other studies.

Amosite. Mortality due to lung cancer was increased three- to four-fold
(83 observed /22.8 expected) for 820 factory workers exposed to amosite
asbestos.[63] The higher risks were observed for the subgroup followed 20
years or longer after initial employment (SMR = 5.1, 52 observed/10.1
expected). This cohort is a somewhat unusual population because of its
limited duration of intense work exposure (1941-1945) and long period of
observation. Other excess cancers, including 14 mesotheliomas, were
also reported.

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Mixed. Newhouse and Berry (1979)[64] reported increased risks of lung cancer mortality for both males (SMR = 2.4, 103 observed/43.2 expected) and females (SMR = 8.4, 27 observed/3.2 expected) in a follow-up study of 4,600 male and 922 female employees of an East London asbestos factory in which crocidolite and amosite were used. Approximately 10% of all deaths resulted either from pleural or peritoneal mesothelioma.

Except for 10 cases of mesothelioma, no increased cancer mortality was observed among more than 11,000 males and females employed during 1941 or later at a British factory producing friction materials.[65,66] In a case-control study that corrected for total asbestos exposure, 5 of 6 cases had definitely worked with crocidolite, whereas 2 of 10 controls had.

A cohort of 1,345 retired asbestos products workers employed from 1941 to 1967 had increased risks for lung cancer (SMR = 2.7, 63 observed/23.3 expected) and gastrointestinal cancer mortality (SMR = 1.4, 55 observed/39.3 expected).[67] Overall mortality among the 1,075 retirees successfully traced to 1973 was 73%. The lung cancer risk was strongly associated with the amount of exposure, expressed as million particles per cubic foot multiplied by number of years of exposure (mppcf-yr), ranging from a SMR of 2.0 up to 7.8. Lung cancer risk differed by type of asbestos exposure (SMR of 2.5 for chrysotile alone vs. 5.2 for mixed chrysotile and crocidolite exposures). Five mesothelioma deaths were observed. Study results suggest that effects of asbestos exposure on lung cancer risk may continue long after the termination of exposure. Studies of a retiree cohort may result in an underestimation of actual risks, since deaths among employees under age 65 would be omitted. The Consumer Product Safety Commission (1983)[68] suggests that the risks may be understated by as much as two-fold.

No increase in lung cancer mortality or cancer of any other site, except mesothelioma, was observed in the cohort of 5,645 employees of an asbestos-cement product manufacturing facility studied by Hughes and Weill (1980).[69] In the high exposure subgroup, lung cancer risk was increased for employees exposed to crocidolite, and two mesothelioma deaths were reported. The low overall mortality, 10.6%, and the low tracing rate, approximately 75%, suggest that this study may have resulted in an underestimate of mortality risks.

Finkelstein (1983)[70] studied 328 asbestos-cement workers hired before 1960 and employed for a minimum of 9 years. Mesothelioma was strongly associated with exposure level for production workers, whereas a dose-response relationship was not observed for lung cancer. Excess lung and gastrointestinal cancers were observed.

Clemmesen and Hjalgrim-Jenson (1981)[71] studied cancer incidence among 6,372 Danish males who worked in asbestos-cement factories between 1944 and 1976. There were 55 cases of respiratory cancer compared to 33

expected, based on Danish Cancer Registry incidence rates. Three mesotheliomas were observed in addition to excess prostate, laryngeal, and stomach cancers. Cancer incidence in the unexposed employees at the same factories was not increased.

Jones et al. (1980b)[72] studied a cohort of 578 females exposed to crocidolite from western Australia during the manufacture of gas masks. The 12 cases of lung cancer (SMR = 1.9, 12 observed/6.3 expected) and the 17 mesothelioma cases (13 pleural and 4 peritoneal) were all exposed to crocidolite, whereas no cases of mesothelioma or lung cancer occurred among the 102 females exposed only to chrysotile. Overall, 10% of deaths were due to mesothelioma. Risk of mesthelioma was strongly associated with duration of exposure, although no dose-response relationship was observed for lung cancer.

Similar results were reported among 1,304 females who manufactured gas masks at three locations followed from 1951 to June 30, 1980.[8] Deaths from lung cancer (SMR = 2.0, 22 observed/11 expected) and ovarian cancer (SMR = 2.2, 17 observed/7.8 expected) were increased. Lung cancer excess was higher for those exposed predominantly to crocidolite compared to those exposed predominantly to chrysotile. Five of the six mesotheliomas occurred in those exposed predominantly to crocidolite.

All studies of occupational cohorts exposed to asbestos during manufacturing processes had an overall increased risk of lung cancer or a dose-response relationship in the exposure subgroups.[69,77] Elevated risk ratios (1.1) for gastrointestinal cancer were observed in six of the nine cohorts reviewed.[62,63,65,67,70,71]

Insulation

Mixed. All three of the cohorts involved in end product use of asbestos as insulators were exposed to mixed types of asbestos. One of the largest studies is that of Selikoff et al. (1979),[74] who studied 17,800 members of an insulator's union. Overall mortality in this cohort was 12.8%; 2,271 deaths were reported through 1976. Lung cancer risk was increased four-fold (429 observed/105.6 expected) and increases were observed for gastrointestinal cancer (SMR = 1.6, 94 observed/59.4 expected), cancer of the larynx, pharynx, buccal cavity (SMR = 1.7, 25 observed/14.8 expected), and kidney (SMR = 2.2, 18 observed/8.1 expected). Dose-response relationships were not examined because of the lack of exposure data. Mesotheliomas (63 pleural and 112 peritoneal) accounted for 7.7% of the deaths. Analysis of the relationship between smoking and lung cancer risk using data from the American Cancer Society indicated a consistent multiplicative effect, in that a 10-fold increase in risk of lung cancer was associated with smoking in both asbestos-exposed and unexposed groups. A five-fold increase in lung cancer risk was associated with asbestos exposure in both smokers and nonsmokers.[10]

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Elmes and Simpson (1977)[75] reported an unusually high risk of lung cancer (SMR = 7.0, 35 observed/5 expected) and gastrointestinal cancer (SMR = 5.9, 13 observed/2.2 expected) for a cohort of 162 insulators and pipe coverers employed in Northern Ireland during 1940. Overall mortality in this cohort was 75.3% by 1975; 54% of the deaths were due to cancer. Thirteen cases of mesothelioma (eight pleural and five peritoneal) were reported. No difference in cancer risk was apparent for workers first employed before or after 1933. Ascertainment bias is unlikely to explain the magnitude of the risks reported for this cohort.

Shipyards

Mixed exposures. Rossiter and Coles (1980)[76] studied 6,076 dockyard workers employed before 1947. They reported no increase in lung cancer mortality (SMR = 0.7, 84 observed/119.7 expected) or gastrointestinal cancer (SMR = 0.8, 63 observed/83.3 expected). Mesothelioma was reported for 31 (3%) of the 1,043 deaths. However, since less than 20% of this cohort have died, excess cancers may not be fully apparent.

In a study of 2,190 Italian dockworkers, Puntoni et al. (1979)[77] observed increased risks for lung cancer (SMR = 2.2, 123 observed/54.9 expected), gastrointestinal cancer (SMR = 1.3, 74 observed/58.6 expected), laryngeal cancer (SMR = 1.9, 15 observed/7.7 expected), and kidney cancer (SMR = 2.0, 29 observed/14.7 expected).

EXPOSURE

Talc

Values between 800,000 and 960,000 tons have been reported as the amount of talc used commercially in the U.S. each year.[78,79] Talc is used in a number of industries, for a variety of purposes; e.g., the manufacture of ceramics, paints, paper, rubber, roofing, insecticides, stucco, plastics, textiles, and soaps. Pulverized talc is also used as an ingredient in such consumer products as cosmetic talcums, paper mache, and modeling compounds, in spackling, patching compounds and putties, in automotive and boat body repair fillers, and caulking compounds. The uses of talc in food products include rice coating, peanut polishing, candy molding, and salami dusting. It is also used as a filler and excipient for pharmaceutical pills, and for dusting contraceptive diaphragms. Each product carries with it a distinct and individual inhalation and/or ingestion potential of the mineral components. An estimated 30,000 tons of cosmetic-grade talc are used in cosmetic,[80] pharmaceutical, and food products.

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Talc Contamination

The table below shows the principal minerals that can be combined with talc in natural deposits.[89-91]

MINERALS COMMONLY ASSOCIATED
WITH TALC IN NATURAL DEPOSITS

Carbonates: calcite, dolomite, magnesite
Amphiboles: tremolite, anthophyllite
Serpentines: chrysotile, antigorite, lizardite
Others: quartz, mica, chlorite, rutile, pyrophyllite

A 1968 study conducted by United States researchers[92] on 22 talc samples for cosmetic use showed values between 8 and 39% fibrous particles, whereas a similar study on 80 industrial talc samples conducted by N.B.S. researchers[93] indicated the presence of fibrous particles in the samples in percentages which vary from 2 to 30%. In both cases the fraction of these percentages made up of asbestos was not specified. Research conducted in Great Britain[94] on talc powders for various uses has shown that of the 27 samples examined, 3 contained tremolite. More complete and significant data are indicated for 20 talcs for cosmetic use and one talc for pharmaceutical use sampled in the New York area from 1971 to 1975: of the cosmetic products analyzed, 10 contained tremolite and anthophyllite in amounts varying from 0.1 to 14 wt.%, and showed a detectable quantity of chrysotile. (This is in conflict with Pooley who stated that no chrysotile has[95] been found in cosmetic talc.) In an Italian article published in 1982[96], 15 samples of talc products (for industrial, cosmetic, and pharmaceutical uses) were analyzed for asbestos contamination using transmission electron microscopy and the associated analytical techniques such as electron diffraction and x-ray microanalysis. In eight of the 15 samples, the presence of asbestos was detected; in seven cases tremolite fibers were observed and in one case, chrysotile (see Table 9).

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TABLE 9. PERCENTAGE OF FIBROUS PARTICLES AND ASBESTOS FIBERS IN SOME COSMETIC TALCS.

KEY: (a) % fiber in the particular matter
(b) % fiber 5 um in the particular matter
(c) % asbestos fiber in the total fiber
(d) % asbestos fiber in the particular matter, and
(e) variety of asbestos

	(a)	(b)	(c)	(d)	(e)
A	6.1±0.9	1.6±0.5	<2	<0.1	--
B	21.6±1.6	5.0±0.9	<2	<0.4	--
C	11.1±1.1	3.2±0.6	<2	<0.2	--
D	4.9±0.5	0.7±0.2	32±4.7	1.6±0.3	Tremolite
E	10.3±0.7	3.2±0.4	<2	<0.2	--
F	5.1±0.6	1.8±0.4	10±3	0.5±0.2	Tremolite

Consumer talc products marketed before 1973 were variably contaminated by asbestos. In October, 1976, the Cosmetic, Toiletry, and Fragrance Association (CTFA)[97] revised their guidelines for talc and recommended that no sample containing asbestos detectable by x-ray diffraction and optical microscopy with dispersion staining should be sold. Adherence to the revised CTFA guidelines is voluntary and monitoring of samples is left to individual manufacturers.

Samples of cosmetic talc products were analyzed in 1979 by the Division of Cosmetics Technology using x-ray diffraction (XRD). Samples found to be contaminated with tremolite or anthophyllite by XRD were also examined by optical microscopy (OM) to determine crystal morphology. In all cases, the amphiboles found (tremolite and anthophyllite) were present in the massive (non-fibrous) form. The level of detectability is approximately 0.1% for tremolite and 2% for anthophyllite. None of the samples was found to contain serpentine at a detectability limit of 1-2% (XRD). These samples were submitted for SEM analysis and, if fibers were found, the samples were to be examined by energy dispersive x-ray analysis (EDXA) to determine the nature of any fiber-like particle detected. The results of the latter (SEM and EDXA) analyses are not known to this reviewer. No analyses of cosmetic talc have been performed by FDA since 1979. As noted previously, there are non-fibrous forms of minerals with essentially the same chemical composition as the asbestos varieties. In some cases the non-fibrous form has the same name as its fibrous counterpart; e.g., tremolite. According to the U.S. Department of the Interior, non-fibrous (non-asbestiform) tremolite is the common form of this mineral, while fibrous tremolite (asbestiform) is a very rare form for this mineral.[97]

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Asbestos

As stated above, asbestos bodies can be recovered from the lungs of virtually everyone in the population, on autopsy. These observations suggest that the entire population is being exposed to asbestos.

Several studies have assessed the environmental air pollution by asbestos using the transmission electron microscope (TEM) or the scanning electron microscope (SEM). European cities have shown levels as follows: 0.1-1 ng (10^{-9} gm^{-3} or ng^{-3}) of chrysotile asbestos in English cities, 10^{-2}-10^{4} asbestos fibers per cubic meter of air in Dusseldorf,^{R} and 0.1-10 ng^{-3} of chrysotile asbestos in Paris. Higher concentrations (0.1-100 ng^{-3} of chrysotile asbestos) have been found in U.S. cities. The highest concentrations have been found in New York City (see Table 7-6).

Asbestos fibers have been detected in rural locations (0.01-0.1 ng m^{-3}) removed from known sources of emission suggesting the existence of background air pollution by asbestos fibers (especially chrysotile) in industrial countries.

It is to be noted that an appreciation of the extent of air contamination by asbestos depends upon which of two approaches to its measurement is adopted. If the conventional practice of counting only fibers longer than 5 um is followed, the concentrations away from immediate industrial activities are low or undetectable and even some of those in and around asbestos industries approach tolerable levels. But, if the concentration of smaller fibers is taken into account and particularly the mass concentrations revealed by electron microscopy, the situation changes. Up to 10 ng/m^3 seems to be virtually ubiquitous in urban communities.

It is to be noted also that analysis of ambient air samples for asbestos has utilized techniques different from those used in occupational circumstances because typical urban air may contain up to 100 ug/m^3 of particulate matter in which one is attempting to quantify asbestos concentrations from about 0.1 ng/m^3 to perhaps 1000 ng/m^3. Thus asbestos may constitute only 0.0001 to 1% of the particulate matter in a given sample.

It is difficult to make quantitative estimates of exposure to asbestos. A common unit of cumulative dose for occupational exposures is obtained by multiplying the average concentration of fibers in workplace air by the number of years that an individual worked there (full-time equivalent). The concentration of fibers in workplace air is expressed as fibers > 5 μm long/cm^3, as counted by the light microscope (LM) under specified conditions ((U.S. National Institute for Occupational Safety and Health, 1977); (fibers/cm^3) yr. It is to be noted that cumulative exposure measures do not take into account dose rate per unit time,

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duration of exposure, and ages at exposure. These three factors, particularly the third one, could be very important in determining effects on health.

Another measure of exposure that allows comparison of different exposure situations is expressed as "lifetime fibers." This quantity is derived by integrating over time the product of fiber concentration in air (the only source of exposure considered here) and the intake rate.

When interpreting health-effects information obtained from occupational studies, it may be necessary to convert nonoccupational exposures to equivalent occupational dose expressed in (fibers/cm^3) yr. Assuming an inhalation rate of 12000ml/minute; an 8-hour work day; 5 days/week; 50 weeks/year, the amounts of inhaled fibers workers could accumulate in one year, according to work group, are shown below.

worker group	exposure level	duration	exposure per year	total life-time exposure
insulation workers (amosite, chrysotile)	15 f/ml	25 yrs	2.16×10^{10} f/yr	5.4×10^{11} f
British textile workers (chrysotile)	15-30 f/ml	20 yrs	$2.16-4.32 \times 10^{10}$ f/yr	$4.32-8.64 \times 10^{11}$ f
amosite factory workers	35 f/ml	1.46 yrs	5.04×10^{10} f/yr	7.36×10^{10} f
cement workers (chrysotile, crocidolite)	9 f/ml	12 yrs	1.296×10^{10} f/yr	1.56×10^{11} f

Similar calculations for the general population are shown below:

If ambient air concentrations are assumed to be 10 ng/m^3, using the EPA conversion factor of 30 fibers (f)/ng, the population as a whole is exposed to 3×10^{-4} f/ml. Using the further assumptions:

(1) average breathing rate - 12.72 liters/min.
(2) 24 hours per day, and
(3) 52 weeks per year as the exposure duration;

It is calculated that an individual is exposed to 2.0×10^6 f/year.

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Using the assumptions and the data generated in the baby-powdering experiment[114] (concentration - 8.58 f/cc during powdering; 4.38 f/cc during settling; with 13.6% and 86.4%, respectively, of the time - with exposure time of 43.8 minutes per week; breathing rate of 05.8 l/min.), exposure of a baby from baby powder could be 6.6×10^6 f/year. It is to be noted that these calculations assume that all of the talc is asbestos. If a more realistic value of 1% asbestos is used, the number of fibers is calculated to be 6.6×10^4 f/yr.

The carcinogenic potential and the hazards of exposure to asbestos have been well documented. Also, several types of asbestos are known to be geological contaminants in talc ore. Since the accepted best index of exposure to asbestos requires counting the respirable fibers in the worker's breathing zone, a problem arises in the methodology of distinguishing asbestos fibers from talc. Characteristically, talc has a tendency to curl and stand on its edge, which may result in many erroneous counts by optical microscopy.[98]

The latest USPHS/NIOSH method for counting asbestos fibers requires phase contrast microscopy at X400-500 magnification, and arbitrarily defines a fiber as a particulate with a length to width ratio of 3:1 or greater, and a maximum width and minimum length of 5 micrometers.[99] This method is a crude determination of total fiber exposure because of the resolution limitations of optical microscopy. Most airborne asbestos fibers are less than 5 um in length, and those that are longer may have diameters too small to be resolved by phase contrast microscopy. With regard to the measurement of asbestos exposure from talc, some authors have stated that scanning electron microscopy (SEM) should be considered as an adjunct to the USPHS/NIOSH method when counting fibers in a dust environment. Phase contrast microscopy may suffice in an asbestos environment, but the resolution limitations of optical microscopy and the inability to distinguish rolled talc particles and talc "shards" from actual asbestos fibers will allow only a crude determination of the total fiber exposure.

Other than what was presented above, it is not known whether cosmetic talc (used today) is contaminated with asbestos or asbestiform minerals, what form is involved (tremolite-fibrous or nonfibrous), or what levels of asbestos, if contaminated.
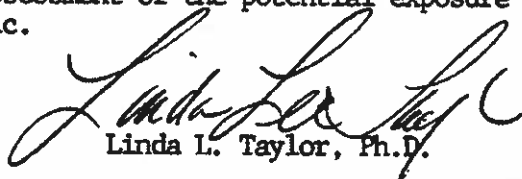
In a recent (August, 1984) report[100] by the NAS Committee on Nonoccupational Health Risks of Asbestiform Fibers, who evaluated the human health risks associated with nonoccupational exposure to asbestiform fibers with emphasis on inhalation of outdoor and indoor air, it was concluded that nonoccupational exposure to asbestiform fibers in air presents a risk to human health. The Committee made a quantitative estimate of the risk of excess lung cancer and mesothelioma that might occur in persons breathing low levels of asbestos in the air. A concentration of 0.0004 fibers/cm³ was deemed reasonable to use in

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such calculations because a variety of measurements of indoor and outdoor air indicated that 0.0004 f/cm^3 is the approximate average level that may be encountered. If a person inhaled air containing asbestos at that level throughout a 73-year lifetime, the committee's best judgement is that the lifetime risk of mesothelioma would be approximately nine in a million (range 0 to 350 per million, depending on assumptions regarding the relationship of dose to risk). Risks for continuous lifetime exposures to higher or lower levels would be proportionately higher or lower. Epidemiological data and the estimates derived from them indicate that the corresponding lifetime risk for lung cancer would be about 64 in a million for male smokers (range 0 to 290), 23 in a million for female smokers (0 to 110), and 6 and 3 in a million, respectively, for male and female nonsmokers. The risk to nonsmokers appears greater for mesothelioma than for lung cancer. The Committee also emphasized the strong dependence of mesothelioma rates on time from first exposure and exposure of children to asbestos (although mainly from school exposure). (See NAS Risk Assessment - Attachment III.)

The only information available on cosmetic exposure is that of baby powder use noted above. Infants exposed to asbestos from talc could be exposed to an additional amount above background of the order of 0.04 to 0.08 f/cc for approximately 2 years. This would result in an increase of 0.05% in the cumulative lifetime exposure of $1.95 \times 10^8 f$ to $1.951 \times 10^8 f$, with a similar increase in the lifetime risk (e.g., 9 to 9.0045 mesotheliomas per million). However this estimate is based on a linear dose response function, assuming no dose-rate effect. Cumulative exposure measures do not take into account dose rate, duration of exposure, or age at exposure. Although the cumulative amount of asbestos would appear to be of no consequence, the estimated exposure level is 100 to 200 times greater than background. Data on acute exposures of this magnitude are not available.

This memo is to request a risk assessment of the potential exposure to asbestos from use of cosmetic talc.

Linda L. Taylor, Ph.D.

APPENDIX I

Epidemiological Studies on Asbestos

1. In a follow-up study[57] of a birth cohort consisting of 10,939 men
    and 440 women (exposed for at least one month), dust exposure and
    mortality of chrysotile miners were analyzed using the "man-years"
    method and the "case- and multiple-control" approach.

    Among men the overall excess mortality was 2% at Asbestos and 10% at
    Thetford Mines, which was the dustier region (see Table 2). The
    women, mostly employed at Asbestos, had a standardized mortality
    ratio (SMR) of 0.90. During the five decades, 1926-75, 4350 men
    died compared with 4107 expected on the basis of Quebec age- and
    year-specific death rates, a SMR of 1.06. There had been a net
    excess of 33.9 deaths at Asbestos (1.6% of the 2074.1 expected) and
    208.8 at Thetford Mines (10.3% of the 2033.2 expected); SMRs of 1.02
    and 1.10, respectively. Table 2 provides data on deaths of the men
    by age and cause of death.

    Four exposure levels were used in these analyses; the mean
    concentrations were: low: 2.5 to 4.2; medium: 4.3 to 9.4; high:
    14.4 to 23.6; very high: 46.8 to 82.6 million particles per cubic
    foot (mppcf). Quantitative exposure was estimated as cumulative
    dust exposure during the first 20 years from onset of employment.
    Tables 6 and 7 analyze the 3291 deaths, 20 or more years after
    first employment, occurring from 1951 to 1975. Comparison with
    Table 2 shows that, although 26.3% of all observed deaths were thus
    excluded from the analysis because they occurred before 1951 or
    within 20 years of first employment, over 90% of deaths from
    pneumoconiosis and from lung cancer were included, and percentages
    were also high for malignant neoplasms of other sites (except the
    larynx) and stroke.

    When account is taken only of length of service (Table 6), trends
    of risk, as measured by the ratios of observed to expected
    deaths--that is, SMRs in which the standardization was by both age
    and era--were generally without clear trends, probably reflecting
    differences in selection and other factors. Exceptions were deaths
    attributed to pneumoconiosis and accidents: of the 42 deaths from
    pneumoconiosis, 36 were in men with at least 20 years' service.

TABLE 2. Deaths of men, by year, age, and certified cause of death

Cause of death (ICD code*)	Age at death	Year of death				
		Before 1946	1946-55	1956-65	1966-75	Total
All causes	<45	564	136	54	--	754
	45-64	111	438	842	702	2093 } 4463
	≥65	--	--	389	1227	1616
Pneumoconiosis (523-524)	<45	0	0	1	--	1
	45-64	1	6	10	13	30 } 46
	≥65	--	--	7	8	15
Malignant neoplasms: Lung (162-164)	<45	2	2	2	--	6
	45-64	0	12	51	72	135 } 250
	≥65	--	--	20	89	109
Oesophagus and stomach (150-151)	<45	5	2	1	--	8
	45-64	4	22	34	17	77 } 154
	≥65	--	--	12	57	69
Colon and rectum (152-154)	<45	4	1	0	--	5
	45-64	1	8	20	18	47 } 88
	≥65	--	--	6	30	36
Other abdominal (155-159)	<45	5	2	1	--	8
	45-64	1	6	15	14	36 } 80
	≥65	--	--	6	30	36
Larynx (161)	<45	0	0	0	--	0
	45-64	2	5	6	5	18 } 21
	≥65	--	--	1	2	3

Cause	Age						Total
Other	45	12	4	1	--	17	
(140-148; 160; 165-205)	45-64	2	28	52	48	130	276
	65	--	--	28	101	129	
Heart disease	45	28	25	18	--	71	
(400-443)	45-64	25	154	355	285	819	1543
	65	--	--	166	487	653	
Respiratory tuberculosis	45	118	30	1	--	149	
(001-008)	45-64	20	31	27	7	85	248
	65	--	--	5	9	14	
Other respiratory	45	60	3	0	--	63	
(470-522; 525-527)	45-64	5	12	28	37	82	234
	65	--	--	17	72	89	
Cerebrovascular	45	6	2	3	--	11	
(330-334)	45-64	4	12	42	38	96	268
	65	--	--	39	122	161	
Accidents	45	170	41	17	--	228	
(800-999)	45-64	18	44	71	51	184	461
	65	--	--	9	40	49	
All other known causes	45	114	23	9	--	146	
	45-64	25	82	112	82	301	669
	65	--	--	67	155	222	
Cause not known	45	40	1	0	--	41	
	45-64	3	16	19	15	53	125
	65	--	--	6	25	31	

*Code in the 7th revision of the International Classification of Diseases

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TABLE 6. Deaths, by cause, in relation to duration of service

Cause of death (see table 2)	Length of gross service (yr)									
	Very short (1)		Short (1 5)		Medium (5- 20)		Long (20)		Complete cohort	
	0	SMR	0	SMR	0	SMR	0	SMR	0	SMR
All causes	885	1.07	629	1.09	679	1.15	1098	1.07	3291	1.09
Pneumoconiosis	1	1.15	3	5.00	2	3.39	36	34.62	42	13.55
Malignant neoplasms:										
Lung	47	0.97	29	0.83	50	1.37	104	1.61	230	1.25
Oesophagus and stomach	37	1.30	25	1.27	18	0.91	50	1.47	130	1.27
Colon and rectum	22	0.78	13	0.67	23	1.16	21	0.62	79	0.78
Other abdominal	20	1.98	12	0.92	14	1.04	21	0.90	67	0.98
Larynx	6	1.48	5	1.75	1	0.34	4	0.78	16	1.07
Other	67	1.12	43	1.04	48	1.13	79	1.08	237	1.09
Heart disease	370	1.06	251	1.02	287	1.15	424	0.97	1332	1.04
Respiratory tuberculosis	7	0.62	7	0.89	21	2.68	22	1.56	57	1.39
Other respiratory	29	0.66	46	1.52	22	0.71	59	1.12	156	0.99
Cerebrovascular	62	0.95	49	1.12	50	1.13	82	1.11	243	1.07
Accidents	52	1.36	38	1.32	37	1.18	56	0.96	183	1.17
All other known causes	130	1.03	94	1.07	94	1.05	132	0.85	450	0.98
Cause not known	35	--	14	--	12	--	8	--	69	--

Columns headed 0 give the numbers of deaths of men, 20 years or more after first employment, occurring during 1951-75; figures under headings SMR are ratios of deaths observed to those expected on basis of male mortality in Quebec.

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TABLE 7. Deaths, by cause, in relation to dust concentration

(a) Gross service: less than one year

Cause of death (see table 2)   Accumulated dust exposure (see table 4)

| | Low | | Medium | | High | | Very high | |
	0	SMR	0	SMR	0	SMR	0	SMR
All causes	311	1.12	260	1.13	162	0.95	152	1.03
Pneumoconiosis	0	0	0	0	1	5.66	0	0
Malignant neoplasms:								
Lung	19	1.17	12	0.91	9	0.88	7	0.80
Oesophagus and stomach	12	1.24	12	1.50	9	1.54	4	0.81
Colon and rectum	5	0.52	7	0.88	6	1.03	4	0.81
Other abdominal	3	0.48	6	1.17	4	1.04	7	2.12
Larynx	2	1.45	2	1.77	1	1.19	1	1.40
Other	20	0.99	23	1.38	13	1.05	11	1.04
Heart disease	136	1.15	112	1.15	63	0.87	59	0.94
Respiratory tuberculosis	4	1.05	1	0.32	1	0.44	1	0.48
Other respiratory	11	0.74	10	0.82	3	0.33	5	0.66
Cerebrovascular	25	1.14	18	0.98	9	0.67	10	0.90
Accidents	16	1.30	19	1.86	10	1.27	7	0.90
All other known causes	45	1.06	29	0.82	26	1.00	30	1.33
Cause not known	13	--	9	--	7	--	6	--

See footnote to table 6

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7(b) Gross service: one year, less than five years

Cause of death (see table 2)   Accumulated dust exposure (see table 4)

	Low		Medium		High		Very high	
	0	SMR	0	SMR	0	SMR	0	SMR
All causes	141	1.12	246	1.09	130	1.12	112	1.04
Pneumoconiosis	0	0	3	12.80	0	0	0	0
Malignant neoplasms:								
Lung	5	0.66	13	0.95	6	0.82	5	0.78
Oesophagus and stomach	8	1.83	7	0.90	4	1.03	6	1.64
Colon and rectum	2	0.46	4	0.52	4	1.04	3	0.82
Other abdominal	2	0.70	7	1.37	2	0.75	1	0.41
Larynx	2	3.17	1	0.89	1	1.71	1	1.90
Other	14	1.53	16	0.98	9	1.08	4	0.52
Heart disease	51	0.95	99	1.03	59	1.19	42	0.92
Respiratory tuberculosis	0	0	5	1.64	1	0.61	1	0.65
Other respiratory	10	1.49	16	1.34	10	1.66	10	1.78
Cerebrovascular	18	1.83	17	0.98	10	1.19	4	0.49
Accidents	11	1.89	12	1.10	3	0.47	12	2.14
All other known causes	16	0.83	40	1.16	16	0.91	22	1.33
Cause not known	2	--	6	--	5	--	1	--

See footnote to table 6

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7(c) Gross service: five years, less than 20 years

Cause of death (see table 2)   Accumulated dust exposure (see table 4)

	Low		Medium		High		Very high	
	0	SMR	0	SMR	0	SMR	0	SMR
All causes	161	1.10	194	1.07	170	1.22	154	1.26
Pneumoconiosis	0	0	0	0	1	7.36	1	8.42
Malignant neoplasma:								
Lung	13	1.41	14	1.22	7	0.83	16	2.17
Oesophagus and stomach	6	1.21	6	0.99	5	1.07	1	0.25
Colon and rectum	4	0.81	7	1.14	9	1.92	3	0.74
Other abdominal	6	1.78	3	0.72	3	0.95	2	0.75
Larynx	0	0	0	0	1	1.44	0	0
Other	9	0.85	19	1.44	11	1.10	9	1.03
Heart disease	66	1.06	81	1.05	72	1.22	68	1.31
Respiratory tuberculosis	3	1.55	9	3.94	5	2.64	4	2.28
Other respiratory	5	0.64	5	0.51	5	0.69	7	1.12
Cerebrovascular	8	0.73	13	0.94	14	1.34	15	1.67
Accidents	8	1.07	10	1.06	10	1.33	9	1.28
All other known causes	29	1.30	21	0.77	25	1.17	19	1.01
Cause not known	4	--	6	--	2	--	0	--

See footnote to table 6

7(d) Gross service: 20 or more years

Cause of death (see table 2)   Accumulated dust exposure (see table 4)

	Low		Medium		High		Very high	
	0	SMR	0	SMR	0	SMR	0	SMR
All causes	367	0.98	253	0.89	183	1.07	295	1.50
Pneumoconiosis	4	10.49	7	23.75	5	30.10	20	101.52
Malignant neoplasms:								
Lung	28	1.21	20	1.08	24	2.20	32	2.65
Oesophagus and stomach	17	1.36	6	0.64	8	1.44	19	2.89
Colon and rectum	7	0.56	4	0.43	1	0.18	9	1.39
Other abdominal	10	1.18	3	0.46	2	0.51	6	1.35
Larynx	2	1.07	1	0.69	0	0	1	1.03
Other	33	1.23	16	0.79	11	0.90	19	1.36
Heart disease	138	0.87	115	0.95	77	1.06	94	1.12
Respiratory tuberculosis	5	1.01	5	1.31	3	1.27	9	3.06
Other respiratory	18	0.92	10	0.68	14	1.62	17	1.74
Cerebrovascular	32	1.15	18	0.89	10	0.84	22	1.58
Accidents	16	0.82	19	1.16	9	0.85	12	1.01
All other known causes	52	0.92	29	0.68	18	0.70	33	1.10
Cause not known	5	--	0	--	1	--	2	--

See footnote to table 6

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Among those in the very short and short service groups (those with
gross service of less than 5 years (Tables 7(a) and (b)), careful
study of differences between groups according to severity of
exposure showed no consistent pattern. Table 7(c) deals with men
with gross service between 5 and 20 years; their service had also
been completed before the start of the study interval. There were
fairly consistent trends for higher SMRs the greater the dust
exposure for total mortality, for pneumoconiosis (although based on
only 2 deaths), heart disease, and stroke. In addition SMRs were
highest in the group with the most severe exposure, for lung cancer
and "other" respiratory diseases. The authors stated that all
these findings are understandable as pulmonary fibrosis could well
contribute directly to cardio-pulmonary disease and, in addition,
might adversely affect the probability of survival in any
life-threatening condition. Table 7(d) concerns 3105 men with at
least 20 years service, and an average of almost 32 years of
employment. Here the most severely exposed had the highest SMR not
only for total mortality but for all listed causes other than
laryngeal cancer and accidents. Further, the tendency for
increased risk with each augmentation in exposure was completely
consistent for pneumoconiosis and for heart disease, and positive,
although rather less consistent, for total mortality, lung cancer,
respiratory tuberculosis, and other respiratory diseases.
The other form of a priori analysis, with exposure calculated to
age 45 at which age the study interval started, is summarized in
Table 8. The total number of deaths observed in this analysis was
3448 (77.3% of the deaths), with SMR = 1.07, very close to that for
all causes in the complete cohort as seen in Table 6. Indeed, for
each cause of death, SMRs from both methods of analysis were always
close. Clear trends were found for SMRs to be higher the heavier
the exposure, for total mortality, pneumoconiosis, lung cancer,
cancer of the colon and rectum, respiratory tuberculosis, other
respiratory diseases and stroke. The trends were most clear-cut in
pneumoconiosis and lung cancer. The lung cancer trend was
essentially linear as shown in the Figure below, where exposures of
30 mppcf-year or more have been broken down further, into 4
classes. The trend for respiratory tuberculosis was also
consistent in the two areas, but not those for the other causes
listed.

Dust exposure and mortality in chrysotile mining, 1910-75

TABLE 8. Deaths, by cause, in relation to dust exposure accumulated to age 45

Cause of death (see table 2)	Dust exposure (mpcf-y) accumulated to age 45					
	< 30 0	SMR	30 < 300 0	SMR	≥ 300 0	SMR
All causes	1668	1.02	1138	1.04	642	1.30
Pneumoconiosis	5	2.98	12	10.81	27	54.00
Malignant neoplasms:						
Lung	91	0.93	81	1.18	70	2.25
Oesophagus and stomach	68	1.22	42	1.14	26	1.58
Colon and rectum	34	0.62	28	0.77	18	1.11
Other abdominal	37	1.00	21	0.84	10	0.88
Larynx	9	1.11	6	1.08	2	0.81
Other	129	1.10	83	1.06	38	1.08
Heart disease	696	1.06	463	0.99	240	1.14
Respiratory tuberculosis	21	0.94	25	1.67	15	2.20
Other respiratory	71	0.84	55	0.98	40	1.62
Cerebrovascular	119	0.96	86	1.08	46	1.32
Accidents	104	1.28	60	1.00	33	1.16
All other known causes	237	0.95	154	0.92	74	0.99
Cause not known	47	--	22	--	3	--

See footnote to table 6
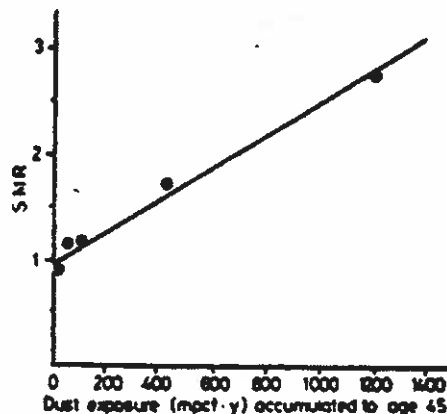
Lung cancer SMRs in relation to dust exposure accumulated to age 45. The line has been fitted by a modified least-squares technique.

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Table 9 shows deaths from lung cancer.

TABLE 9. Deaths from lung cancer in relation to dust exposure and smoking habit

Smoking habit	Dust exposure (mpcf.y) accumulated to age 45							
	< 30		30 < 300		≥ 300		All	
	0	SMR	0	SMR	0	SMR	0	SMR
Non-smokers	5	0.18	6	0.36	8	1.24	19	0.38
Moderate smokers	73	1.14	64	1.35	52	2.31	189	1.41
Heavy smokers	13	2.12	11	2.39	10	4.50	34	2.63
All smoking habits	91	0.93	81	1.18	70	2.25	242	1.23

See footnote to table 6

Table 10 summarizes the findings from the Miettinen approach--that is, more than one control for each case, excluding those for smoking habit; the

TABLE 10: Dust exposure in deaths from pneumoconiosis and from malignant disease and in controls numbers of deaths areas table 2 (but see

	Dust exposure (mpcf.y) accumulated up to nine years before death of case						
	30	30	300	300	1000	1000	All
Pneumoconiosis							
Deaths	7	9		13		17	46
Controls(3)*	63	49		21		5	138
Relative Risk+	1		1.65		5.57	30.60	--
Lung cancer							
Deaths**	89	73		56		27	245
Controls(3)	333	243		127		32	735
Relative risk	1		1.12		1.65	3.16	--
Cancer of oesophagus and stomach							
Deaths	74	41		22		17	154
Controls(2)	143	105		53		7	308
Relative risk	1		0.75		0.90	4.69	--
Cancer of colon and rectum							
Deaths	39	29		13		7	88
Controls(2)	88	70		15		3	176
Relative risk	1		0.93		1.96	5.26	--
Other abdominal cancers							
Deaths	43	25		7		5	80
Controls(2)	83	46		26		5	160
Relative risk	1		1.05		0.52	1.93	--
Cancer of larynx							
Deaths	13	6		2		0	21
Controls(3)	36	21		5		1	63
Relative risk	1		0.79		1.11	0.00	--

*Figures in brackets are numbers of controls for each death. Method of selecting controls is described in text; those reported here were not matched for smoking habit.
+Risk calculated by method of Doll in relation to those with exposure less than 30 mpcf.y.
**Excluding five deaths coded to 162-164, but found to be due to malignant mesothelioma.

numbers of deaths are as in Table 2 (but see footnote ** in Table 10) because there were no restrictions on the start of the study interval. Four groups of dust exposure are distinguished, and the data are presented without regard to the matching. Matching was taken into account in the full analysis, however, which generally confirmed the tendencies shown in the two a priori approaches and relative risks were fairly similar at Asbestos and Thetford Mines.

Linear dose-response relations have been fitted (Berry, G., unpublished) for lung cancer (without regard to smoking habits); using the data on which Table 10 is based, but taking into account the matching of controls for each case in terms of date of birth and place of employment, the fitted line was:

$$\text{Relative risk} = 1 + 0.0014 \ (\text{mppcf-y})$$

the standard error of the estimate of the slope being 0.0005. The linear fit accounted for X^2, with one degree of freedom, of 21.37, leaving only a very low value for deviations from linearity.

There were in all 11 deaths (including one women) from malignant mesothelioma observed to the end of 1975. All were of the pleura and appeared to follow a clear exposure trend.

The authors concluded that essentially linear relations have been shown between indices of exposure, based on dust concentration (mppcf) multiplied by length of service, and lung cancer, pneumoconiosis, and total number of deaths.

Because of concern regarding the risk from concentrations of asbestos dust nearer current standards, the data for the 1904 men in the cohort employed for at least 20 years in the low and medium dust exposure groups were analyzed. The concentrations to which these men were exposed (Table 4) averaged 6.6 mppcf, or perhaps 20 f/ml. The total mortality was 620 deaths, and the SMR was 0.94. The authors stated that this might be a true healthy worker effect, but not all cause-specific SMRs were below unity. There were excesses for pneumoconiosis (10.3 excess deaths, leading to X^2 on the usual basis, and with one degree of freedom, of 159.27), for lung cancer (6.4, X^2 = 0.99); cancer of esophagus and stomach (1.1, X^2 - 0.06); "other" cancers (1.7, X_2^2 = 0.06); respiratory tuberculosis (1.3, X^2 = 0.17); and stroke (1.8, X^2 - 0.07). Apart from pneumoconiosis, these values of X^2 are so low, even for lung cancer (where the associated p-value is 32.0%), that the observed excesses do not reach conventional levels of statistical significance. Moreover, the lung cancer SMR for the low dust exposure group (1.21) was higher than that of the medium exposure group (1.08); the authors stated that only the greatly enhanced SMRs for those with high and very high exposure allow the conclusion that there was a

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response to exposure. Nevertheless, the lung cancer SMR for all 1904 men was 1.15, in close conformity with that which might be predicted from the figure (about 1.20) or the relative risk of 1.16 from the fitted line (Berry, G., unpublished).

It is noted that exposure to asbestos was presented as dust exposure in mppcf. The current trend is towards providing information in terms of fibers rather that dust counts, although there is an almost complete lack of epidemiological data based on fiber measurements. The problem with this is there is no easy conversion. The authors note that studies showed that, at relevant dust levels, the conversion factors range from about 3 to 7 fibers/ml for each mppcf; although other data point to a lower range, 1 to 5. This is a recurring problem.

CONCLUSION:

The study suggests an overall small increase in lung cancer associated with asbestos exposure. A consistent dose-response gradient was observed: SMR of 0.9 (low exposure 30 mppcf-yrs) to 2.3 for highest exposure category (300 mppcf-yrs.).

2. In this cohort study of chrysotile miners and millers, only workers with at least 20 years of employment were chosen.

Dust measurements after 1969 were reviewed but no quantitative exposure data were provided. Fiber concentrations for various areas of the mills and mines ranged from 9 to 36 fibers longer than 5 micrometers/ml of air.

Table 4 shows the various causes of death observed in 130 deaths.

TABLE 4: Categorization of causes of death according to death
certificate information compared with categorization following
review of all available medical records and pathological
material in 130 cases

Cause of Death as Ascertained (BE)*	No.	Underlying Cause of Death as Categorized on Certificate of Death, (DC)*				
		Lung Cancer	Mesothelioma	All Other Cancer	Asbestosis Including Pneumoconiosis	All Other Causes
Lung cancer	25	18		3	2	2
Mesothelioma	1		1			
All other cancer	18	1		17		
Asbestosis	24	3			14	7
All other causes	62			1	1	60
Totals	130	22	1	21	17	69

*BE - best evidence
DC - death certificate cause

The expected mortality experience was calculated using national
rates of Canada (Table 5).

TABLE 5: Expected and Observed Deaths Among 544 Asbestos Miners and
Millers, Thetford Mines, Quebec, Jan.-Nov., 1961 ADG, 1977*

	Total		
	Exp.	Obs.	O/E
Total deaths	159.9	178	1.11
Total cancer all sites	36.7	49	1.34
Lung cancer	11.1	28	2.52
Pleural mesothelioma	**	1	--
Cancer of the gastrointestinal tract	9.5	10	1.05
All other cancers	16.1	10	0.62
Total Noninfectious pulmonary diseases	6.7	30	4.48
Asbestosis	**	26	--
All other causes	116.5	99	0.85
Person-years		7,408	

*Expected deaths are based upon age-specific death rate data for
Canadian white males.
**Death rates not available but these have been rare causes of death in
the general population.

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Asbestosis and lung cancer were major causes of death among these
workers. Table 7 details the mortality experience according to time
from onset of exposure and shows an increase in mortality between 30
and 50 years from first exposure to asbestos. There is, however,
little excess mortality after 50 or more years from first exposure.
The authors stated that perhaps this occurred as individuals at high
risk of death (because of their particular susceptibility or because
of other associated factors, as cigarette smoking) may have died
preferentially in earlier years.

TABLE 7: Ratios of Observed to Expected Deaths Among 544 Asbestos
Miners and Millers, Thetford Mines, Quebec, Jan.-Nov. 1961 -
Aug. 1977

	Ratio of Observed to Expected Deaths (Number of Deaths in Parentheses)			
	Years from Onset of Employment			
	20-29	30-39	40-49	50 +
Total deaths	0.65 (8)	1.27 (60)	1.28 (66)	0.91 (44)
Total cancer	0.00 (0)	0.98 (11)	1.95 (24)	1.30 (14)
Lung cancer	0.00 (0)	1.94 (7)	4.19 (16)	1.67 (5)
Noninfectious pulmonary diseases (incl. asbestosis)	-- (4)	5.29 (9)	3.64 (8)	3.60 (9)
Causes other than cancer or noninfectious pulmonary diseases	0.42 (4)	1.16 (40)	0.91 (34)	0.59 (21)
	Number of deaths			
Asbestosis	3	8	8	7
Mesothelioma	0	0	1	0
Person-years of observation	1,623	3,067	1,805	914

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CONCLUSION:

The study results indicate that a small increase in lung cancer risk occurs as asbestos exposure increases, but the lack of quantitative exposure data makes it difficult to evaluate this association.

3. Mortality of Italian chrysotile asbestos workers was studied[82] using two different reference groups. In the first analysis the observed number of deaths was compared with the expected number in the population of all Italy. Person-years of observation were calculated according to the method of Case and Lea[55a] and multiplied by age-specific death rates to compute the expected number of deaths. Secondly, a case control study of carcinoma of lung and larynx was undertaken. Only two exposure categories were considered, the first with cumulative exposure up to 100 fiber-years and the second, all those with a cumulative exposure greater than 100 f/yr. (The lower of the two exposures corresponds to the British standard of 2f/cc for 50 years' working life).

In Table 3 the mortality of the cohort is divided into 2 groups according to period since first employment: deaths occurring up to 19 years since first employment and deaths occurring over 20 years since first employment. The overall mortality compared to the national figures is also shown.

One death from pleural mesothelioma occurred 35 years after starting employment in a worker with 33 years exposure.

A significant excess of laryngeal cancer is seen when examining mortality over the whole period of observation. Four of these deaths occurred after 20 years since first employment. Two of the six workers dying from laryngeal cancer had less than one year of exposure. There is also a marked excess of respiratory diseases, both influenza and pneumonia and "other" respiratory diseases, consisting chiefly of chronic obstructive lung disease. Asbestosis was reported in 9 cases.

Mortality from lung cancer is shown in Table 4. No deaths were observed before 1961, nor did any deaths occur from this cause in subjects under the age of 50. However, among those of 50 years or more, the SMR rises to 111 in the quinquennium 1966-70 and reaches 226 between 1971 and 1975; for men of all ages it is 206 in the same period.

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TABLE 3: Number of deaths observed and expected by period since first exposure, and cause. (Period of observation from 1946 to 1975)

Period since first exposure (yr) over	Up to 19			20 and			Total		
Person-years observation	12683			8776			21459		
Cause of death	Observed	Expected	SMR	Observed	Expected	SMR	Observed	Expected	SMR
All causes	112	54.2	207**	220	160.2	137**	332	214.4	155**
All malignant neoplasms (140-205)	12	10.0	120	38+	37.0	103	50+	47.0	106
Lung and pleura (162-163)	1	1.7	59	10+	8.7	115	11+	10.4	106
Larynx (161)	2	0.4	500	4	1.5	267	6	1.9	316*
Gastrointestinal (151-159)	4	4.8	83	15	14.5	103	19	19.3	98
Other sites	5	3.1	161	9	12.3	73	14	15.4	91
Non-malignant respiratory diseases (470-527)	12	2.3	522**	20	11.8	169*	32	14.1	227**
Influenza and pneumonia (480-483)	8	1.6	500**	4	4.6	87	12	6.2	194*
Other respiratory diseases(470-475, 500-527)	4	0.7	571**	16	7.2	222**	20	7.9	253**
Asbestosis (523.2)	2	--	--	7	--	--	9	--	--
Tuberculosis of the lung (001-008)	13	3.9	333**	5	3.3	152	18	7.2	150**
Cardiovascular diseases (400-468)	22	14.8	149	100	67.7	148**	122	82.5	148*
Cirrhosis of the liver (581)	9	2.1	429**	22	7.8	282**	31	9.9	313**
Accidents (800-999)	30	7.8	385**	15	9.5	158	45	17.3	260**
All other causes	9	13.3	68	17	23.1	74	26	36.4	71
Unknown	5	--	--	3	--	--	8	--	--

*p < 0.05; **p < 0.01

+These numbers include one suspected case of mesothelioma of the pleura

Figures in parentheses are ICD (7th Revision) code numbers

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TABLE 4: Observed and expected deaths from lung cancer (162-163) by age and calendar time

Age		1946-60	1961-65	1966-70	1971-75	1946-75
	Calendar years of follow-up					
Up to 49	Observed	0	0	0	0	0
	Expected	0.5	0.2	0.3	0.3	1.3
	SMR	--	--	--	--	--
50 and over	Observed	0	1	3	7*	11
	Expected	1.7	1.6	2.7	3.1	9.1
	SMR	--	63	111	226	121
All ages	Observed	0	1	3	7*	11
	Expected	2.2	1.8	3.0	3.4	10.4
	SMR	--	56	100	206	106

*These numbers include one suspected case of mesothelioma of the pleura

Table 5 shows the distribution of the deaths of men with lung cancer and their controls in the two exposure categories, in the upper part of the table, and the deaths from laryngeal cancer with their controls, in the lower half of the table. Ten of the deaths from lung cancer are in the higher exposure group with a relative risk of 2.89. However, tests of the significance of the association of lung cancer and high exposure gave a two-tailed P value of 0.18, thus demonstrating no statistically significant difference between the proportion of cases and controls reaching the higher exposure level. Nor is there a statistically significant excess of laryngeal cancer in the higher exposure categories (relative risk 3.33, two-tailed P value 0.28), although all but one of the deaths occurred in this group.

TABLE 5: Distribution of patients with lung and laryngeal cancer and their matched controls according to cumulative dust exposure.

Subjects	Dust exposure	
	Up to 100 fibre/yr	101 and over fibre/yr
Lung cancer	2	10[+]
Controls	22	38
Relative risk	1	2.89*
Laryngeal cancer	1	5
Controls	12	18
Relative risk	1	3.33**

[+]Including one case of lung cancer diagnosed in hospital but reported in death certificate as "cardiac failure" and one suspected case of mesothelioma of the pleura.
*two-tailed p value 0.18
**two-tailed p value 0.28

Table 7 shows the distribution of the whole cohort according to the selected exposure categories. For this analysis, workers included in the higher exposure category contributed to person-years observation in the lower category "up to 100 fibre/years" from the date of first employment to the date they reached the cumulative dust exposure of "more than 100 fibre/yr," after which they contributed to the higher category. The mean value of cumulative dust exposure in the higher category was about five times that in the lower (75 fibre/yr compared with 376 fibre/yr). About two-thirds of the cohort reached the higher exposure category. In Tables 7 and 8, man-years from 1 January 1946 only are included in the total. Thus, those who had accumulated a dose of 100 fibre/yr by 1946, immediately entered the higher exposure category.

The age-standardized death rates and the associate measure of risk for overall mortality and some selected causes of death are shown in Table 8. The relative risk for lung cancer obtained by examining the whole cohort (2.54) is similar to that calculated for the case control study (2.89, Table 5). A higher death rate for laryngeal and gastrointestinal cancer is also seen in the more highly exposed group, although comparison with the national statistics showed no

excess for gastrointestinal cancers. Non-malignant respiratory diseases, including asbestosis, tuberculosis and cardiovascular diseases, showed an increase in relative risk, whereas death rates for all other causes were almost equal in the two exposure groups.

TABLE 7: Distribution of workers according to cumulative dust exposure. Period of observation from 1946 to 1975

Dust exposure as fibre/yr	Up to 100 fibre/yr	101 and over fibre/yr	Unknown
Mean value within categories	74.7	376.2	--
Number in study	927*	611	6**
Person-years observation	8365	12976	118

*Including the 611 workers in the category "101 and over fibre/yr" before they had reached such cumulative exposure. Person-years are additive, whereas number of workers are not.
**Including 4 dead

TABLE 8: Crude and age-standardised death rates per 1000 person-years and relative risks by selected causes.

Cause of death	Cumulative dust exposure				Relative risk*
	Up to 100 fibre/yr		101 and over fibre		
	Death rate		Death rate		
	Crude	Age-standardised	Crude	Age-standardized	
All causes	11.72	13.31	17.73	16.73	1.26
Lung cancer (162-163)	0.24	0.28	0.77	0.71	2.54
Laryngeal cancer (161)	0.12	0.14	0.39	0.36	2.57
Gastrointestinal cancer (151-159)	0.48	0.57	1.16	1.09	1.91
Non-malignant respiratory diseases excluding influenza and pneumonia (470-475, 500-527)	0.48	0.46	1.39	1.28	2.21
Tuberculosis of the lung (001-008)	0.48	0.46	1.08	1.10	2.39
Cardiovascular diseases (400-468)	4.06	4.68	6.47	5.94	1.27
All other causes	5.86	6.60	6.47	6.24	0.95

*Based on age-standardised death rates

CONCLUSION:

The gradient of risk for lung cancer with time since onset of exposure (SMR 0.6 for < 20 years vs. 1.2 for > 20 years) and calendar time (SMR 0.6 for 1961-1965 vs. 2.1 for 1971-1975) was observed. Significantly higher risk was noted only for laryngeal cancer. Increased relative risk for lung cancer (2.9) and laryngeal cancer (3.3) was found when case-control groups were compared by exposure level.

4. Mortality of workers manufacturing friction materials using chrysotile was studied[65] on a population of 13460 workers. Exposure conditions are shown in Table 1.

Table 1   Mean concentration of asbestos in air (f/ml)

Period	Office/laboratory	Storage/distribution	Grinding	Forming
Pre-1931	10-20	>20	>20	>20
1932-50	<0.5	2-5	5-10	2-5
1951-69	<0.5	2.4	2-5	1-2
1970-79	<0.5	0.5-1	0.5-1	0.5-1

The observed mortality was compared with that expected, based on sex-, age-, and period-specific death rates for England and Wales, using the subject-years method. Attention was restricted to the period following 10 years exposure, and follow-up was to the end of 1979. In addition to mortality from all causes, the separate causes of death considered were cancer of lung and pleura, cancer of the gastrointestinal tract, and all other cancers. Table 7 shows the total mortality. Apart from 10 pleural mesotheliomas there was no sign of any excess mortality.

Table 7   Observed and expected mortality after 10 years from first exposure. (Number of pleural mesotheliomas included in parentheses)

Cause of death	Net subject-years		Women	
	Men		Women	
	Obs	Exp	Obs	Exp
All causes	1330	1361.8	297	325.10
Lung and pleural cancer	151 (8)	146.5	8 (2)	11.3
Gastrointestinal cancer	104	107.2	24	27.4
Other cancers	77	87.2	41	46.11
Other causes	1106	1102.4	211	229.3

When the subjects were divided into groups according to duration of exposure, there was still no sign of excess mortality nor of any trend in mortality with duration of employment. Dividing the subjects according to the period of first employment again showed no excess mortality apart from the pleural mesotheliomas. This applied even to those with 30 years' follow-up who were first employed before 1950, when dust levels were high (Table 1).

Among deaths from other cancers, there were 2 in men due to cancer of the larynx (3.6 expected). Eight of the women died of cancer of the ovary (8.1 expected), and 22 of cancer of the breast (24.4 expected). The mortality experience of workers who completed 10 years' service is shown in Table 8.

Table 8   Observed and expected mortality after completing 10 years' employment

Follow up after 10 years exposure (years) No. subjects-years	Men				Women			
	< 10		> 10		< 10		> 10	
	2484-21,800		18086-19,025		627-5578		457-6177	
Cause of death	Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp
All causes	188	195.7	412	450.8	14	21.3	7	99.4
Lung and pleural cancer	23	21.3	36.7	37.4	11	11.7	2.3	2.3
Gastrointestinal cancer	24	16.3	24	18.8	11	1.5	4	2.2
Other cancers	-	12.0	21	28.2	3	4.5	24	2.7
Other causes	132	175.8	425	430.4	11	13.5	42	270

Except for deaths from mesothelioma, there was no excess in this group, even 10 years after completing 10 years' employment. A similar result was obtained when restricting attention to those who had completed 20 years' exposure.

An additional 187 deaths have occurred since the original analysis. Only one of 40 deaths in women and 12 of 147 in men were due to lung cancer. One of the men certified as dying from pleural mesothelioma was 50 and had worked at the factory for two weeks in 1960 (when aged 29) as a grinder exposed to chrysotile (only known asbestos exposure). With regard to mesothelioma, the cases observed here were analyzed in a case-control study using the method of Liddell, et al. The effect of exposure to crocidolite was examined. Four matched controls were chosen for each mesothelioma, where matching was for (1) sex, (2) year started work in factory (± 1 year), (3) year of birth (± 4 years), (4) survival up to time of death of mesothelioma, and (5) employed at factory during crocidolite period for same time as case.

Eighty percent of those dying of mesothelioma had worked on the crocidolite contract compared with only 8% of the controls. Those with mesothelioma, however, had also been exposed to higher levels of chrysotile than the controls; 90% had been exposed to more than 5 f/ml compared with 25% of the controls. The confounding effect of exposure to chrysotile was eliminated by considering only cases of mesothelioma and their controls who had been exposed to chrysotile at a level of at least 5 f/ml. This left 6 cases with 10 controls. Five of the 6 had had definite crocidolite exposure.

A case-control study of deaths due to lung cancer was carried out for males who had started work before the end of 1960 and who survived for at least 10 years after start of exposure. There were

106 deaths from lung cancer satisfying these criteria, and three controls were chosen for each case, matched for: (1) year started at factory; (2) date of birth; and (3) survival up to time of death from lung cancer. Within the restricted set of men there were 86 who had died of gastrointestinal cancer, who were also included in this study (without additional controls). Each occupational history was integrated with respect to time to give the cumulative exposure up to the date of death for the cases, and for controls up to the date of death of the corresponding case of lung cancer. The total duration was also calculated. These two measures were also evaluated up to 9 years before the above dates, on the basis that recent exposure is irrevalent to the risk of lung cancer. A fifth measure evaluated was the cumulative dose weighted by the time elapsed since the exposure occurred. This measure was evaluated up to the date of death and attaches most importance to the earliest exposure.

The distribution of duration of exposure and cumulative exposure up to death are given in Tables 13 and 14.

Table 13   Distributions of duration of exposure up to death

| Duration of exposure (years) | No of subjects | | | Odds-ratios | |
	Controls	Lung cancers	Gastrointestinal cancers	Lung cancer	Gastrointestinal cancer
0-0	74	26	16	1.00	1.00
1-4.9	86	38	24	0.96	1.24
5-9.9	25	5	4	0.81	1.30
10-19.9	55	25	26	1.01	1.56
20-0.5	52	15	11	0.82	0.45
Total	117	106	56		

Table 14   Distributions of cumulative exposure to death

| Cumulative exposure (t-h.mt) | No of subjects | | | Odds-ratios | |
	Controls	Lung cancers	Gastrointestinal cancers	Lung cancer	Gastrointestinal cancer
0-9	135	48	36	1.00	1.00
10-49	124	37	40	0.79	1.18
50-99	41	13	9	1.36	0.83
100-356	15	4	1	0.88	0.24
Total	311*	105*	86		

*Five of the eleven 16 controls (1 lung cancer) information available on dust levels was insufficient to calculate cumulative exposure
t-2/mg Fibge-years/ml

The odds ratio, i.e., the approximate risks of cancer, relative to the lowest exposure group, are also given.

For lung cancer there is no indication of an increased risk with either duration of exposure or cumulative exposure. For gastrointestinal cancer, there is no sign of an increased risk with cumulative exposure, and although there appears to be a trend with duration of exposure up to 20 years, this trend is not supported by

the numbers with more than 20 years' exposure and could have
occurred by chance. There was also no sign of increased risk with
duration of exposure or with cumulative exposure calculated to nine
years before death or with the measure of exposure weighted by
elapsed time (tables not given). Restricting the analysis to cases
who survived for at least 15 years after first
exposure also did not show any dose-response relationship.

For lung cancers, a linear relationship between relative risk and
cumulative exposure was fitted using methods appropriate to matched
data. The coefficient was estimated as 0.00058 per fiber-year/ml.
That is, for a cumulative exposure of 100 fibers-years/ml, the
relative risk was estimated as 1.06; the upper confidence limit was
1.80.

CONCLUSION:

No gradient of risk was observed with quantitative exposure levels.

No evidence of excess mortality due to cancer at any site, except
mesothelioma, even when examined by duration of exposure or period
of initial employment.

No increased risk of lung cancer or gastrointestinal cancer was
associated with either duration or cumulative exposure in the
case-control analysis.

5. A report[83] on dust exposure and mortality of workers in a chrysotile
asbestos friction products plant consisted of data on a cohort of
3641 men employed for at least one month. Individual exposures were
estimated (in mppcf-years) from impinger measurements. Table 1
shows deaths by cause and age at death.

Table 1 Male deaths by age and certified cause

Cause of death (ICD code)	Age at death (y)			Total
	<45	45-64	≥65	
All causes	139	616	511	1267
Malignant neoplasms				
Lung (162-64)	1	47	41	89
Oesophagus and stomach (150-51)	0	12	13	25
Colon and rectum (153-54)	3	9	20	32
Other abdominal (155-59)	4	9	12	25
Larynx (161)	0	3	1	4
Other (140-48, 160, 165-205)	11	50	40	101
Heart disease (400-443)	39	273	198	510
Respiratory tuberculosis (001-008)	3	6	2	11
Other respiratory (470-522, 525-527)	2	27	24	53
Pneumoconiosis (523-24)	0	7	5	12
Cerebrovascular (330-34)	5	30	56	91
Accidents (800-999)	35	42	15	92
Other known causes	30	87	66	183
Cause not known	6	14	18	39*

*Including one age unknown

Exposure information is presented in Tables 2 and 3.

Table 2 *Estimated average dust concentrations (mpcf) for main processes 1930–70*

	1930-9	1940-9	1950-9	1960-9
Pulverising waste asbestos products	6	4	2	1
Sheet packings				
Fibre room	13 4	10	8	6
Mixing	2 4	2	1 5	1
Other	5 0	1 5	1	0 5
Millboard wet machines	3 1	2	2	0 5
Wire mould extruded brake lining				
Mixing	8 2	3	2	1
Other	1	1	0 5	0 2
Paper				
Autotransmission etc	—	—	0 5	0 2
Novabestos process	—	—	0 2	0 2
Grooving	—	—	0 5	0 2
Metal fabrication	—	—	1	0 5
Brake shoes	—	—	0 5	0 2
Core	—	—	0 5	0 2
Disc brake	2	1 5	1	0 5
Treatcure	2	1 5	1	0 5
Brake finish/hot press				
Drymould mix	24	10	7 5	5
Grinding	4 3	3	2	1
Other	1 5	1 5	1	0 5
Ring finish (grinding)	5 6	4	2	1
Packing	1	1	0 5	0 1
Warehouse	2	2	0 2	0 1

Table 3 *Age at start, duration of employment, and dust exposure (men only)*

	Duration of gross service (y)				
	<1	1-<5	5-<20	≥20	Total
No	1253	938	577	747	3515
Average age at start (y)	29 62	31 96	31 85	29 64	30 95
Gross service (y)	0 38	2 53	10 58	30 54	9 05
Net service (y)	0 37	2 12	9 00	28 82	8 04
Average dust concentration (mpcf)	2 28	2 06	1 56	1 06	1 84

Table 4 summarizes the mortality experience of the cohort by
duration of work. The SMR based on Connecticut rates was 108.5
(107.9 on U.S. rates). The excess was mainly due to people who had
worked for less than 1 year (SMR 129.9); those who worked one or
more years had an SMR of 101.2. The lowest SMR (97.2) was for those
who had worked 20 or more years. SMRs were raised for the three
main groups of malignant neoplasms. Again this was mainly due to
high SMRs in men employed for less than one year; in none was there
evidence of increasing risk with increasing duration of exposure.
No mesotheliomas were observed.

Table 4 Male deaths 20 years after first employment, by cause, in relation to duration of service

Cause of death [a]	Duration of gross service (y)								Complete cohort	
	<1		1-<5		5-<20		>20			
	o	SMR	o	SMR	o	SMR	o	SMR	o	SMR
All causes	246	129.0	189	105.0	110	104.8	238	97.2	803	108.5
Malignant neoplasms	60	144.0	50	125.7	29	114.0	63	118.3	202	126.5
Respiratory	23	180.8	19	149.4	9	122.6	21	133.4	73	148.7
Digestive	17	132.0	16	128.3	5	60.6	21	116.9	59	113.4
Other	19	120.4	25	104.9	15	190.3	21	107.2	70	115.9
Heart disease	99	125.3	79	103.0	44	81.7	100	93.1	322	102.5
Respiratory tuberculosis	0	—	0	—	0	—	4	283.3	4	145.4
Other respiratory	13	196.3	8	—	1	126.2	8	92.2	33	—
Pneumoconiosis	16		(3)		11		(2)		11	
Cerebrovascular	18	137.6	14	108.4	15	142.7	20	102.4	67	119.0
Accidents	11	121.1	5	69.2	5	101.7	7	66.6	28	90.1
Other known	37	123.5	24	90.4	29	147.1	35	87.9	125	107.7

[a] As in table 1, except that ICD codes 160-64 are here grouped under "respiratory" malignant neoplasms and the "other respiratory" category includes only bronchitis, pneumonia, and pneumoconiosis (ICD 490-502, 523-4)

Table 5 gives SMRs by total accumulated dust exposure. The same lack of any clear or systemic exposure-effect pattern is present. The SMR for respiratory cancer for men in the 2 highest dust groups combined (125.8) was higher than for the 2 intermediate dust groups combined (103.3) but still substantially below that for the lowest exposure category (167.4). A similar pattern of relative risk was obtained from the Mantel-Haenszel analysis (Table 6), which showed an increasing risk only if the minimal exposure group is ignored.

Table 5 Male deaths 20 years after first employment, by cause, in relation to dust exposure (mpcf y)

	Accumulated dust exposure (mpcf y)									
	<10		10-<20		20-<40		40-<80		>80	
	o	SMR	o	SMR	o	SMR	o	SMR	o	SMR
All causes	546	113.8	89	92.3	71	96.6	62	110.2	35	103.1
Malignant neoplasms	134	126.1	22	109.6	19	126.1	19	143.9	8	117.9
Respiratory	55	167.4	6	101.7	5	105.4	6	162.8	1	55.2
Digestive	34	102.6	9	135.1	8	153.4	5	120.2	3	126.6
Other	45	114.0	7	84.5	6	101.0	8	176.0	4	150.4
Heart disease	60	101.9	14	83.6	13	76.6	18	106.4	13	93.0
Respiratory tuberculosis	2	123.6	0	—	0	—	0	—	2	1112.9
Other respiratory	21	125.1	5	135.6	2	74.4	2	109.0	3	230.8
Pneumoconiosis	(9)		(1)		11		(1)		(0)	
Cerebrovascular	43	122.9	8	101.7	7	118.4	5	117.1	4	135.4
Accidents	22	101.0	3	86.5	0	—	2	86.3	1	94.2
Other known	81	109.5	15	102.9	15	128.5	10	112.2	2	43.4

The more detailed analysis for respiratory cancer in Table 8 shows that the same pattern is shared by men in the lowest accumulated dust category regardless of duration of employment.

Table 8 Male deaths from respiratory cancer 20 years after first employment in relation to duration of service and dust exposure

Duration of service (y)	Dust exposure (mpcf y)					
	<10		10-<40		>40	
	o	SMR	o	SMR	o	SMR
<1	24	180.0	0	—	0	—
1-<5	17	166.3	2	83.2	0	—
>5	14	150.0	9	109.9	7	125.4

Table 6   Relative risks of respiratory cancer by dust exposure from (1) Mantel-Haenszel analysis and (2) SMRs

| | mpcf/y | | | | | Chi-square | |
	<10	10-<20	20-<40	40-<80	≥80	Difference	Linearity
Mantel-Haenszel:							
Observed	54	4	5	6	1		
Expected	51 1	8·7	4·6	4 1	1·5		
Relative risk	1	0·40	0·91	1·40	1·13	4·50	0·00
From SMRs.							
Relative risk	1	0·59	0·64	0·9N	0·31		

The other respiratory group of diseases that included pneumoconiosis also showed little indication of an exposure response. Six of the 12 whose deaths were from pneumoconiosis (ICD 523) had worked in the plant for less than a year and only 3 of the other 12 had a total dust exposures index of 10 mppcf-yrs. or more. Table 7 shows details from death certificates given ICD code 523. In no case was asbestosis mentioned but anthracosilicosis or silicosis were given as the cause of death in all but 2 cases. It was further noted that all 12 had either been born or had died in the coal mining area of Pennsylvania.

Table 7   Deaths attributed to pneumoconiosis (ICD 523)

| Case No | Employment | | | Birth place | Death | | Certified cause |
	Age at start (y)	Duration	Total dust (mpcf y)		Age (y)	Place	
1	36	2 months	0 1	Sandy Run, Pa	64	Freeland, Pa	Anthracosilicosis
2	26	6 months	0 2	Taylor, Pa	57	Taylor, Pa	Silicosis and emphysema
3	35	2 months	0 1	Wilkes-Barre, Pa	57	Wilkes-Barre, Pa	Anthracosilicosis
4	29	5 months	0 2	Wilmington, De	58	Wilkes-Barre, Pa	3° anthracosilicosis
5	38	10 months	0 7	Pennsylvania	68	Wilkes-Barre, Pa	Anthracosilicosis
6	22	3 months	1 1	Wyoming, Pa	53	Wyoming, Pa	Anthracosilicosis
7	50	1 y 10 m	2 0	Mexico	79	Windhes, Pa	Coal workers pneumoconiosis
8	47	3 years	6 8	Scranton, Pa	75	Scranton, Pa	Anthracosilicosis
9	35	3 years	17·4	Nanticoke, Pa	58	Nanticoke, Pa	Silicosis
10	51	20 years	8 3	Scranton, Pa	72	Bridgeport, Ct	Pulmonary silicosis
11	40	16 years	21 8	Nanticoke, Pa	68	Bridgeport, Ct	Pneumoconiosis
12	31	30 years	51 4	Nanticoke, Pa	62	Bridgeport, Ct	Pneumoconiosis

CONCLUSION

The authors concluded that if it is accepted that the high mortality from all causes (including respiratory cancer) in men employed for less than 1 year was probably due to some form of selection, then the results suggest that the adverse health effects of employment in this chrysotile friction products plant were small.

6.   Workers[73] in an asbestos textile factory, which were exposed to dust levels higher than current standards permit, were divided into 5 cohorts on the basis of duration and period of work in scheduled areas (Table 1).

Table 1 *Number of workers in each exposure cohort*

Cohort	Sex	Years in scheduled areas	Years in scheduled areas before 1933	Number	Person-years observation
1	Male	20 or more	10 or more	60	1000
2	Male	20 or more	Less than 10	74	1377
3	Male	20 or more	None	263	2040
4	Male	10-19	None	470*	724
5	Female	10 or more	None	234	4380
Total				1405	14073

*Including the 263 men in cohort 3 before they had completed 20 years in scheduled areas.

The number of deaths in each group attributed to lung cancer (includes mesothelioma), other cancers, respiratory diseases and other causes are compared in Table 2 with the number expected, which is calculated from national death rates by 5-year age-groups.

Table 2 *Number of deaths observed and expected, by exposure cohort and cause*

Cause of death	Cohort	Observed deaths	Expected deaths	Ratio observed/expected	Probability of observed number or more
Lung cancer and pleural mesothelioma (162, 163 and 238)	1	13 (2)	1.48	10.1	<0.001
	2	10 (5)	3.03	3.3	0.001
	3	6 (2)	3.36	1.6	0.111
	4	24 (2)	12.02	1.9	0.003
	5	3 (1)	0.92	3.3	0.066
Other cancers (140-239)	1	6	4.14	1.6	0.080
	2	3	4.39	0.7	0.001
	3	6	6.61	0.9	0.007
	4	11	17.78	0.6	0.966
	5	6	7.43	0.8	0.773
Respiratory disease (460-519)	1	16	3.06	3.0	<0.001
	2	7	4.12	1.6	0.147
	3	6	3.93	1.3	0.246
	4	23	17.30	1.3	0.105
	5	4	1.81	2.3	0.110
Other causes	1	27	18.29	1.3	0.083
	2	23	17.89	1.3	0.130
	3	36	26.37	1.4	0.067
	4	69*	75.08	0.9	0.773
	5	11	13.34	0.8	0.776
All causes	1	66	27.78	2.3	<0.001
	2	43	29.93	1.5	0.002
	3	30	44.67	1.3	0.002
	4	127	122.94	1.0	0.300
	5	24	23.70	1.0	0.083

*Coded according to the eighth revision of the International Classification of Disease (World Health Organisation, 1967).
1Deaths due to pleural mesothelioma are included in the observed number for lung cancer and also given separately in parentheses.
*Includes one case in which a pleural mesothelioma was a contributory cause of death.

Lung cancer mortality in the area of the factory was lower than the national average among men (SMR = 87) and similar for women (SMR = 104) in 1959-63.

Workers first exposed before 1933 (cohorts 1 and 2) suffered a marked excess of lung cancer and respiratory disease, particularly those with 10 or more years' exposure prior to 1933. There is also some excess mortality from lung cancer and mesothelioma (36 observed, 19.3 expected; p   0.001) and respiratory disease (35 observed, 25 expected; p = 0.03) in those who entered after 1933 (cohorts 3, 4 and 5 combined), although the excess is very much less than in the first 2 cohorts. There were 16 deaths attributable to gastrointestinal cancers compared with 15.70 expected. No excess for any of these rubics approached statistical significance in any cohort, and no peritoneal mesothelioma was reported. In order to

distinguish between exposures of 1933 and after 1950, observed and expected deaths for those first exposed between 1933 and 1950, and those first exposed later were determined (Table 3). There is clear evidence of some excess of lung cancer and respiratory deaths among those first exposed between 1933 and 1950, although very much less than in cohorts 1 and 2. There have been few deaths among those first exposed after 1950, but there still appears to be an excess of deaths from lung cancer 15 or more years after first exposure (5 observed, 1.86 expected; p = 0.04)).

Table 3 *Number of deaths observed and expected, by date of first exposure*

Cohort	Cause	Observed deaths‡	Expected deaths	Ratio observed/expected	Probability of observed number or more
Men and women first exposed 1933-1950 (n = 646)	Lung cancer				
	Other cancers				
	Respiratory				
	Other causes				
Men and women first exposed 1951 or later (n = 347)	Lung cancer				
	Other cancers				
	Respiratory				
	Other causes				

This is shown in Table 4, in which deaths from lung cancer including pleural mesotheliomas in these groups are distributed according to the time since first exposure; the relative risk increases progressively with time since first exposure in both groups.

Table 4 *Observed and expected deaths from lung cancer by date of first exposure and time since first exposure*

Cohort	Period since first entering scheduled area (years)	Observed deaths†	Expected deaths	Ratio observed/expected	Probability of observed number or more
Men and women, first exposed 1933-1950 (n = 646)	0-14				
	15-19				
	20 and over				
	Total				
Men and women first exposed 1951 or later (n = 347)	0-14				
	15-19				
	20 and over				
	Total				

The 6 workers first exposed after 1950 who died of lung cancer were all smokers; five worked in areas where dust levels were high in 1951 and one may have had previous exposure from another job. No mesotheliomas have occurred in this group although in view of the long latency period none would be expected yet. Asbestosis was found in 3 of the 6 cases. The numbers are too small for the magnitude of the excess of lung cancer in those first employed after 1950 to be estimated with any precision. Dust levels associated with various processes are shown in Table 5.

Table 5 *Dust levels accompanying different textile processes, 1953-1974*

Department	Process	Yearly mean dust levels				
		Castle thermal precipitator (particles per ml)		Long running thermal precipitator or millions membrane (fibres per ml)		
		1953	1969	1961	1969	1974
Filtering	Mixing	380	—			—
	Opening	440	—	now totally enclosed		
	Bag filling	—	110	5	3	3
	Mechanical bagging	—	120	4	3	3
Carding	Fine cards	380	380	5	5	3
	Medium cards	610	480	6	6	3
	Coarse cards	1140	620	7	5	4
	Shuttand silver cards	400	380	5	5	4
Spinning	Fine spinning	170	110	4	3	3
	Roving frame	310	120	3	3	4
	Intermediate frame	330	160	3	4	1
Weaving	Beaming	190	230	3	3	<1
	Pim winding	330	120	3	3	<1
	Cloth weaving	180	140	3	3	<1
	Lining weaving	130	110	2	1	<1
Packing	Packing	140	80	6	4	3

CONCLUSIONS:

Results for Groups 1 and 2 were similar to that of Doll (1955)[101] and Knox, et al. (1968)[102], in that there was a 10-fold increase in risk of lung cancer in Group 1 and a three-fold increase for Group 2.

There was approximately a 2-fold increase in lung cancer for Group 3 and no increase for cancer of other sites. A 2-fold increase in lung cancer was seen in Group 4 and a 3-fold increase in Group 5. No increase in gastrointestinal cancer was observed for all groups combined.

7. In a study[84] of asbestos textile factory workers, excess lung cancer mortality has been reported. Observed and expected deaths due to lung cancer, other cancers, respiratory disease and other causes are shown in Table 1, together with death rates for asbestosis and mesothelioma. In men first exposed before 1951 (cohort 1), there were 22 deaths due to lung cancer compared with 13.85 expected (P[1] 0.05) 20 or more years after first exposure; while in later employees (cohort 2) there were 8 compared with 1.62 expected (P 0.0   If it were assumed that all men not known to have died or e   ed were alive on the follow-up date, 31 December 1978, these o   d/expected ratios would become 22/14.12 (cohort 1; P 0.05) and 8/1.75 (cohort 2; P 0.001), respectively.

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[1]All significant levels are one-sided.

Table 1: Mortality experience of 679 male asbestos textile workers

[illegible]	[illegible]	Man-years	Lung cancer		Pleural mesothelioma		Other cancers		Asbestosis		Other respiratory disease		[illegible]	
			O	E	O	rate ×10³	O	E	O	rate ×10³	O	E		
[illegible]	10-	[illegible]	[illegible]	1.41	[illegible]	[illegible]	1	2.[illegible]	[illegible]	[illegible]	1	[illegible]	[illegible]	[illegible]
[illegible]	15-	1460	4	[illegible]	[illegible]	[illegible]	[illegible]	1.[illegible]	[illegible]	1.1	3	[illegible]	7	[illegible]
n [illegible]	20-	1760	3	3.97	1	[illegible]	6	5.[illegible]	[illegible]	1.1	1	[illegible]	[illegible]	[illegible]
	25-	1496	10	4.54	[illegible]	1.3	6	5.[illegible]	[illegible]	1.3	9	[illegible]	[illegible]	[illegible]
	30-	[illegible]	8	3.14	[illegible]	[illegible]	5	4.[illegible]	[illegible]	[illegible]	4	[illegible]	[illegible]	[illegible]
	35+	507	1	[illegible]	[illegible]	1.9	4	[illegible]	[illegible]	3.0	5	1.[illegible]	[illegible]	[illegible]
	Total	[illegible]	[illegible]	[illegible]	7	-	[illegible]	[illegible].07	10	-	26	[illegible]	[illegible]	[illegible]
1951 or later	10-	[illegible]	1	1.30	0	[illegible]	0	1.62	0	[illegible]	1	[illegible]	[illegible]	[illegible]
[illegible]	15-	[illegible]	1	1.74	0	[illegible]	3	2.16	0	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
n [illegible]	20-	[illegible]	7	[illegible]	0	[illegible]	[illegible]	1.64	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	46	[illegible]	[illegible]	0	[illegible]	1	[illegible]	0	[illegible]	[illegible]	[illegible]		[illegible]
	Total	[illegible]	12	4.65	[illegible]	-	[illegible]	5.80	0	-	1	[illegible]	[illegible]	[illegible]

The excess mortality 20 or more years after first exposure due to nonmalignant respiratory disease in men first employed before 1951 (28 observed, 18.63 expected; P 0.01) was largely accounted for by deaths specifically attributed to asbestosis. The observed incidence of mesothelioma rose steadily from 0.0006 per annum at 20-25 years after first employment to 0.004 per annum beyond 35 years among pre-1951 employees. The absence of deaths due to asbestosis or mesothelioma in later employees may be due to their relatively short period of follow-up rather than to a substantial reduction in risk. Applying the incidence rates for asbestosis and mesothelioma observed in cohort 1 in successive five-year periods to the corresponding man-years of observation of cohort 2, only 1.9 deaths due to asbestosis and 0.4 due to mesothelioma would so far have been expected, and it has been reported that 10 men in cohort 2 have already been certified as having asbestosis (Berry et al., 1979)[103]. There is no evidence of excess mortality due to any other cause of death: 14 deaths (12.60 expected) were attributed to gastrointestinal cancers (ICD nos. 151-154) in the two cohorts, including 6 (5.38 expected) 25 or more years after first exposure; and no peritoneal mesotheliomas have occurred.

Exposure data are shown in Table 2.

Table 2. Previous and revised estimates of mean dust levels in fibres/ml (weighted by the number of men at each level) in selected years

	1936	1941	1946	1951	1956	1961	1966	1971	19[illegible]
Previous estimates corresponding to early fibre counts (Peto et al., 1977)	13.3	14.5	13.2	10.8	5.3	5.2	5.4	3.4	-
Revised estimates corresponding to modern counting of static samples*	No measurements prior to 1951			32.4	23.9	12.2	12.7	4.[illegible]	[illegible]

* These estimates are based on preliminary data on 126 men first employed between 1951 and 1955, and should be regarded as provisional.

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The authors stated that the average dust levels were in the region of 30 f/ml in 1951 and remained high until about 1974. It was further stated that levels prior to 1951 were probably not much higher than this:

The cumulative exposures of the eight men first exposed in 1951 and who later died of lung cancer 20 or more years after first exposure are compared with those of unaffected controls (Table 3). The analysis is based on cumulative exposure up to the end of 1971, and the control group consisted of 42 men born between 1901 and 1914 who entered the factory between 1951 and 1955. The eight lung cancer cases all entered the factory before 1956 and died in 1972 or later; all but one, who was born in 1925, were within the age range of the controls, and all were cigarette smokers. There is no evidence that their exposures were anomalously heavy, although this may merely reflect the inevitable inaccuracy of individual exposure estimates.

Table 3. Estimated exposures of men first exposed between 1951 and 1955 .

	Cumulative exposure (fibres/ml-years) to December 1971						
	0-	100-	150-	200-	300-	400+	Total
Men dying from lung cancer over 20 years after first exposure	1	1	0	4	1	1	8
Other men born 1901-1914	2	4	4	14	9	9	42

The observed relative risk for lung cancer 20 or more years after first exposure in post-1950 employees was 4.9 (8 observed, 1.62 expected; 95% confidence limits, 2.1-9.7). This is significantly higher (P = 0.01) than that observed in men entering between 1933 and 1950 (22 observed, 13.85 expected); but, as the majority of pre-1951 employees in this study were still employed in 1951, it seems likely that this apparently marked increase in risk is largely due to chance. The eventual relative risk for lung cancer among men with estimated cumulative exposures of about 200-300 fibres/ml-years (the order of magnitude of the average exposures of men first employed in 1951 or later (Table 3)) is therefore probably between 2 and 3. This is in reasonably close agreement with an earlier analysis (Peto, 1978)[109], which was based on the assumption that the relative risk would be about 2 in men who had suffered cumulative exposures of about 200 fibres/ml-years and indicated that lifelong exposure to 2 fibres/ml might eventually cause lung cancer in about 4% of men.

CONCLUSION:

The risk of lung cancer 20 years after exposure in post-1950 workers was 4.9 (8 obs. vs. 1.6 exp.), which is significantly higher than in workers initially exposed in 1933-1950 (20 obs. vs. 13.8 exp.). A relative risk of 2 to 3 for lung cancer among men with cumulative exposures of 200-300 (fibers/cm^3)(yrs.) was estimated. No clear-cut gradient in risk of lung cancer was associated with increased exposure, suggesting that exposure estimates may be imprecise.

8. Chrysotile textile workers (South Carolina)[85] were studied to investigate the risk of exposure to this asbestos-type mineral.

The mortality and exposure data were analyzed in two ways. The first followed the orthodox man-years life table approach of Hill[104] and others, whereby standardized mortality ratios (SMRs) are derived from comparison of observed numbers of deaths with numbers expected from mortality rates in a standard population. In this case age-, sex-, race (colour)-, and year-specific rates for South Carolina were used. The second approach, essentially internal and case-control in type, followed the Mantel-Haenszel (or log rank) procedure,[105] yielding relative risks from entirely intracohort comparisons. In calculating SMRs a "lag time" of 10 years before death (or end of 1977) was imposed in determining exposure, and only deaths 20 years or more from first employment were included. In the Mantel-Haenszel analysis the same exclusions were applied, controls being selected from all other members of the cohort of the same sex and colour (black or white) who met the following criteria: (1) alive at death of case, (2) same year of birth, if in or after 1900, or within five years if before 1900, (3) within five years of date of first employment, before or after 1938. The statistical significance of differences between observed and expected numbers in this analysis and for departures from linearity were calculated as X^2 values by the method of Peto and Pike.[106] Lines were fitted to exposure-response results by Liddell using the method of Hanley and Liddell (to be published).

Estimates of dust concentration in millions of particles per cubic feet (mppcf) and duration of exposure in years were established for each worker. Tables 2 and 3 give exposure estimates.

Table 2 *Estimated average prevailing dust concentrations (mppcf) in main departments. 1930-71)*

	1930		1940		1950		1960		1970
Preparation		3·5	•	2·0		1·0		•	0·8
Carding	3·1	•	1·5		•	1·2	•	0·9	
Spinning	3·5		•·	2·0		•		1·6	
Winding	2·8	•	1·7		•		1·1		
Twisting	6·1		4·0		•	1·1			
Weaving	2·1	•	1·5		•		•	1·2	
Finishing and inspection	1·4		•	1·0	•	0·8		•	0·5

*Apparent improvement usually associated with technical change

Table 3. *Age at start, duration of employment, and dust exposure (men only)*

	Length of gross service (years)				
	<1	1, <5	5, <20	⩾20	Total
No	950	574	421	465	2410*
Average age at start (years)	25·6	25·9	26·5	25·2	25·77
Gross service (years)	0·39	2·43	10·50	31·86	8·71
Net service (years)	0·37	1·81	7·55	29·51	7·59
Average dust concentration (mpcf)	2·11	1·86	1·67	1·23	1·80

*Excluding five whose employment histories were incomplete

Mortality of the males of known age shown by age and cause is presented in Table 1.

Table 1 *Male deaths by age and certified cause*

Cause of death (ICD code)	Age at death			Total
	<45	45–64	⩾65	
All causes	178	502	177	857
Malignant neoplasms:				
Lung (162–164)	1	47	18	66
Oesophagus and stomach (150–151)	0	13	2	15
Colon and rectum (152–154)	2	3	4	9
Other abdominal (155–159)	0	10	2	12
Larynx (161)	0	2	1	3
Other (140–48, 160, 165–205)	6	23	12	41
Heart disease (400–443)	38	189	70	297
Respiratory tuberculous (001–008)	8	4	2	14
Other respiratory (470–522; 525–527)	10	27	11	48
Pneumoconiosis (523–4)	2	12	7	21
Cerebrovascular (330–334)	5	30	21	56
Accidents (800–999)	67	42	3	112
Other known causes	24	89	19	132
Causes not known	15	11	5	31

Table 4 summarizes the mortality experience based on the modified life table analysis. Overall, the SMR (all causes) is 27% above expectation and perhaps twice that in men employed 5 years or more.

Table 4 *Male deaths 20 years after first employment, by cause, in relation to duration of service*

Cause of death*	Length of gross service (years)									
	<1		1 <5		5, <20		⩾20		Complete cohort	
	O	SMR	O	SMR	O	SMR	O	SMR	O	SMR
All causes	159	107·4	113	122·7	120	156·1	178	136·7	570	127·4
Malignant neoplasms:										
Respiratory	8	78·2	10	163·9	15	304·1	26	317·3	59	199·5
Abdominal	6	107·9	5	146·4	7	240·3	8	151·4	26	151·7
Other	12	130·2	7	124·9	9	195·9	7	46·2	35	127·5
Heart disease	69	108·9	34	87·6	45	141·7	70	120·8	218	113·7
Respiratory tuberculosis	1	231·8	1	347·8	1	307·9	1	131·5	4	222·8
Other respiratory	3	53·3	3	85·6	2	78·3	27	557·5	35	207·3
Pneumoconiosis	10	—	(1)	—	(0)	—	(20)	—	(20)	—
Cerebrovascular	9	83·0	14	193·0	6	107·3	9	76·2	38	107·2
Accidents	18	121·2	8	89·7	5	75·8	9	85·0	40	97·0
Other known	30	116·9	28	175·5	23	177·7	21	92·3	102	132·4
Not known	3		3		7		0		13	

*As in table 1 except that ICD codes 160–164 are here grouped under "respiratory" malignant neoplasms and the "other respiratory" category includes only bronchitis, pneumonia, and pneumoconiosis (ICD 490–502, 523–4)

As there is (a) a 7% excess of deaths even in men employed less than one year, unexplained by any asbestos related cause of death, and (b) a 32% overall excess in deaths of "other known causes," the SMRs are probably somewhat inflated, mortality in South Carolina having presumably provided an imperfect basis for comparison. Much of the excess, however, is clearly attributable to respiratory cancer, pneumoconiosis, and gastrointestinal cancers. Table 5 shows the cohort mortality, related to dust exposure. There is a steady gradient from 115.5 to 264.4 for mortality (all causes) and a much steeper slope for respiratory cancer and also for selected other respiratory diseases (which include pneumoconiosis). No clear trend is apparent in the other diagnostic categories.

Table 5 *Male deaths 20 years after first employment, by cause, in relation to dust exposure (mpcf.v) accumulated to 10 years before death*

Cause of death	Dust exposure (mpcf v)									
	<10		10 <20		20 <40		40 <80		≥80	
	O	SMR	O	SMR	O	SMR	O	SMR	O	SMR
All causes	376	115.5	55	125.5	63	156.9	43	170.8	33	264.4
Malignant neoplasms:										
Respiratory	31	143.1	5	182.7	8	304.2	7	419.5	8	1031.9
Abdominal	14	114.9	4	231.6	4	247.0	4	383.6	0	—
Other	28	140.0	3	109.2	1	44.9	0	—	3	383.5
Heart disease	143	103.5	28	143.6	29	166.6	10	88.6	8	149.9
Respiratory tuberculosis	3	264.4	0	—	0	—	1	634.4	0	—
Other respiratory:	8	65.9	2	119.5	6	421.7	13	1407.8	6	1296.0
Pneumoconiosis	(0)	—	(0)	—	(3)	—	(9)	—	(8)	—
Cerebrovascular	29	115.3	2	50.0	4	124.4	2	93.4	1	99.8
Accidents	31	99.2	2	54.1	5	152.9	1	49.4	1	120.0
Other known	79	140.4	9	116.9	4	630	5	111.5	5	263.3
Not known	18		0		2		0		1	

Table 6 shows the results of the posteriori Mantel-Haenszel analysis for certain diagnostic groups only. The number of deaths included in this analysis falls short of those used in tables 4 and 5--for example, 490 compared with 570 from all causes; in the remainder no matching control could be found. There is clear confirmation of a statistically significant linear trend in lung cancer, pneumoconiosis, and deaths (all causes) but no convincing association for the abdominal cancers.

One death ascribed to mesothelioma was found--a man born in 19?? who died in 1967. He was first employed at the plant in 1925, worked as a mule spinner from 1933 to 1955 and as an oven helper until he left in 1965. The tumour was stated to be peritoneal but there was no necropsy.

Table 6 — Dust exposure in male deaths from selected cancers and controls (Mantel-Haenszel analysis)

Cancers	Dust exposure (mpcf) accumulated up to 10 years before death of case					Chi square	
	< 10	10-19	20-39	40-79	≥80	Difference	Cancers
Pneumoconiosis (ICD 523)						17.36	10.80
Deaths	0	0	3	10	4		
Expected	3.1	2.2	1.8	4.1	3.7		
Relative risk	—	—	—	—	—		
Lung cancer (ICD 162.4)							24.08	20.43
Deaths	55	3	8	7	6		
Expected	52.4	5.4	5.3	3.7	2.2		
Relative risk	1	0.98	2.95	4.32	15.00		
Abdominal cancer (ICD 150-9)							4.06	2.03
Deaths	13	4	2	4	0		
Expected	15.5	2.9	2.5	2.1	0		
Relative risk	1	1.64	1.30	7.63	—		
All causes							14.42	10.63
Deaths	381	45	53	37	24		
Expected	348.0	46.2	46.5	32.4	15.0		
Relative risk	1	1.05	1.43	1.51	2.17		

This study shows that the relationship of lung cancer mortality to accumulated dust exposure is virtually linear.

The pattern of mortality in this cohort of chrysotile textile workers is similar to that reported for Quebec chrysotile miners and millers, particularly those employed at Thetford Mines.[57] Overall, the SMRs for the factory workers are somewhat higher than for the miners (perhaps due in part to questions of comparability with the reference populations). There is the same scarcity of deaths attributed to mesothelioma and, in both cohorts, the relationship of lung cancer mortality to accumulated dust exposure is virtually linear. It is only when actual levels of exposure are examined that the astonishing difference between the experience of these two chrysotile-exposed cohorts is seen. This is illustrated in Fig. 1 where, to facilitate comparison, the SMRs in both cohorts are based on exposure accumulated to age 45.[57] In fact, the slope of the exposure-response line for lung cancer in the textile workers is 50 times more steep than that observed in miners and millers. This confirms almost exactly the findings of Dement et al.[61] in their study of a cohort from the same plant; the agreement is very close (see Fig. 2). The data shown in this graph are based on mortality for white men only, 15 years or more from first employment and therefore differ somewhat from the figures in Table 5.

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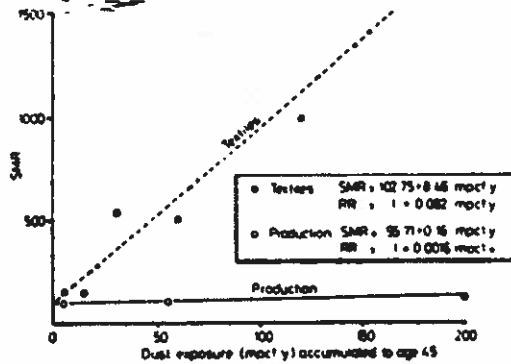
Fig 1 *Respiratory cancer SMRs in relation to dust exposure accumulated to age 45 in chrysotile production and textile manufacture*
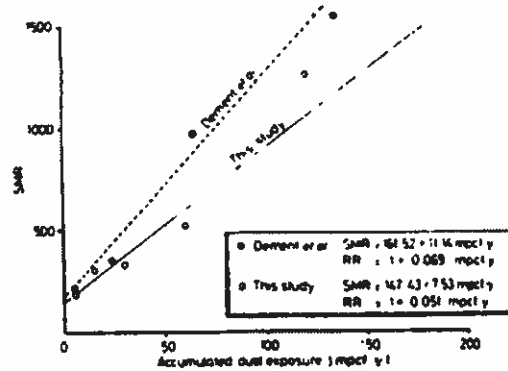
Fig 2 *Respiratory cancer SMRs in white men 15 years or more from first employment in relation to accumulated dust exposure. Comparison of this study and that of Dement et al*

CONCLUSION:

Various reasons were discussed to determine whether the differences observed were due to errors in exposure estimates, etc. Assuming errors, the difference remains at least 10 fold.

9. Another cohort[86] of chrysotile asbestos factory (textile) workers in a Pennsylvania plant was studied, which included those employed during 1938-1959 for at least one month. Crocidolite and amosite were used at this plant also. Exposure data are shown in Tables 2 and 3.

Table 2 *Estimated average prevailing dust concentrations (MPCF) in main departments 1930-70*

	1930		1940		1950		1960		1970
Textile									
Preparation	15 0 *	14 6	*	3-5	*		2 0	*	1 5
Carding	12-0 *	9-3	*	3 2			*2 0	*	1 6
Spinning	7 0		*	2 4			*	1 8	*	1 5
Twisting	7 2		*	4-0		*	1 8	*0 5 *	3 1
Winding	3 0		*	1-5		*			0-8
Cloth weaving	7 0	*3-4	*			3-0			
Tape weaving	7 3	*3 1	*		1 4		*	1 2	
Felted tape	2 0		*	1 0	*		0-5		
Rope	4 0		*	3 5	*		1 2	*	0 5
Friction:									
Woven brakes			2 0	1 5		1 0		0 7	
Extruded brakes			2-0	1-5		1 0		0-8	
Dry mix			10-0	6-0		4-0		3-8	
Cleaning			2-0	1 5		1 5		1-5	
Brake finishing			2 0	1 5		1 0		0 7	
Sanding and finishing			2 0	1 5		1 0		0 7	
Finishing and shipping			0 5			0-2		0 2	
Packings, gaskets			1 3	1 3		0-6		0 7	
Maintenance, etc			0 5	0 5		0-2		0-2	

*Asterisks shown against textile processes indicate approximate date of improvements usually associated with technical change Figures for friction and other departments are estimates for each decade

Table 3 *Age at start, duration of employment, and dust exposure (male only)*

	Length of gross service				
	<1	1, <5	5, <20	≥20	Total
No	1248	906	855	1013	4022*
Average age at start (years)	28-80	24-30	30-77	27-22	28-92
Gross service (years)	0-40	2 39	11-01	30-63	10-71
Net service (years)	0-38	1-87	8-06	27-51	9-18
Average dust concentration (mpcf)	2 60	2-40	2-73	1 58	2-32

*Excluding two whose employment histories were incomplete.

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Mortality was analyzed as in #8 above, using Pennsylvania death
rates for reference. Mortality data by age and certified cause are
presented in Table 1.

Table 1   Male deaths by age and certified cause

Cause of death (ICD code)	Age at death			Total
	<45	45-64	>65	
All causes	191	667	534	1392
Malignant neoplasms.				
Lung* (162-164)	3	49	18	70
Oesophagus and stomach (150-151)	1	7	6	14
Colon and rectum (153-154)	2	21	12	35
Other abdominal* (155-159)	3	16	5	24
Larynx (161)	0	0	0	0
Other* (140-148, 160, 165-205)	16	57	40	113
Heart disease (400-443)	43	285	245	573
Respiratory tuberculous (001-008)*	5	4	2	11
Other respiratory (470-522, 525-527)	6	17	25	48
Pneumoconiosis (523-524)	2	48	24	74
Cerebrovascular (330-334)	3	33	44	80
Accidents (800-999)	74	44	20	138
Other known causes*	23	73	80	176
Cause not known	10	13	13	36

*In 13 cases in these categories, mesothelioma was given as the cause of death, in one death ascribed to asbestoss, mesotheloma was also
mentioned.

The SMR for all causes of death was 109.0. Those employed for less
than 1 year had a SMR of 87.2, and those who had worked 20 or more
years, 127.2.   (Table 4)

Table 4   Male deaths 20 years after first employment, by cause, in relation to length of service

Cause of death*	Length of gross service years									
	<1		1, <5		5, <20		>20		Complete cohort	
	0	SMR	0	SMR	0	SMR	0	SMR	0	SMR
All causes	171	87.2	154	106.2	187	104.5	383	127.2	895	109.0
Malignant neoplasms										
Respiratory	9	64.6	3	32.9	14	128.8	27	158.9	53	105.0
Abdominal	8	72.9	11	133.7	11	105.9	24	131.3	54	112.7
Other	19	133.4	16	152.0	15	118.5	32	155.3	82	141.1
Heart disease	77	92.7	77	125.1	78	100.2	153	115.7	385	108.5
Respiratory tuberculosis	0	-	1	133.4	0	-	2	67.3	3	51.7
Other respiratory	4	54.2	2	38.1	11	161.0	50	442.4	67	215.0
Pneumoconiosis	(2)	-	(1)	-	(10)	-	(46)	-	(59)	-
Cerebrovascular	7	54.9	10	106.5	10	77.7	20	87.6	47	81.2
Accidents	13	117.5	15	181.1	8	87.2	9	60.1	45	103.5
Other known	30	75.2	15	52.4	37	103.0	62	103.1	144	87.2
Not known	4		4		3		4		15	

*As Table 1 except that ICD codes 160-164 are here grouped under "respiratory" malignant neoplasms and the "other respiratory"
category includes only bronchitis, pneumonia, and pneumoconiosis (ICD 490-502, 523-4)

Malignant neoplasms, heart disease, and "other respiratory" disease
were mainly responsible for the higher SMR in these long term
workers. The other respiratory category included bronchitis and
pneumonia (ICD 470-502) and pneumoconiosis (ICD 523-4) and was
chosen for study because expected figures for pneumoconiosis alone
were not available. Table 5 shows SMRs by cause and by accumulated
dust exposure. The SMR for all causes rose steadily from 93.1 for

men with an exposure at under 10 mpcf.y to 215.2 in the highest
category (80 mpcf.y). Respiratory, abdominal, and other malignant
diseases and the non-malignant other respiratory group all
contributed to this rising trend. On 14 death certificates a
diagnosis of mesothelioma was specified: 10 were pleural tumours
and four peritoneal. These deaths occurred in the period 1960-75.
One (in 1960) was 16 years after first employment; the remaining 13
occurred 25-53 years after first employment. Two of the deaths from
mesothelioma had been given the ICD code 199 (malignant neoplasms of
other and unspecified sites); another 30 deaths 15 or more years
after first employment were given the code 199. Seventeen of these
30 deaths occurred before 1965, the year after which most of the
deaths from mesothelioma occurred. The diagnosis given in many of
these cases was consistent with an unrecognized peritoneal
mesothelioma.

Table 5 *Male deaths 20 years after first employment, by cause, in relation to dust exposure (mpcf.y) accumulated to 10 years before death*

Cause of death* (See table 4)	Dust exposure (mpcf.y)									
	<10		10 < 20		20 < 40		40 < 80		≥80	
	O	SMR	O	SMR	O	SMR	O	SMR	O	SMR
All causes	470	93 1	86	82 1	130	125-6	105	174-9	104	215 2
Malignant neoplasms										
Respiratory	21	66-9	5	83-6	10	156-0	6	160-0	11	416-1
Abdominal	26	90-2	8	130-5	5	79 7	8	218-8	7	237-2
Other	47	130-4	5	68 5	11	148-6	7	164-7	12	372-8
Heart disease	221	102-7	41	89-2	60	130-6	34	130-5	29	108-5
Respiratory tuberculosis	1	34-3	0	—	—	—	1	169-7	1	163-6
Other respiratory	8	43 6	5	122-0	10	263-0	14	623-3	30	1689-2
Pneumoconiosis	(4)	—	(1)	—	(9)	—	(9)	—	(36)	—
Cerebrovascular	27	78-3	1	13 3	10	133-5	8	187-2	1	29-3
Accidents	33	120 1	3	56 2	1	18-6	6	193-9	2	91-0
Other known	74	73-3	17	80-0	23	109-7	21	172-2	9	97-8
Not known	12		1		0		0		2	

The Mantel-Haenszel (log rank) analysis[105] (table 6) bore out the
exposure-response relationships observed in Table 5. There is a
small shortfall (5% overall) between the numbers of cases used in
the analysis and in the man-years analyses presented in Tables 4
and 5. The deficiency is explained by failure to find matching
controls for every selected case.

Table 6 Dust-exposure in male deaths from selected causes and controls (Mantel-Haenszel analysis[a])

	Dust exposure (mpcf.y) accumulated up to 10 years before death of case					Chi square Difference	Linearity
	<10	10 < 20	20 < 40	40 < 80	≥80		
Pneumoconiosis (ICD 523)						39·56	39·17
Deaths	3	4	10	11	28		
Expected	14·6	8·1	10·9	8·1	14·3		
Relative risk	1	4·04	13·72	14·93	37·90		
Lung cancer (ICD 162-4)						5·77	4·98
Deaths	20	4	10	6	11		
Expected	24·4	5·2	8·0	5·6	7·7		
Relative risk	1	0·83	1·54	2·90	6·82		
Abdominal cancer (ICD 150-9):						3·23	1·09
Deaths	26	8	5	8	7		
Expected	28·8	6·8	7·0	5·3	6·1		
Relative risk	1	1·15	0·66	2·45	2·85		
All causes						34·66	26·12
Deaths	451	81	121	100	99		
Expected	476·6	104·5	118·6	80·4	72·0		
Relative risk	1	0·82	1·20	1·6	2·12		

The present cohort in the Pennsylvania plant was constituted in exactly the same way as that in the South Carolina chrysotile textile plant described elsewhere.[85]

The Pennsylvania cohort was exposed to a somewhat higher average dust concentration: 2.32 mpcf compared with 1.80 mpcf in South Carolina. The mortality pattern in Pennsylvania resembled that in South Carolina in showing a rising SMR with increasing dust exposure for all causes of death, for respiratory cancer, and for pneumoconiosis. For respiratory cancer, however, the SMR for the lowest exposure group (less than 10 mpcf.y) was 115.5 in South Carolina but only 69.9 in Pennsylvania. By contrast with South Carolina, where the SMRs tended to be above 100 for causes unrelated to asbestos, and for all causes in very short-term employees,[85] the opposite was true in Pennsylvania. It seems likely that in both cohorts lack of comparability with the relevant state populations may be the explanation. Having regard for this possibility, the use of relative risks is perhaps more appropriate than SMRs for comparing the respiratory cancer mortality of the two cohorts. Table 7 shows that the relative risks of death from all causes, respiratory cancer, and pneumoconiosis in the two plants were extraordinarily similar. In both cohorts the relationships of respiratory cancer to exposure were essentially linear (figure) with slopes that were nearly identical (South Carolina, RR = 1 + 0.059 mpcf.y; Pennsylvania, RR = 1 + 0.051 mpcf.y).

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Table 7. Relative risks based on SMRs by cumulative exposure in two plants

	mpcf.y				
	<10	10 < 20	20 < 40	40 < 80	≥80
All causes:					
South Carolina plant	1·0	1·09	1·36	1·48	2·29
Pennsylvania plant	1·0	0·88	1·35	1·88	2·31
Respiratory cancer					
South Carolina plant	1·0	1·28	2·13	2·93	7·21
	(1·32)	(1·68)	(2·80)	(3·86)	(9·49)
Pennsylvania plant	1·0	1·25	2·33	2·39	6·22
	(1·26)	(1·58)	(2·94)	(3·03)	(7·87)
Bronchitis, pneumonia, and pneumoconiosis.					
South Carolina plant	1·0	1·81	6·40	21·36	19·67
Pennsylvania plant	1·0	2·79	6·03	14·29	38·74

Figures in italics are relative risks calculated from SMRs at zero exposure derived from fitted line.

Similar proportions of all deaths in the two cohorts were from malignant disease (17% in South Carolina and 18% in Pennsylvania), but the types of malignancy differed. In South Carolina respiratory cancer accounted for 47%, abdominal 25%, and other types 28% whereas in the Pennsylvania plant the corresponding proportions were reversed, 27%, 29%, and 44%. Moreover, in South Carolina no systemic relationship with exposure was seen for abdominal or other types of malignant disease whereas in Pennsylvania there was evidence of such a relationship.
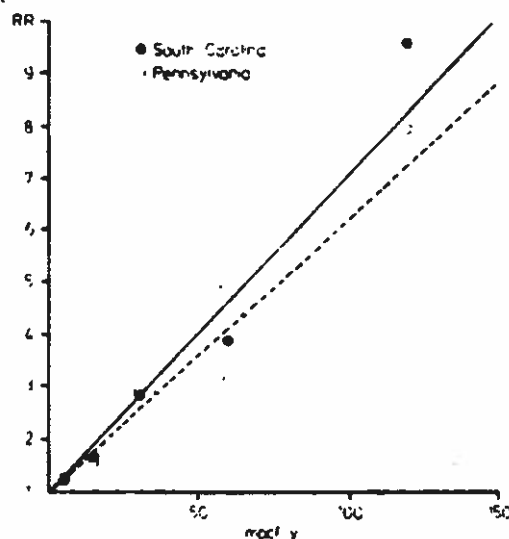
Relative risk of respiratory cancer and accumulated dust exposure in two mainly textile plants (lines fitted by F.D.K. Liddell using the methods of Hanley and Liddell)

The increased risk of mesothelioma in the Pennsylvania plant (14 cases in 1392 male deaths (1%) compared with one case in 867 (0.1%) in South Carolina) raises the question of whether the abdominal and more particularly other types of cancer included undiagnosed cases of mesothelioma. There is some support for this idea in the substantial number coded to ICD 199 (malignant disease of other and unspecified sites) and the fact that 17 of these deaths occurred before 1964 when malignant mesothelioma started to become more generally recognized. Once again there is evidence in this study of the special risk of mesothelioma associated with exposure to even quite small proportions of amphibole, in this case predominantly amosite.

CONCLUSION

The very similar exposure-response relationships for respiratory cancer and asbestosis observed in this and the South Carolina plant support the previous conclusion that the risks of these diseases in chrysotile production (mining and milling) and in textile manufacture are quite different. In the third plant studied, a friction materials plant in Connecticut, there was little or no excess risk of respiratory cancer or asbestosis.[85] This was also true in a friction materials plant in the United Kingdom.[86] Possible reasons for the striking epidemiological differences--fibre size distributions in particular--have been discussed elsewhere.[85, 107]

10. Mortality was studied[70] among asbestos-cement workers who had been hired prior to 1960 and who had been employed for a minimum of 9 years.

Table 1 gives the mortality rates for each of the three exposure groups of production workers, for the interval 20-33 years from first exposure.

Table 1 Mortality rates in the interval 20-33 years from first exposure and estimated dust exposure of three groups of workers (number of deaths in parentheses)

Cause	Exposure group			
	Group A	Group B	Group C	Ontario men[†]
	Rates (per 1000 man-years)[*]			
Mesothelioma	1.9 (1)	3.9 (2)	11.9 (6)	—
Lung cancer	13.6 (5)	26.1 (7)	11.9 (6)	1.6
Gastrointestinal cancer	0 (0)	2.5 (1)	6.0 (3)	0.6
All malignancies	17.3 (7)	35.9 (11)	31.8 (16)	4.7
Mesothelioma crude rates	2.5 (1)	4.6 (2)	11.9 (6)	—
Estimated exposure range (f-s ml)	8-69	69-121	122-420	
Estimated mean exposure (f-s ml)	44	92	180	
Standard deviation	19.4	15.8	57	

[*]Standardised to age distribution of group C
[†]Based on Ontario vital statistics 1970-4

exposure levels (in f-y/ml) were: Group A-44; Group B-92; and Group C-180.

The mortality observed among the employees was compared with the mortality predicted from Ontario population rates (Table 2). To increase the man-years of observation in each cell, the second group, listed as P + M in the table combines the experience of the production and maintenance employees, all of whom were exposed to asbestos.

Table 2   *Mortality among the factory workers compared with the population of Ontario*

Cause	Group	Years since first exposure											
		15–19			20–24			25–33			Total: 20–33		
		Obs	Exp	O/E	Obs	Exp	O/E	Obs	Exp	O/E	Obs	Exp	O/E
All causes	P	8	8·9	1	16	11·8	1·4	34	11 6	2 9	50	23 4	2 1
	P + M	11	11·9	1	22	15·5	1 4	39	15 1	2 6	61	30·6	2·0
	C	7	5·0	1·4	7	5·9	1·2	7	7 4	1	14	13·3	
All malignancies ICD. 140–209	P	2	1·9	1	9	2·8	3·2	20	2 9	6 9	29	5 7	
	P + M	2	2 5	1	11	3 7	3·0	23	3·7	6 2	34	74	
	C	3	1·1	2 7	3	1·4	2·1	1	1 8	1	4	3 2	
Lung cancer ICD 162	P	1	0·6	1	6	1 0	6·0	11	1 0	11·0	17	2 0	8·5
	P + M	1	0·8	1	7	1 2	5·8	12	1 3	9 2	19	2 5	7 6
	C	0	0·3	0	0	0·5	0	1	0·6	1	1	1 1	1
Mesothelioma ICD 163, 158, 228	P	1	-	-	2	-	-	4	-	-	6	-	-
Gastrointestinal cancer ICD. 150–154	P	0	0·5	0	1	0 7	1	2	0·7	2 9	3	1 4	2 1
	P + M	0	0·7	0	1	0·9	1	3	0·9	3 3	4	1·8	2 2
	C	1	0 3	1	1	0 3	1	0	0·4	0	1	0·7	1
Non-malignant respiratory disease ICD. 460–519	P	1	0·4	1	1	0·7	1	3	0 8	3 8	4	1 5	2·7
	P + M	1	0·6	1	3	0·9	3 3	4	1 0	4·0	7	1 9	3 7
	C	0	0·3	0	0	0·4	0	1	0 5	1	1	0·9	1
Ischaemic heart disease ICD· 410–414	P	4	3·9	1	2	4 7	0 4	5	4 6	1	7	9·3	0·8
	P + M	7	4·9	1 4	3	6·2	0 5	6	6·0	1	9	12 2	0·7
	C	3	2·1	1	1	2·4	0·4	2	2 9	1	3	5 3	0·6

P = Production workers   M = Maintenance workers   C = Unexposed workers

There were 10 deaths from malignant mesothelioma (5 pleural, 5 peritoneal) among the 58 deaths occurring in the production workers--a proportional mortality of 17% (table 3). In addition, one of the maintenance workers died of a pleural mesothelioma. All of these men had been exposed to both chrysotile and crocidolite in the pipe plant. The mean age at death of these 10 men was 51 years and none was over 60 (table 4).

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Table 3 *Mortality rates from mesothelioma and lung cancer among the production workers (based on best evidence)*

Time since first exposure (years)		Age				
		35-44	45-54	55-64	65-75	75 or more
Mesothelioma 15-33	No of cases	2	5	3	0	0
	Man-years	413	865	694	244	21·5
	Rate (per 1000 man-years)	4 8	5·8	4 3	0	0
20-33	No of cases	1	5	3	0	0
	Man-years	124	493	485	213	21·5
	Rate (per 1000 man-years)	8·0	10·1	6 2	0	0
Lung cancer 15-33	No of cases	0	0	13	6	1
	Man-years	413	865	694	244	21·5
	Rate (per 1000 man-years)	0	0	18·7	24·6	46·5
20-33	No of cases	0	0	11	6	1
	Man-years	124	493	485	213	21 5
	Rate (per 1000 man-years)	0	0	22·7	28·2	46·5
	Ontario rates (based on vital statistics 1970-4) (per 1000 man-years)	0·1	0·5	1·7	3·5	3·8

The mortality rates for mesothelioma among the production workers are displayed in table 3 as a function of age. Table 5 gives the crude incidence rates for mesothelioma among all the asbestos-exposed employees, as related to the time interval since first exposure. Peto et al.[53] have suggested that the incidence of mesothelioma follows a power function relationship with time. The data are consistent with this suggestion, with an exponent value of between three and four.

There were 20 deaths from lung cancer among the 58 deaths in the production workers--a proportional mortality of 34%. Pathological information about 17 of these 20 cases indicates four were adenocarcinomas, eight were squamous, four were small cell undifferentiated, and one was a large cell undifferentiated tumor. As a group, these men were first exposed to asbestos in this plant at an older age, and they died later in life than the men dying of mesothelioma (table 4).

Table 4 *Some characteristics of the cases of mesothelioma and lung cancer (Classified according to best evidence)*

	Mean	Range	Standard deviation
Mesothelioma (n = 10)			
Age at first exposure	25	19-32	4 3
Age at death	51	42-57	5 4
Latency (years)	25	17-30	3 8
Lung cancers (n = 20)			
Age at first exposure	39	31-52	6 4
Age at death	64	55-78	5 9
Latency (years)*	25	17-29	3 6

*Latency is the interval from first exposure to death

Table 5 *Incidence rates of mesothelioma among the production and maintenance workers exposed to asbestos*

	Time since first exposure (years)			
	15-19	20-24	25-29	30-34
No of cases	1	4	5	1
Man-years of risk	1182	1061	555	104
Incidence rate (per 1000 man-years)	0·8	3·7	9·0	9·6

CONCLUSION

Workers at this asbestos-cement factory exposed to historical dust conditions have experienced increased mortality rates from respiratory and malignant diseases. The lung cancer mortality rates

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did not increase steadily with increasing estimates of cumulative exposure; in fact, the men in Group C experienced the lowest cancer rates of all. This may have been due to the small numbers involved, to differences in smoking habits, etc. Rates of death from mesothelioma were related to the magnitude of the cumulative exposure.

The cumulative exposure among production workers was estimated (to within a factor or 3 to 5) to have been about 100 f-y/ml, and the SMR for the period after 20 years was 850. The authors concluded that the lung cancer rates, at a cumulative exposure of 100-f-y/ml, may be raised several-fold.

11. Table 1 presents observed deaths and standardized mortality ratios (SMRs) for selected causes of death for the cohort[87] of production and maintenance-service workers (1075 men) for the intervals 1941-69 and 1970-3, which correspond to the original follow-up and the update periods, and for the total follow-up period 1941-73. For the period 1941-73, this cohort had an overall mortality rate 20.4% higher than that of all United States white males. This excess is due almost entirely to cancer and diseases of the respiratory system. For cancer, the greatest excess is in cancer of the respiratory system but with some excess also in cancer of the digestive system and all other cancers. For respiratory disease, the excess is due entirely to pneumoconiosis and pulmonary fibrosis, 19 cases of which were due to asbestosis (ISC 523.2). The pattern of deaths was similar during both of the follow-up periods, although overall mortality and cancer rates were somewhat higher during 1970-3. The increase in overall mortality for 1970-3 was primarily due to a large increase in death rates for stroke. Whether this increase is in any way related to occupational exposures is unknown.

TABLE 1

OBSERVED DEATHS AND SMRs FOR SELECTED CAUSES OF DEATH BY PERIOD OF FOLLOW-UP, 1075 MEN RETIRING FROM A UNITED STATES ASBESTOS COMPANY 1941-67 AND FOLLOWED THROUGH 1973

Cause of Death	1941-73		1941-69		1970-3	
	Observed Deaths	SMR	Observed Deaths	SMR	Observed Deaths	SMR
All causes	781	120 4	616	115 8	165	141 6
Cancer (140-205)	173	159 0	138	154.5	35	179 5
Digestive (150-159)	55	137 8	46	136.1	9	147 5
Respiratory (162-163)	63	270 4	49	270 7	14	269 2
All other cancers	55	120 6	43	115.0	12	146.3
Stroke (330-334)	74	96 4	48	76.7	26	183 1
Heart disease (400-443)	321	106 5	269	108.4	52	97 7
Respiratory disease (470-527)	68	173 0	54	178.2	14	155 6
Pneumoconiosis and pulmonary fibrosis (523-525)	31	.	25	—	6	—
Asbestosis (523 2)	19	-	16	—	3	—
All other causes	113	92 5	96	94.6	17	82.5
Death certificates not located	32	-	11	—	21	—

Estimates of exposure were based on midget impinger counts expressed in million particles per cubic foot (mppcf). Five classifications were used. These were:

no exposure (0), less than 5 mppcf (2.5), 5-10 mppcf (7.5), 10-30 mppcf (20.0), 30-50 mppcf (40.0), 50 or more mppcf (62.5).

To compute cumulative dust exposure for each man, the dust level at each job and time period was multiplied by years at that job and summed across all jobs during his working lifetime. This total cumulative exposure can be thought of as mppcf-years.

TABLE 2

OBSERVED DEATHS AND SMRs FOR RESPIRATORY CANCER BY TOTAL
DUST EXPOSURE AND PERIOD OF FOLLOW-UP, 1075 MEN
RETIRING 1941-67 AND FOLLOWED THROUGH 1973

Total Dust Exposure (mppcf-years)	Number of Men	Mean Exposure (mppcf-years)	1941-73		1941-69		1970-73	
			Deaths	SMR	Deaths	SMR	Deaths	SMR
Under 125	437	62	19	197.9	15	200.0	4	190.5
125-249	224	182	9	180.0	8	200.0	1	100.0
250-499	265	352	19	327.6	13	309.5	6	375.0
500-749	105	606	9	450.0	8	470.6	1	333.3
750+	44	976	7	777.8	5	714.3	2	1000.0

Table 2 shows the relationship between total dose expressed as mppcf-years and mortality from respiratory cancer. For each dose interval, actual means are shown. These data, plotted on arithmetic paper, are also shown in Figure 1.*

*The relationship shown is not simply the result of time and the consequent fulfilling of latent period requirements. As noted in a previous paper, the dose rate makes an important contribution.[110]

There were 5 mesothelioma deaths observed in this cohort, of which 3 occurred during 1970-1973.

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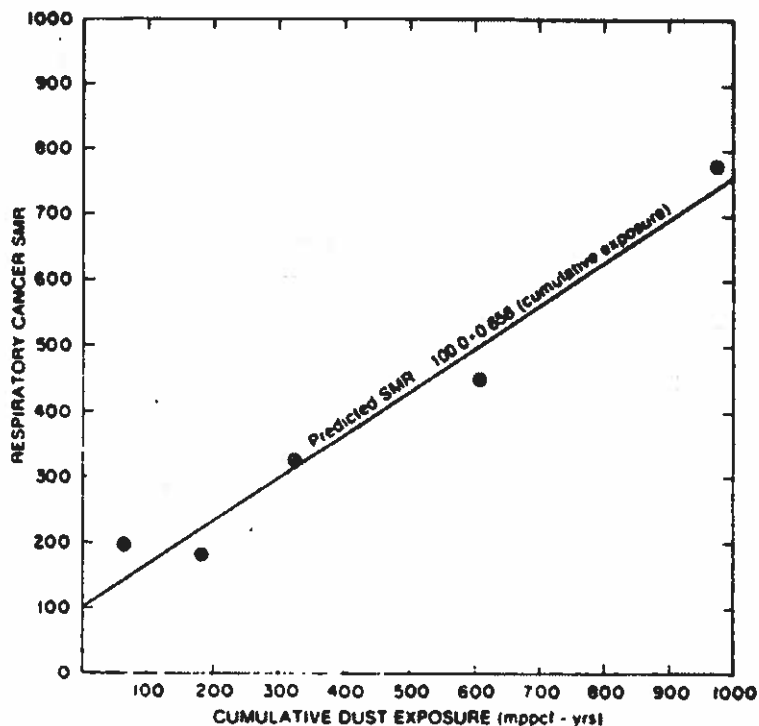
Fkat at 1 Total asbestos dust exposure and respiratory cancer mortality.

In an earlier report, it was speculated that the mathematical form
of the dose-response relationship was the cumulative normal. The
theoretical basis for this conjecture was the response curve in
bioassay experiments. Schneiderman[108] has fitted a different curve
to these data, while Peto[109] believes it is best described by a
simple linear relationship. It does appear that omitting the
Canadian data and adding 4 more years of follow-up change the
relationship and make a linear relationship more likely. By use of
the five data points from Table 1, this relationship can be
expressed by the equation: predicted SMR - 100.0 + 0.658
(cumulative exposure).

The correlation between cumulative exposure and respiratory cancer
SMR is 0.982. This prediction line is superimposed in Figure 1.

CONCLUSION

Respiratory cancer risk increased as the quantitative exposure level
increased. The SMR for the lowest level was 2.0; for the highest
level, 7.8.

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The effects of asbestos exposure with respect to lung cancer risk continued well past the termination of exposure.

The study population of retirees are "survivors," and mortality experience may not reflect actual risks associated with asbestos exposure. Most likely, risks were underestimated.

12. Mortality of asbestos factory workers exposed to crocidolite, chrysotile, and/or amosite in the production of textiles or insulation materials has been reported.[64] The levels of exposure were reported as follows:

(1) before 1945 the dust levels in certain jobs were said to average 20 fibers/ml or higher;

(2) jobs classified as "low-moderate" were probably 5-10 f/ml;

(3) in non-production jobs and some departments the levels were below 5 f/ml;

(4) after 1955, many areas were probably above 2 f/ml.

Laggers were considered separately.

The male cohort consisted of 4600 men and 922 women. There have been 775 deaths among the male workers. An analysis of the 545 deaths that occurred among workers, excluding laggers, who had been followed for 10 years or longer is presented in Table 1. Asbestos-related disease is rarely if ever manifest in those dying within 10 years of first exposure. In the Tables, the deaths from mesothelial tumors are given in parentheses but are included in the total number of observed deaths in any particular diagnostic category.

TABLE 1

MORTALITY EXPERIENCES OF MALE FACTORY WORKERS

	Exposure Category							
	Low to Moderate				Severe			
	<2 Years (884)		>2 Years (554)		<2 Years (937)		>2 Years (512)	
Cause of Death	Observed	Expected	Observed	Expected	Observed	Expected	Observed	Expected
All causes	118(4)	118.0	89 (7)	95.3	162°(16)	122.2	176°(19)	102.5
Cancers of lung and pleura (ICD 162, 163)	17(3)	11.01	16†(1)	9.0	31°(6)	12.8	56°(7)	16.4
Gastrointestinal cancer (ICD 150-158)	10	9.0	9 (4)	7.3	20‡(6)	9.5	19‡(8)	8.2
Other cancers	6	7.4	8 (1)	5.8	16‡(3)	7.9	16°(4)	6.3
Chronic respiratory disease	19	17.5	16	14.7	20 (1)	17.6	22‡	15.9

°p <0.001
†p <0.05
‡p <0.01.

There were 46 deaths from mesothelial tumors, 19 pleural and 27 peritoneal. All have been validated by histologic examination. Nearly all of the pleural tumors were identified among the intrathoracic tumors (carcinoma of the lung and pleura, ICD 162, 163). The peritoneal tumors were included with gastrointestinal tumors if certified as a peritoneal mesothelioma (ICD 158) or if confused with carcinoma of the bowel or pancreas. They were included with "other cancers" if certified as carcinomatosis (ICD 199) or as sarcoma or other tumors. Two deaths from mesothelial tumors were identified among causes of death not shown in the Tables. There were, apart from pleural mesothelioma, 103 deaths from carcinoma of the lung, which remains the most common tumor of asbestos workers.

Statistically significant excess mortality from chronic respiratory disease is seen only among those with long and severe exposure. Asbestosis was given as the cause of death in 13 instances but as the underlying cause of death in 34 of the deaths from lung cancer and in 27 of the deaths from either pleural or peritoneal mesothelioma. In four instances, coronary thrombosis was the actual cause of death. In the majority of the above cases, exposure had been long and severe.

Table 2 shows the mortality experiences of the laggers. The majority of these men were first employed after 1955. It is the custom, however, for laggers to work on contract for various employers, and some may have had previous exposure, so the authors are not entirely sure of their durations of exposure. Only approximately 2% of the entire group has been followed for 30 years or longer, but to date their experience is not dissimilar from that of other severely exposed male workers.

TABLE 2

LAGGERS AND MATES (1368 MALES)

	Observed	Expected
All causes	83*(10)	57 2
Cancers of lung and pleura (ICD 162,163)	25*(14)	5.6
Gastrointestinal cancer (ICD 150-158)	8 (5)	4 3
Other cancers	8	4 1
Chronic respiratory disease	12	7 4

*$p < 0.001$.

Mortality experience was also examined according to the length of follow-up, and an analysis of the standardized mortality ratios (SMRs) for cancers of the lung and pleura is presented in Table 3. In general, the SMR increases with increased length of follow-up and with increasing exposure, but for those with long exposure, the SMRs are higher in the group with follow-ups between 20 and 30 years. Only 20% of these workers have been followed up for 30 years or

lo████r, and currently about half of the deaths from mesothelial
tu████ occurred between 20 and 30 years after their first

TABLE 3

CANCERS OF THE LUNG AND PLEURA IN MALES (SMRs)

Length of Follow-up (years)	Low to Moderate Exposure		Severe Exposure	
	< 2 Years	> 2 Years	< 2 Years	> 2 Years
10-20	104	112	255	463
20-30	159	261	218	675
30+	278	184	265	446

employment. However, as has been demonstrated previously,[111] the
number of deaths from mesothelial tumors will continue to rise for
some time.

In Table 4, a finer subdivision of job categories and of periods of
employment in the factory are presented. It is noteworthy that in
categories 1 and 2, ground workers, canteen workers, and production
workers with very little and short exposures to dust, the SMR was
176, and there were three deaths from mesothelial tumors. Up to
1955, the estimated level of asbestos in the air was 2-5 fibers/ml.

TABLE 4

CANCERS OF LUNG AND PLEURA (SMRs)

Exposure Category	Duration of Exposure		
	>2 Years	2-5 Years	5 or More Years
Low to moderate			
1-2	176	0	216
3	126	351	152
Severe			
4	247	227	714
5	238	236	567

However, looking at the death rates for mesothelial tumors graded by
exposure category (Table 5), it is found that the rates reveal a
very definite relationship to length and severity of exposure.

TABLE 5

MESOTHELIOMA DEATH RATES

Exposure Category and Duration (years)	Pleura	Peritoneum	S years	Rate per 100,000 S years
Males				
Low to moderate				
<2	3	1	12.031	33
>2	3	4	7.500	93
Severe				
<2	6	10	15.428	104
>2	7	12	7.827	243
Laggers				
<2	3	2	7.893	63
>2	1	4	2.690	186
Females				
Low to moderate	1	0	2.066	48
Severe				
<2	8	5	9.538	136
>2	4	3	4.388	360

Over 400 women were employed in the traditionally female jobs of carding, spinning, and doubling; 100 were employed in mattress making. Crocidolite was used heavily in textile departments, exposure was generally estimated to be very high, and women were also employed in other production departments, as well as in offices, canteens, and other low-exposure departments. The same pattern of analyses has been adopted, and Table 6 shows the observed versus the expected mortality in the general population, for groups with 10 years or more of followup.

TABLE 6

MORTALITY EXPERIENCES OF FEMALE FACTORY WORKERS

	Exposure Category					
	Low to Moderate (98)		Severe			
			<2 Years (396)		>2 Years (199)	
Cause of Death	Observed	Expected	Observed	Expected	Observed	Expected
All causes	34*(1)	22.0	88†(13)	65.6	78‡(7)	30.4
Cancers of lung and pleura (ICD 162,163)	3*(1)	0.5	15‡(7)	1.9	21‡(4)	0.8
Gastrointestinal cancer (ICD 150-158)	3	1.9	14†(4)	5.7	9†(2)	2.6
Other cancers	4	3.2	16 (2)	11.9	16‡(1)	5.3
Chronic respiratory disease	3	2.3	6	6.8	10†	3.2

*$p < 0.05$
†$p < 0.01$.
‡$p < 0.001$

In the low-moderate exposure group, there was one death from a mesothelial-pleural tumor. In all, there were 13 pleural-mesothelial tumors identified and eight peritoneal tumors, approximately the same proportion of all deaths (10%) as among the males. Among the severely exposed women with long exposures, there was a greater excess of lung cancer than among males with similar exposure. Also, apart from peritoneal mesotheliomas, there was an excess of deaths from gastrointestinal tumors and other cancers. Cancers of the ovary, uterus, and breast were analyzed separately. In the group of severely exposed women with long periods of employment, statistically significant excesses of cancer of the breast (obs., 6; exp., 2.1; p   0.05) and ovary (obs., 3; exp., 0.74; p   0.05) were noted. Not too much reliance can be placed on a single set of figures from one comparatively small cohort of women, and other factors related to marital status and parity that may operate in industrially employed women may be of importance. As in the males, the mesothelioma death rate (Table 5) relates clearly to the degree and length of exposure.

CONCLUSION

In the male cohort, SMR of 5.4 for lung cancer was observed in the severely exposed workers (20 f/cc) with   2 years of exposure (54/10.4) and 2.4 for those in the low to moderately exposed group (5-10 fibers/cc) (31/12.8). Risk increased with duration of follow-up and severity of exposure. Nineteen pleural and 27 peritoneal mesotheliomas were observed.

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In the female cohort, the SMR of 6.0 (3/0.5) for lung cancer was observed in low to moderately exposed group; 7.9 (15/1.9) and 26.3 (21/0.8) in the severely exposed groups with 2 years and 2 years of employment, respectively. An apparent excess of breast (6/2.1) and ovarian (3/0.7) cancer was observed in the severely exposed group. Thirteen pleural and 7 peritoneal mesotheliomas were observed.

13. The experience of insulation workers in the U.S. has been reported by Selikoff, et al.[74] With regard to exposure data, reconstruction of work situations and extrapolation to the past suggests that these workers would have been exposed to dust levels of 4-12 fibers/ml (as time weighted averages). While there might have been periods of little or no exposure, there could also have been times of peak exposures much higher than the calculated averages.

TABLE 2

EXPECTED AND OBSERVED DEATHS AMONG 632 ASBESTOS INSULATION WORKERS NEW YORK-NEW JERSEY, 20 OR MORE YEARS AFTER ONSET OF WORK JANUARY 1, 1943-DECEMBER 31, 1962
(8545 Man-years of Observation)

Underlying Cause of Death	Expected[*]	Observed
Total deaths–all causes	195 4	253
Total cancer–all sites	32.1	95
Cancer of lung	6 0	42
Pleural mesothelioma	†	3
Peritoneal mesothelioma	†	4
Cancer of esophagus, stomach, colon-rectum	9 7	29
Cancer of larynx, pharynx, buccal cavity	1 7	2
Cancer of kidney	0.7	0
All other cancer	14 0	15
Noninfectious pulmonary diseases, total	4.0	14
Asbestosis	†	12
All other causes	159 3	144

[*]Expected deaths are based upon white male age-specific U.S. death rates of the U.S. National Center for Health Statistics, 1949-1962. Rates for specific causes of death for 1943-1948 were extrapolated from rates for 1949-1955.

†Rates are not available, but these have been rare causes of death in the general population.

Table 2 shows the mortality rates for workers with 20 + years of exposure followed to 1962. The authors point out that while deaths related to asbestos exposure seen in insulation workers may sometimes occur in less than 20 years from first exposure (lung cancer, asbestosis, and occasionally, mesothelioma), these are not common and, therefore, data on experience beyond the 20-year point was thought to more clearly define the influence of exposure. Observation of survivors was extended to 1976 (Table 3). The same overall pattern of causes of death continued, although distribution of deaths by cause changed somewhat, reflecting a number of epidemiological influences. Thus, pleural and peritoneal mesothelioma, which tend to occur somewhat later than bronchogenic

carcinoma, became proportionately more common. Thus change also reflects the smaller proportions of older men who ever smoked cigarettes, and also a "survivor effect." Since the smokers in the original group had increased mortality risk (especially from lung cancer and cardiovascular disease) there would likely have been comparatively fewer of these and still fewer who continued smoking at least the same amount, among the cohort survivors, as the years went by. Except as influenced by other factors associated with advancing lapsed time since onset of exposure, this would make for fewer deaths of lung cancer, with more men at risk of dying of other asbestos-associated disease.

TABLE 3

EXPECTED AND OBSERVED DEATHS AMONG 632 NEW YORK–NEW JERSEY
ASBESTOS INSULATION WORKERS JANUARY 1, 1943–DECEMBER 31, 1976
(13,925 Man-years of Observation)

Underlying Cause of Death	Expected*	Observed
Total deaths, all causes	328.9	478
Total cancer, all sites	57.0	210
Cancer of lung	13.3	93
Pleural mesothelioma	†	11
Peritoneal mesothelioma	†	27
Cancer of esophagus	1.4	1
Cancer of stomach	5.4	19
Cancer of colon-rectum	8.3	23
Cancer of larynx, pharynx, buccal cavity	2.8	6
Cancer of kidney	1.3	2
All other cancer	24.5	28
Noninfectious pulmonary diseases, total	9.3	45
Asbestosis	†	41
All other causes	262.6	223

*Expected deaths are based upon white male age-specific U.S. death rates of the U.S National Center for Health Statistics, 1949–1976. Rates for specific cause of death for 1943–1948 were extrapolated from rates for 1949–1955.

†Rates are not available, but these have been rare causes of death in the general population.

Lung cancer remained the most important cause of excess deaths, with 93 observed, 13.3 expected. Gastrointestinal cancer was also increased as seen in the original report (43 observed, 15.1 expected). Seventy-six percent of the original cohort enrolled in 1943 had died by 1976.

Variations in distribution of deaths by cause over time are shown in Table 4.

TABLE 4

EXPECTED AND OBSERVED DEATHS AMONG 632 NEW YORK-NEW JERSEY ASBESTOS INSULATION WORKERS
JANUARY 1, 1943-DECEMBER 31, 1976

Number of Men Attaining Category Man-years of Observation	Less than 20 Years		20-34 Years		35 or More Years	
	325 1970		561 6263		498 5692	
Underlying Cause of Death	Expected*	Observed	Expected*	Observed	Expected*	Observed
Total deaths, all causes	9.0	9	80.4	119	239.5	330
Total cancer, all sites	1.1	2	13.5	53	42.4	155
Cancer of lung	0.2	0	3.0	26	10.1	67
Pleural mesothelioma	†	0	†	4	†	7
Peritoneal mesothelioma	†	0	†	3	†	24
Cancer of esophagus	0.02	0	0.4	0	1.0	1
Cancer of stomach	0.1	0	1.5	6	3.8	13
Cancer of colon-rectum	0.2	0	1.9	7	6.2	16
Cancer of larynx, pharynx, buccal cavity	0.05	2	0.8	2	1.9	2
Cancer of kidney	0.03	0	0.4	0	0.9	2
All other cancer	0.5	0	5.5	5	18.5	23
Noninfectious pulmonary diseases, total	0.1	0	1.6	4	7.6	41
Asbestosis	†	0	†	3	†	38
All other causes	7.8	7	65.3	62	189.5	154

*Expected deaths are based upon white male age-specific U.S. death rates of the U.S. National Center for Health Statistics, 1949-1976. Rates for specific causes of death for 1943-1948 were extrapolated from rates for 1949-1955.
†Rates are not available, but these have been rare causes of death in the general population.

The experience of workers exposed after 1943 (reflecting postwar "cleaner" conditions) has also been reported. In the 15,520 man-years of observation during the less than 20-year period (Table 6), there was no unusual mortality experience. Altogether there were fewer deaths than expected, and there was no increase in cancer deaths.

TABLE 6

EXPECTED AND OBSERVED DEATHS AMONG 833 NEW YORK-NEW JERSEY ASBESTOS
INSULATION WORKERS FIRST EMPLOYED JANUARY 1, 1943-DECEMBER 31, 1962,
AND OBSERVED FROM FIRST EMPLOYMENT-DECEMBER 31, 1976
(Duration from Onset of Employment)

Number of Men Attaining Category Man-years of Observation	Less than 20 Years		20-34 Years	
	833 15,520		523 3281	
Underlying Cause of Death	Expected*	Observed	Expected*	Observed
Total deaths, all causes	39.8	23	24.8	39
Total cancer, all sites	5.1	5	5.0	15
Cancer of lung	1.1	2	1.8	8
Pleural mesothelioma	†	0	†	2
Peritoneal mesothelioma	†	0	†	1
Cancer of esophagus, stomach, colon-rectum	0.7	1	0.8	2
Cancer of larynx, pharynx, buccal cavity	0.2	1	0.3	1
Cancer of kidney	0.1	0	0.1	1
All other cancer	3.0	1	2.0	0
Noninfectious pulmonary diseases, total	0.5	0	0.6	7
Asbestosis	†	0	†	6
All other causes	34.2	18	19.2	17

*Expected deaths are based upon white male age-specific U.S. death rates of the U.S. National Center for Health Statistics, 1949-1976. Rates for specific causes of death for 1943-1948 were extrapolated from rates for 1949-1955.
†Rates are not available, but these have been rare causes of death in the general population.

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In the 3281 man-years of observation 20-34 years from onset of exposure, there were 3 times as many cancer deaths as expected, primarily due to lung cancer.

CONCLUSION

No dose-response inference is possible because of the lack of exposure data.

14. Observations on 17,800 asbestos insulation workers in the U.S. and Canada followed from 1967 to 1976 is discussed below.[64] During the decade of observation 2271 deaths occurred (Table 12), whereas only 1658.9 deaths were expected. The excess deaths were primarily the result of an increased number of instances of cancer at several sites.

TABLE 12

DEATHS AMONG 17,800 ASBESTOS INSULATION WORKERS IN THE UNITED STATES AND CANADA JANUARY 1, 1967 DECEMBER 31, 1976

NUMBER OF MEN 17,800

MAN-YEARS OF OBSERVATION 166,853

Underlying Cause of Death	Expected*	Observed		Ratio o/e	
		(BE)	(DC)	(BE)	(DC)
Total deaths, all causes	1658 9	2271	2271	1.37	1 37
Total cancer, all sites	319 7	995	922	3.11	2 88
Cancer of lung	105.6	486	429	4.60	4 06
Pleural mesothelioma	†	63	25	—	—
Peritoneal mesothelioma	†	112	24	—	—
Mesothelioma, n.o.s.	†	0	55	—	—
Cancer of esophagus	7.1	18	18	2.53	2.53
Cancer of stomach	14 2	22	18	1.54	1.26
Cancer of colon-rectum	38 1	59	58	1.55	1 52
Cancer of larynx	4.7	11	9	2.34	1 91
Cancer of pharynx, buccal	10.1	21	16	2.08	1 59
Cancer of kidney	8.1	19	18	2.36	2.23
All other cancer	131.8	184	252	1.40	1.91
Noninfectious pulmonary diseases, total	59 0	212	188	3.59	3 19
Asbestosis	†	168	78	—	—
All other causes	1280 2	1064	1161	0 83	0 91

*Expected deaths are based upon white male age-specific U.S. death rates of the U.S. National Center for Health Statistics, 1967-1976.

†Rates are not available, but these have been rare causes of death in the general population

(BE): Best evidence. Number of deaths categorized after review of best available information (autopsy, surgical, clinical).

(DC). Number of deaths as recorded from death certificate information only.

Apart from lung cancer, mesothelioma, gastrointestinal cancer, cancer of the larynx, pharynx and oral cavity and cancer of the kidney, there was still an excess of cancer of other sites, with 184 observed, 131.8 expected (Table 13).

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TABLE 13

DEATHS AMONG 17,800 ASBESTOS INSULATION WORKERS IN THE UNITED STATES
AND CANADA JANUARY 1, 1967-DECEMBER 31, 1976
NUMBER OF MEN 17,800
MAN-YEARS OF OBSERVATION 166,853

Underlying Cause of Death	Expected*	Observed		Ratio o/e	
		(BE)	(DC)	(BE)	(DC)
Total deaths, all causes	1658.9	2271	2271	1.37	1.37
Cancer, all sites	319.7	995	922	3.11	2.88
Deaths of less common malignant neoplasms					
Pancreas	17.5	23	49	1.32	2.81
Liver, biliary passages	7.2	5	19	0.70	2.65
Bladder	9.1	9	7	0.99	0.77
Testes	1.9	2	1	—	—
Prostate	20.4	30	28	1.47	1.37
Leukemia	13.1	15	15	1.15	1.15
Lymphoma	20.1	19	16	0.95	0.80
Skin	6.6	12	8	1.82	1.22
Brain	10.4	14	17	1.35	1.63

*Expected deaths are based upon white male age-specific U.S. death rates of the U.S.
National Center for Health Statistics, 1967-1976.
(BE): Best evidence. Number of deaths categorized after review of best available information
(autopsy, surgical, clinical).
(DC): Number of deaths as recorded from death certificate information only.

From a purely statistical point of view, in view of the increased
incidence of cancer of several sites among asbestos insulation
workers, it was expected that a proportion of these men would suffer
multiple cancers simultaneously, even beyond the tendency of such
findings to be made among individuals with cancer, in general.[12]
Again, this would not be reflected in tabulations of causes of death
by single underlying cause, as is the usual practice. Analysis
demonstrated one hundred malignant neoplasms present but not causing
death (Table 14). Sometimes these additional neoplasms were

TABLE 14

MORTALITY EXPERIENCE AMONG 17,800 ASBESTOS INSULATION WORKERS IN THE UNITED
STATES AND CANADA 1967 1976 OBSERVATIONS IN 2271 CONSECUTIVE DEATHS

Malignant Neoplasms Present, but not Causing Death* Site	Number
Lung	24
Pleural mesothelioma	2
Peritoneal mesothelioma	1
Esophagus	0
Stomach	1
Colon	19
Oropharynx	3
Larynx	5
Kidney	3
Other	42†
	100‡

*Twenty-one of these neoplasms were mentioned on the death certificate (but were not
categorized as underlying cause of death).
†Including leukemia 5, lymphoma 3, bladder 5, prostate 13, thyroid, etc.
‡In 92 individuals; total includes multiple cancers in eight cases.

mentioned on the death certificate but as an "other significant condition," not in the section on the underlying cause of death. Forty were present among the 1064 cases where death was due to causes other than cancer or asbestosis (Table 15). Among the 168 deaths of asbestosis, cancer was also present in 7, 6 of these being bronchogenic carcinoma. Analysis of the circumstances leading to death, however, indicated that the underlying cause was asbestotic pulmonary insufficiency, and that the lung cancers were present but with no decisive influence at the time of death. Nineteen other cancers were present among the 486 deaths of lung cancer and 10 other cancers accompanied the 175 deaths of mesothelioma. There were 9 "incidental" neoplasms among the 99 deaths of gastrointestinal cancer. Although experiences are so far limited, it may not be wholly unexpected that there were proportionately more incidental neoplasms accompanying deaths of colon-rectum cancer, compared to those of lung cancer (8.5% vs. 3.9%). One may speculate that this could be due to the longer

TABLE 15

MORTALITY EXPERIENCE AMONG 17,800 ASBESTOS INSULATION WORKERS IN THE UNITED
STATES AND CANADA 1967-1976: OBSERVATIONS IN 2271 CONSECUTIVE DEATHS
NUMBER OF INCIDENTAL MALIGNANT NEOPLASMS (NOT CAUSING DEATH) IN RELATION
TO UNDERLYING CAUSE OF DEATH AS ESTABLISHED BY BEST EVIDENCE (BE)

Underlying Cause of Death	Number of Deaths of Underlying Cause	Incidental Malignant Neoplasms	
		No. of Deaths	Total Cancers
Cancer all sites	995	45	50
Cancer of lung	486	17	19
Pleural mesothelioma	63	4	4
Peritoneal mesothelioma	112	5	6
Cancer of esophagus	18	1	1
Cancer of stomach	22	3	3
Cancer of colon-rectum	59	5	5
Cancer of larynx	11	0	0
Cancer of pharynx, buccal cavity	21	2	3
Cancer of kidney	19	0	0
All other cancers	184	8	9
Noninfectious pulmonary diseases, total	212	10	10*
Asbestosis	168	7	7*
All other causes	1064	37	40
Total	2271	92	100

*Six of these were lung cancer.

clinical course of many patients with colon-rectum cancer, compared to lung cancer, with greater opportunity, simply in terms of time, to develop additional disease.

Multiple cancers were present, overall, in 2.1% of deaths among these asbestos insulation workers (48 of 2271). It is perhaps to be expected that this was more likely to be the case among those for whom cancer was the primary cause of death (4.5%), while only 3 of the 1276 other deaths had this finding.

It is now well appreciated that most asbestos associated disease is first seen after considerable periods from onset of exposure in both occupational and environmental circumstances. This is true both for the presence and extent of parenchymal fibrosis and pleural fibrosis and/or calcification,[3,13] and for asbestos-associated neoplasms.[14]

Some limited excess disease was observed in less than 20 years from onset of exposure (Table 16). Among 12,683 men with such experience, covering 89,462 man-years of observation, the number of cancer deaths was about doubled, with 42.6 deaths expected and 83 observed. There were no excess deaths of gastrointestinal cancer and only 5 deaths of mesothelioma, with these in the 15-19 years from onset category. Age, year and sex specific mortality data of the U.S. National Cancer for Health Statistics indicated that 11.9 deaths of lung cancer were to be expected. Thirty-six occurred. There were 8 deaths from asbestosis.

TABLE 16

DEATHS AMONG 17,800 ASBESTOS INSULATION WORKERS IN THE UNITED STATES AND CANADA JANUARY 1, 1967-DECEMBER 31, 1976.
ANALYSIS BY DURATION FROM ONSET OF EMPLOYMENT

Total Men Man-years of Observation Underlying Cause of Death	Before 20 Years from Onset 12,683 89,462					20 or More Years from Onset 12,051 77,391				
		Observed		Ratio o/e			Observed		Ratio o/e	
	Expected*	(BE)	(DC)	(BE)	(DC)	Expected*	(BE)	(DC)	(BE)	(DC)
Total deaths, all causes	282.9	325	325	1.15	1.15	1376.0	1946	1946	1.41	1.41
Cancer, all total	42.6	83	77	1.95	1.81	277.1	912	845	3.29	3.05
Cancer of lung	11.9	36	32	3.03	2.69	93.7	450	397	4.80	4.34
Pleural mesothelioma	†	2	2	—	—	†	61	23	—	—
Peritoneal mesothelioma	†	3	0	—	—	†	109	24	—	—
Mesothelioma, a.o.s.	†	0	1	—	—	†	0	54	—	—
Cancer of esophagus	0.6	1	1	—	—	6.5	17	17	2.64	2.64
Cancer of stomach	1.5	1	0	—	—	12.7	21	18	1.65	1.42
Cancer of colon-rectum	4.1	4	4	—	—	34.0	55	54	1.62	1.59
Cancer of larynx	0.4	2	2	—	—	4.3	9	7	2.09	1.63
Cancer of pharynx, buccal	1.3	3	2	—	—	8.8	18	14	2.05	1.59
Cancer of kidney	1.1	3	3	—	—	7.0	16	15	2.29	2.14
All other cancer	21.7	28	30	1.29	1.38	110.1	156	222	1.42	2.02
Noninfectious pulmonary diseases, total	5.2	8	11	1.54	2.12	53.8	284	177	3.78	3.28
Asbestosis	†	8	2	—	—	†	160	76	—	—
All other causes	235.1	234	237	1.00	1.01	1045.1	830	924	0.79	0.88

*Expected deaths are based upon white male age-specific U.S. death rates of the U.S. National Center for Health Statistics, 1967-1976.
†Rates are not available, but these have been rare causes of death in the general population.
(BE): Best evidence. Number of deaths categorized after review of best available information (autopsy, surgical, clinical).
(DC): Number of deaths as recorded from death certificate information only.

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On the other hand, extensive disease was seen among the 12,051 men who had reached 20 or more years from onset during the decade of study. Here, 1376.0 deaths were anticipated; 1946 occurred. There were 160 deaths of asbestosis and 912 of cancer. It was at this time that bronchogenic carcinoma made its heaviest contribution, with 93.7 such deaths expected and 450 observed. One hundred and seventy deaths of mesothelioma were then seen and the increase in gastrointestinal cancer found. Table 17 depicts these data in some detail, in five-year periods from onset of employment. Lung cancer data are given as both expected and observed numbers of death. This practice cannot be followed for mesothelioma, where expected deaths cannot be computed for the general population. Instead, both the number of deaths of pleural and peritoneal mesothelioma, as well as the number of deaths of these causes per thousand persons years at risk are provided. The latter does not take into account variations in achieved age, but this may have less influence than achieved duration from onset of employment. It will be seen that very major increases in numbers of deaths of lung cancer are first seen at 15-24 years from onset of work, with continued further increases. The extraordinary increase in deaths of mesothelioma, both of the pleura and the peritoneum, is not observed until somewhat later, reaching 2.78 deaths per thousand person-years at risk for pleural mesothelioma at 35-39 years from onset of work, and 5.47 deaths of peritoneal mesothelioma per thousand person-years at 45 + years from onset.

TABLE 17

DEATHS AMONG 17,800 ASBESTOS INSULATION WORKERS IN UNITED STATES AND CANADA, JANUARY 1, 1967-DECEMBER 31, 1976
ANALYSES BY DURATION FROM ONSET OF EMPLOYMENT

Duration from Onset (Years)	Number of Men	Person-years of Observation	Lung Cancer					Pleural Mesothelioma			Peritoneal Mesothelioma		
			Exp.*	Observed		Ratio o/e		Number		No./1000 Person-years	Number		No./1000 Person-years
				(BE)	(DC)	(BE)	(DC)	(BE)	(DC)	(BE)	(BE)	(DC)	(BE)
- 10	8,190	26,393	0.7	0	0	—	—	0	0	0	0	0	0
10-14	9,083	29,003	2.7	7	5	2.55	1.82	0	0	0	0	0	0
15-19	9,948	34,066	8.5	29	27	3.40	3.17	2	2	0.06	3	0	0.09
20-24	8,887	31,268	17.0	59	57	3.48	3.36	6	4	0.19	3	2	0.10
25-29	6,596	20,657	21.0	105	96	5.00	4.58	13	5	0.63	19	3	0.92
30-34	3,547	11,590	18.4	112	103	6.08	5.59	9	3	0.78	23	6	1.98
35-39	2,020	5,403	11.5	65	57	5.68	4.98	15	4	2.78	19	5	3.52
40-44	1,108	3,160	8.1	40	131	4.93	3.82	4	3	1.27	16	3	5.06
45+	1,448	5,305	17.8	69	53	3.89	2.98	14	4	2.64	29	5	5.47

*Expected deaths are based upon white male age-specific U.S. death rates of the U.S. National Center for Health Statistics, 1967-1976. Smoking habits not taken into account.

(BE): Best evidence. Number of deaths categorized after review of best available information (autopsy, surgical, clinical).

(DC): Number of deaths as recorded from death certificate information only.

In another reflection of the clinical concerns among these workers, Table 18 indicates that approximately one-third of all deaths were due to lung cancer at 30-34 years from onset, while mesothelioma accounted for 13% of all deaths at 35-39 years.

Altogether, lung cancer was responsible for 21% of all deaths observed in this cohort and mesothelioma for 8%.

TABLE 18

DEATHS AMONG 17,800 ASBESTOS INSULATION WORKERS IN THE UNITED STATES AND CANADA, JANUARY 1, 1967 DECEMBER 31, 1976.
ANALYSIS BY DURATION FROM ONSET OF EMPLOYMENT

Years from Onset of Employment	Total Deaths	Percent of All Deaths							
		Lung Cancer		Mesothelioma					
				Pleural		Peritoneal		Total	
		(BE)	(DC)	(BE)	(DC)	(BE)	(DC)	(BE)	(DC)
< 10	51	0	0	0	0	0	0	0	0
10-14	85	8 2	5.9	0	0	0	0	0	0
15-19	189	15.3	14.3	1.1	1.1	1 6	0	2.7	1.6
20-24	320	18.4	17.8	1.9	1.3	0 9	0.6	2.8	2.5
25-29	388	27.1	24.7	3 4	1 3	4.9	0.8	8.3	5.2
30-34	340	32.9	30.3	2 7	0.9	6.8	1.8	9.4	6.5
35-39	253	25.7	22.5	5 9	1.6	7 5	2.0	13.4	7.9
40-44	203	19.7	15.3	2.0	1.5	7 9	1.5	9.9	6.4
45 +	442	15.6	12.0	3.2	0.9	6.6	1.1	9.7	4.1
Total	2271	21.4	18.9	2.8	1 1	4 9	1.1	7.7	4.6

*Total includes mesothelioma not specified as either pleural or peritoneal.
(BE). Best evidence Number of death categorized after review of best available information (autopsy, surgical, clinical).
(DC). Number of deaths as recorded from death certificate information only.

CONCLUSION

The study results indicate a high increase in risk of lung cancer associated with asbestos exposure, but the lack of exposure data makes it difficult to show a dose-response relationship.

15. Asbestos cement building materials plant workers have been studied[87] to determine the risk of respiratory malignancy in relation to duration, degree, and fiber type of exposure to asbestos. Subjects were classified into 5 total dust categories for which mean length of follow-up and mean age at initial exposure are comparable. (Table 1)

TABLE 1

COHORT BY FOLLOW-UP WITHIN
EXPOSURE CATEGORIES

Total Dust within 20 Yrs of Initial Exposure (mppcf-yr*)	No	Mean Follow-Up (yr.)	Mean Age at Initial Exposure (yr)
≤ 10	3,037	28.7	27.8
11-50	1,303	27.3	27.4
51-100	383	28.1	27.6
101-200	344	27.3	27.7
> 200	878	28.7	28.0

*Million particles per cubic foot-yr.

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Using the standard man-yr approach, expected numbers of deaths for each exposure category were calculated on the basis of race-age-cause-specific rates for both the U.S. and Louisianna male populations for 1950, 1960, and 1970.

Cause-specific standard mortality ratios, SMR (100 x observed number of deaths/expected number), were obtained for various causes for each of the 5 exposure categories (Table 2). SMR for all causes combined remain generally low, but increase slightly with degree of exposure: 60, 64, 75, 80, and 94. SMR for respiratory system neoplasms remain low for the 3 lowest exposure groups, but exceed 100 in the 2 highest categories: 77, 70, 26, 290, and 226. The very low SMR in the middle dust category is probably a chance occurrence; with only 3.8 respiratory neoplasm deaths expected, the probability (assuming a Poisson distribution) of observing one or fewer is 0.11.

TABLE 2

STANDARD MORTALITY RATIOS BY CAUSE WITHIN EXPOSURE CATEGORIES

Cause of Death	Total Dust Within 20 Yr of Initial Exposure (mppcf-yr*)									
	≤ 10 (n = 2,037)		11-60 (n = 1,353)		61-100 (n = 353)		101-300 (n = 340)		> 300 (n = 578)	
	O/E[†]	SMR[‡]	O/E	SMR	O/E	SMR	O/E	SMR	O/E	SMR
All causes	260/433.7	60	141/218.9	64	56/76.1	75	43/53.3	80	103/116.1	94
All malignant neoplasms (140-209)	64/77.3	70	27/37.1	72	7/12.6	56	14/9.6	147	18/19.8	91
Digestive system (150-159)	10/24.6	41	10/11.9	84	3/4.2	71	0/3.0	-	2/6.4	31
Respiratory system (160-163)	19/24.7	77	8/11.4	70	1/3.8	26	9/3.1	290[§]	14/6.2	226[§]
Other (residual)	26/29.0	89	9/13.8	65	3/4.6	61	5/3.4	147	2/7.2	29
Major cardiovascular diseases (390-448)	129/218.7	60	70/113.9	68	33/40.1	82	14/26.5	53	61/67.4	100
All other causes	70/140.7	54	26/47.9	54	12/16.2	74	9/11.6	78	30/23.0	94

* Millions of particles per cubic foot-yr
[†] Ratio of observed to expected deaths.
[‡] Standard mortality ratio
[§] P < 0.01 (number of observed deaths compared to the number expected, assuming a Poisson distribution).

In the 3 lowest exposure categories, the SMR for over-all mortality and respiratory neoplasms are comparable, as demonstrated graphically (figure 1) by the extensive overlap of their respective 95 per cent confidence intervals (based on a Poisson distribution). On the contrary, there was no overlap in either of the 2 highest exposure groups. Assuming no association between trace and cause of death, the close agreement of the over-all and respiratory malignancy SMR in the low exposure groups is additional evidence that, although some underestimation might have occurred because of those lost to view, there are no excess respiratory neoplasms in these categories.
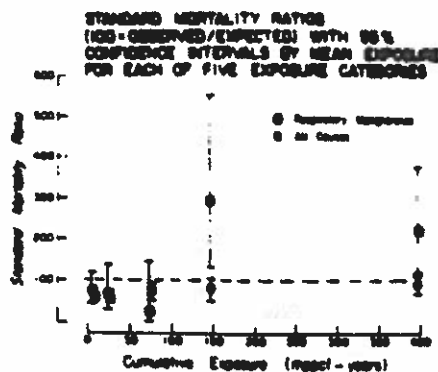
Fig 1 Standard mortality ratios with 95 per cent confidence intervals by mean exposure for each of 5 exposure categories.

No excess mortality occurred in any exposure group for any cause other than respiratory neoplasms.

The analysis was also performed with the number of deaths expected on the basis of Louisiana death rates. Because lung cancer rates are higher in Louisiana than in most states, the expected numbers of respiratory neoplasms are greater than with the U.S. rates, thus resulting in lower SMR. The patterns observed for the 5 exposure categories were the same as with the U.S. rates; over-all mortality SMR were 56, 64, 71, 73, and 83; respiratory neoplasm SMR were 64, 59, 23, 225, and 187. As with U.S. rates, no excess mortality other than for respiratory neoplasms were observed.

Two pleural mesotheliomas were diagnosed in the total study population: one person was employed for 10 months (with known exposure only to chrysotile), the other for 14 yr (with most of his employment in the pipe plant, which resulted in exposure to both chrysotile and crocidolite). Because these men died 18 and 19 yr after initial employment, respectively, neither fulfilled the cohort criterion of a minimum of 20 yr of follow-up and therefore are not included in this analysis. It was considered possible that this tumor was underdiagnosed in this population.

The results of Newhouse[112] suggest that the latent period for the development of asbestos-related neoplasms may be less than 20 yr, as with the 2 mesotheliomas found here. Using Newhouse's methodology, the effect of latency on the mortality experience of this population was assessed by performing the analysis by 5-yr periods after initial employment. In each analysis, persons with follow-up of less than the prescribed minimum are excluded; an individual person's exposure is calculated at the start of the particular time period. Because each period is only 5 yr in length, it was necessary to condense the original 5 exposure categories into three, although the expected numbers of deaths remain very small.

Results for the 2 lowest exposure categories (representing the original 3 lowest groups) indicate no discernible pattern for respiratory neoplasm SMR as time since initial exposure increases; those for the highest exposure category exhibit an increasing trend as long as 30 yr. since initial exposure (Table 3).

TABLE 3

RESPIRATORY MALIGNANCY STANDARD MORTALITY RATIOS BY 5-YR FOLLOW-UP AND TOTAL DUST AT START OF PERIOD

Yr since Initial Exposure	No.	Total Dust at Start of 5-Yr Period (mppcf-yr)					
		< 10		10-100		> 100	
		O/E	SMR	O/E	SMR	O/E	SMR
10-15	8,328	7/4 4	158	1/2.4	42	1/1.3	77
15-20	6,744	6/6.5	94	5/4.3	116	3/2.4	158
20-25	5,648	10/12.1	83	5/6.4	78	5/3.3	154
25-30	4,307	6/10.1	59	3/3.4	88	7/3.0	233*
30-35	1,220	3/1 8	167	1/2 2	46	5/1.5	333*
> 35	313	0/0.5	0	0/1.0	0	4/1 3	308*

For definitions of abbreviations, see table 2.

*P < 0.05 (number of deaths observed compared to number of deaths expected, assuming a Poisson distribution).

To compare the preceding results with those which would have been obtained with a different study design[115], an alternate method of analysis was performed for this cohort (men with at least 20 yr of follow-up) by considering 4 control subjects for each case of lung cancer. These control subjects were selected at random from among men in the cohort who were born in the same year as the cancer patient, were of the same race, had survived at least into the year following that in which the patient died, and if they subsequently died, did not die of a malignancy.

The mean total dust exposure (accumulated within 20 yr. after initial employment) was 164.1 mppcf-yr. for the cancer patients and 77.8 for the control subjects. A 2-way analysis of variance (the matched sets acting as a blocking factor), with Scheffe's multiple comparisons, found that there were no differences among the exposure means of the 4 sequences of control subjects, but that the mean dust exposure for the patients was significantly greater than that of the control subjects (P   0.005).

The distributions of the cancer patients and the control subjects by total exposure to dust are presented in Table 4. The odds ratio, an estimate of relative risk, was calculated for each category relative to the lowest degree of exposure.

TABLE 4

**LUNG CANCER CASES AND MATCHED CONTROLS (4 PER CASE);
TOTAL DUST EXPOSURE AND ODDS RATIOS**

Total Dust within 20 Yr of Initial Exposure (mppcf-yr[*])	No. Cases	No. Controls	Odds Ratio[†] (Relative to Lowest Category)
< 10	17	67	1.00
10-50	7	36	1.14
50-100	1	11	0.52
100-300	8	16	2.66[‡]
> 300	14	20	2.75[‡]
Total	47[§]	160	

[*] Million particles per cubic foot-yr.
[†] Usual estimate of relative risk.
[‡] $p < 0.05$, based on a χ^2 (1) distribution.
[§] The total of 51 respiratory malignancy deaths in table 3 resulted from random allocation of deaths without certification.

The over-all pattern of the odds ratio is similar to that of the respiratory malignancy SMR: the risk in the second exposure category is comparable to that in the lowest, an unexplained dip occurs in the third category (doubtless the same chance occurrence), and a significantly greater risk is observed at the 2 highest exposure categories.

Because information had already been collected on the entire cohort, the case-control approach, using only a subset of the population, does not make full use of the data available. Moreover, although this alternate approach provides estimation of the risk for each exposure category relative to the lowest category, no assessment of the risk experienced in the lowest category is possible. Despite these limitations, the observed pattern of risk across exposure categories was similar to that obtained with man-yr., prospective design, and analysis.

The preceding analysis was based on cumulative dust exposure, which has 2 components: (1) duration of exposure, and (2) average dust concentration. To assess the contribution of each, the population was divided into 9 duration-by-average-concentration categories. For these groups, the mean values of each variable within a fixed category were comparable across the categories of the other, and mean follow-up times were homogeneous (Table 5).

TABLE 5

COHORT BY DURATION AND CONCENTRATION OF EXPOSURE

Average Dust Concentration (mppcf)[*]	Duration of Employment (yr)		
	< 2	2-10	> 10
< 5	n = 1,323	n = 304	n = 108
	4.6[†]	4.3	3.2
	0.8[‡]	4.7	21.6
	28.8[§]	27.5	28.3
5-20	n = 1,581	n = 391	n = 688
	17.9	13.6	13.6
	0.6	4.6	21.7
	27.9	28.2	27.6
> 20	n = 764	n = 288	n = 174
	34.6	29.4	26.7
	0.7	4.4	22.6
	27.1	28.7	28.7

[*] Million particles per cubic foot.
[†] Mean average dust concentration (mppcf).
[‡] Mean length of employment (yr).
[§] Mean length of follow-up (yr).

The SMR for respiratory malignancy for these groups (Table 6) generally indicate increasing risk with duration of employment, which is concentration dependent, and increasing risk with average concentration, which is duration dependent. These results are consistent with others,[88] which indicate that it is not sufficient to equate total exposure with either duration or average concentration; each constitutes an important component of risk, and each exhibits degrees with no apparent excess hazard.

TABLE 6

STANDARD MORTALITY RATIOS FOR RESPIRATORY MALIGNANCY BY DURATION OF EMPLOYMENT AND AVERAGE DUST CONCENTRATION

Average Dust Concentration (mppcf)[*]	Duration of Employment (yr)			
	< 2	2-10	> 10	All Durations
< 5	7/10.0[†]	2/2.2	1/1.9	10/14.1
	70	91	68	71
5-20	12/17.1	1/2.6	12/6.2	30/26.1
	70	36	221[‡]	100
> 20	5/6.2	3/2.6	7/2.2	15/10.0
	84	129	318[‡]	100
All dust concentrations	24/33.4	6/7.6	20/8.3	
	74	80	218[‡]	

[*] Million particles per cubic foot.
[†] Ratio of observed deaths to expected deaths.
[‡] P < 0.01 (based on a Poisson distribution).

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In assessing the possible influence of fiber type exposure on risk of respiratory malignancy, workers with exposure to chrysotile only (n = 4,201) were compared with 2 groups of workers exposed to crocidolite: those with steady employment in the pipe plant (n = 1,004) and those with intermittent exposure to crocidolite through occasional maintenance work in that area (n = 235). Persons with exposure to amosite (n = 205) were excluded from this analysis. All follow-up times were similar, and total fiber exposures were comparable among the fiber type groups within each category of exposure (Table 7).

TABLE 7

COHORT BY TYPE AND LEVEL OF FIBER EXPOSURE*

Exposure	Total Fiber Exposure within 20 Yr of Initial Employment (mppcf-mos†)		
	< 20	20-200	> 200
No crocidolite exposure	n = 2,505	n = 1,237	n = 351
	8.0‡	64.0	663.0
	28.0§	28.2	30.0
Intermittent exposure to crocidolite in pipe plant	n = 44	n = 65	n = 108
	8.3	60.7	663.6
	28.4	27.3	30.0
Steady employment in pipe plant with crocidolite exposure	n = 231	n = 363	n = 466
	10.5	77.0	660.2
	28.8	26.0	27.2

*Subjects with exposure to amosite are excluded (n = 205).
†Millions of particles per cubic foot-months.
‡Mean total fiber exposure (mppcf-mos).
§Mean length of follow-up (yr).

The pattern that emerges from the SMR (Table 8) suggests that the addition of crocidolite to chrysotile enhances the risk for respiratory malignancy, particularly for those workers exposed intermittently in maintenance jobs. The exposure history of this latter group is characterized by exposure to high concentrations of dust for short periods of time.

TABLE 8

STANDARD MORTALITY RATIOS FOR RESPIRATORY MALIGNANCY BY FIBER TYPE

	Total Fiber Exposure within 20 Yr of Initial Employment (mppcf-mos*)			
	< 20	20-200	> 200	Total
No crocidolite exposure	12/21.4	10/13.0	8/4.4	30/38.8
	56	77	182	77
Intermittent exposure to crocidolite in pipe plant	2/0.2	0/0.7	6/1.4	7/2.3
	1,000†	0	357†	304†
Steady employment in pipe plant with crocidolite exposure	1/1.0	1/1.9	7/2.9	9/5.8
	100	53	241†	155

*Million particles per cubic foot-months.
†p < 0.06

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CONCLUSION

The risk increased more steeply with increased quantitative exposure than with increased duration of employment. Excess mortality for lung cancer was observed only for groups with moderate and high cumulative exposure (SMR 2.9 and 2.3).

There was no detectable excess risk of lung cancer in persons employed for less than 2 years or with low exposure. The risk appears high for two subgroups exposed to crocidolite, but only in the high exposure group (200 mppcf-yr.). There was no increased risk observed for gastrointestinal cancer in any subgroup.

There were 2 pleural mesotheliomas observed (one employed less than 1 year and one for 14 years).

There was no increased risk of respiratory cancer for exposures below 10 mppcf-yrs.

There was a low (75%) tracing rate.

16. In a study of female asbestos workers[35], compared with national rates there was an excess overall mortality among those who worked in jobs with low to moderate exposure (Table 2), which was partly accounted for by deaths from cancer.

Table 2

Mortality of Women with Low to Moderate Asbestos Exposure

Registered cause of death	All periods of employment (126 women)	
	Obs.	Exp.
All causes	29[1]	18.1
Cancer of lung and pleura	2[1]	0.3
Other cancer	8	4.4
Respiratory disease excluding cancer	2	2.2
Other disease	17	11.2

[1]P 0.05

In the group with severe exposure who had worked for less than two years (Table 3), there was an excess of cancer of the lung and pleura.

Table 3

Mortality of Women with Severe Exposure

Registered cause of death	Duration of employment			
	Less than 2 yrs (557 women)		More than 2 yrs (239 women)	
	Obs.	Exp.	Obs.	Exp.
All causes	55[3]	49.9	56[3]	24.5
Cancer of lung and pleura	6[3]	1.0	14[3]	0.5
Other cancer	16	12.4	17[8]	6.1
Respiratory disease excluding cancer	10	7.4	11[2]	3.6
Other disease	23	29.1	14	14.3

[2]P   0.01
[3]P   0.001

However, the most marked increased mortality was in those with
severe exposure who had worked for more than two years in the
asbestos factory; in this group there were excess deaths from cancer
of the lung and pleura, from other cancers, and from respiratory
diseases. Three deaths registered as cancer of the pleura were
identified as pleural mesotheliol tumors; in all there were 11
mesotheliomas, six of pleural and five of peritoneal origin.

In this study the results were assessed by comparing the number of
observed deaths with the number of expected deaths[36] The "expected"
deaths were calculated by the "man-years" method, multiplying
years of risk by death rates. Excess mortality has been tested by
treating the observed number of deaths as a Poisson variable with
expectation equal to the man-years expected number of deaths.
Mortality as a function of length of time from first exposure is
shown in Table 5.

Table 5

Mortality by Length of Follow-Up since First Exposure

Registered cause of death	Years since first exposure					
	Less than 10 (922 women)		10 to 20 (692 women)		More than 20 (655 women)	
	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.
All causes	25	23.7	36[1]	29.3	79[3]	39.4
Cancer of lung and pleura	0	0.2	3[1]	0.6	19[3]	1.1
Other cancer	5	4.2	10	7.8	26[3]	10.8
Respiratory disease excluding cancer	9	6.1	5	3.4	9[1]	3.7
Other disease	11	13.2	18	17.5	25	23.8

[1] P 0.05
[3] P 0.001

There were four deaths in all registered as cancer of the ovary; three of these occurred among women with severe and long exposure and, compared with the expected number of 0.6 in this particular group, this was a significant finding (p=0.0025). The histological review suggested that at least two of the other deaths in the group that were registered as carcinomatosis were due to this cause. The possibility that ovarian cancer may be caused by exposure to certain hydrous magnesium silicates such as talc and asbestos has been raised by several researchers. Strong evidence of a link was found by Graham and Graham,[36] who injected mice, hamsters, guinea pigs, and Dutch rabbits with tremolite asbestos. The mice and hamsters showed no lesions, presumably because of a protective layer of peritoneum surrounding their ovaries, which is absent in the guinea pig and rabbit. Both of these latter species developed an atypical papillary pattern of ovarian epithelial hyperplasia, which the authors suggested was similar to early ovarian epithelial tumors in women. Additionally, birefringent bodies were observed in sections of six out of twelve ovarian tumors, and none of nine normal controls. These bodies were thought to be asbestos (but were not examined).

APPENDIX II

1. **Mesothelioma in Pet Dogs Associated with Exposure of Their Owners to Asbestos.** Glickman, L.T., Domanski, L.M., Maguire, T.G., Dubielzig, R.R., and Churg, A./ Environ. Res., _32_, 305-313 (1983)

This paper describes the findings of an epidemiological study of pet dogs and the incidence of mesothelioma and asbestos exposure. Eighteen histologically-confirmed canine mesotheliomas were diagnosed at the Veterinary Hospital of the University of Pennsylvania (VHUP), Philadelphia, from April 1977 to December 1981. An asbestos-related occupation or hobby of a household member and use of flea repellents on the dog were significantly associated with mesotheliomas. In addition, there was a trend indicating an increased risk of mesotheliomas with an urban residence. Lung tissue from three dogs with squamous cell carcinoma of the lung had higher levels of chrysotile asbestos fibers than lung tissue from control dogs. The VHUP is a major veterinary referral center for the Northeast and Middle-Atlantic regions of the U.S. Each year there are approximately 17,000 admissions and visits to the VHUP and an additional 6000 submissions of biopsy specimens to the Pathology Department (could not ascertain whether these numbers refer to all animals or to dogs only).

A cancer and noncancer control patient were selected from hospital records and matched to each mesothelioma case by age and date of diagnosis (± 1 year), sex, and breed. Excluded from the noncancer control group were dogs with any respiratory disease or suspected malignancy. Dogs with respiratory cancer were excluded from the cancer control group.

Because controls had been matched on age, sex, and breed, these characteristics for the cases were first compared to the entire canine hospital population. The odds ratio (OR), an estimate of the relative risk of disease for each category, was determined using the Mantel-Haenszel procedure.[1] Age was controlled in sex comparisons, and sex was controled in age comparisons. Odds ratios for other risk factors were determined for matched pairs using the cancer and non-cancer groups separately.[2] The control groups were then combined and odds ratios calculated for matched triplets. Using a 95% confidence interval, the null hypothesis of an odds ratio equal to one was tested with computer programs developed by Rothman and Boice.[3] Characteristics of the patients with mesothelioma and the source of asbestos exposure of their owners are listed in Table I. The distribution of mesothelioma by site was six (33%) peritoneal, five (28%) pleural, five (28%) both peritoneal and pleural, and two (11%) pericardial.

The mean age (± 1 SD) of the mesothelioma dogs was 8.0 ± 1.9 years; 17 (94%) were male and 15 (83%) were purebreeds. When compared to the entire canine hospital population, males had a relative risk for

TABLE 1

CHARACTERISTICS OF 18 CANINE PATIENTS DIAGNOSED WITH MESOTHELIOMA AT VHUP BETWEEN 1977 AND 1981, AND THEIR EXPOSURE TO ASBESTOS

Patient	Breed	Sex	Age at diagnosis (years)	Year of diagnosis	Site of meso-thelioma[a]	Type of asbestos exposure		
						Owner occupation (or hobby) [c]	Household neighborhood	Other possible
1	Mixed	M	12	1978	P	Auto body repair (1)	Extensive home remodeling	None
2	German Shepherd	M	7	1978	P	Auto mechanic (1)	Change of heating system	None
3	German Shepherd	M	9	1978	P	Truck repair (1) adjacent to shipyard	None	Accompanied owner to job adjacent to shipyard
4	Doberman Pinscher	M	8	1978	P&M	None	None	None
5	Irish Setter	F-S[b]	8	1979	Pe	Plumbing, heating, sheet rock spackling (1)	Cement factory	None
6	Bouvier des Flandres	M	8	1979	P	None	None	Flea powder
7.	Mixed[c]	M	10	1979	P&M	—	—	—
8	Bouvier des Flandres	M	8	1979	M	None	None	None
9	German Shepherd	M	?	1979	P&M	Sheet rock spackling at shipyard (0)	Demolition and construction site	Flea powder
10	Boston Terrier	M	-	1979	P&M	None	None	None
11	Irish Setter	M	4	1980	M	None	Home insulation, construction site	Flea powder
12	German Shepherd	M	10	1981	P&M	Pipefitting at shipyard (0)	None	Flea powder
13	Bernese Mtn Dog	M	4	1977	M	None	None	None
14	Old Eng Sheepdog	M	6	1981	Pe	None	Demolition & construction sites	None
15	German Shepherd	M	8	1981	P	Auto mechanic (1)	Home insulation	None
16	German Short Hair Pointer	M	11	1981	M	—	—	—
17	Mixed	M	8	1981	M	Oil burner and furnace installation (1)	None	Flea powder
18	German Shepherd	M	6	1981	P	Auto body and used parts supply (1)	None	Accompanied owner to work

[a] P = peritoneal, M = pleural, Pe = pericardial
[b] Female-spayed
[c] Not included in case-control analysis. Unable to contact owner for interview

TABLE 2
Matched Pair Analysis of Risk Factors for Canine Mesothelioma

Risk factor	Noncancer controls			Cancer controls		
	Odds ratio	No. DP[a]	Confidence limits (95%)	Odds ratio	No. DP[a]	Confidence limits (95%)
Domestic and owner occupational exposures						
Home remodeling or construction	0.3	8	0.1–1.2	0.4	10	0.1–1.6
Addition of home insulation	0.5	6	0.1–2.6	0.8	[b]	0.2–3.1
Home in vicinity of asbestos-related industry	2.0	6	0.4–10.6	0.8	[b]	0.2–3.2
Occupation or hobby asbestos related	8.0	9	1.4–10.6	2.1	10	0.6–8.7
Urban (vs rural) residence of dog						
First residence	[c]	5	—	1.5	9	0.4–5.1
Longest residence	4.0	5	0.5–30.1	1.2	11	0.4–3.9
Residence at diagnosis	2.0	6	0.5–10.6	1.0	10	—
Management of dog						
Source: stray vs all other	2.0	1	0.2–21.0	[b]	4	—
Time outside (>50% vs <50%)	5.0	6	0.7–34.5	2.5	[b]	0.5–12.2
Supervision: allowed to roam vs confined	2.0	9	0.5–7.8	1.0	8	0.7–11.8
Pesticides used on dog						
Flea powder	5.0	6	0.7–34.5	1.7	8	0.4–6.9
Flea spray	3.0	4	0.4–25.8	1.5	10	0.4–5.1
Flea dip	2.5	7	0.5–12.2	1.5	10	0.4–5.1
Flea collar	1.3	7	0.3–5.9	1.0	6	—
Any pesticide	11.0	5	1.5–82.1	5.0	6	0.7–35.5

[a] Number of Discordant Pairs
[b] Not able to calculate. The cases were all strays while the controls were of known origin
[c] Not able to calculate. The cases all had an urban residence while the controls had a rural residence

TABLE 3
Asbestos Fiber Content in Lung Tissue of Dogs

Patient	Category	Age at Diagnosis (Years)	Fiber type (No. g dry wt)	
			Chrysotile	Amphibole
	Mesothelioma			
12		10	3,100,000	0
14		6	7,200,000	3,300,000
18		6	22,000,000	760,000
	Lung Cancer			
A	Squamous cell carcinoma	12	8,200,000	4,800,000
B	Bronchial alveolar carcinoma	13	200,000	200,000
C	Bronchial–alveolar carcinoma	8	69,000	0
	Controls[a]			
D		5	325,000	80,000
E		9	700,000	0
F		6	800,000	200,000
G		6	2,900,000	720,000
H		8	1,100,000	0
I		8	0	240,000

[a] Non-respiratory disease and noncancer

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mesothelioma of 16.6 ($CL_{95\%}$ 6.4-97.3). When dogs 1 to 4 years of age were assigned a relative risk of 1.0 the greatest risk was observed in dogs 5 to 9 years of age (OR = 16.9, $CL_{95\%}$ 3.4-84.3). The risk for purebreed dogs when compared to dogs of mixed breeding was 1.7 but this difference was not statistically significant ($CL_{95\%}$ 0.51-5.9). The relative risk for individual purebreeds represented by more than one dog with mesothelioma was Bouvier des Flandres (OR = 124.3, $CL_{95\%}$ 62.6-246.7), Irish Setter (OR = 5.3, $CL_{95\%}$ 1.4-9.6), and German Shepherd (OR = 3.3, $CL_{95\%}$ 1.3-8.2).

The cancer and noncancer control patients represented a wide variety of diseases and conditions; not more than two dogs had the same diagnosis. Owners of 16 of the 18 mesothelioma patients were contacted and interviewed. The OR for suspected risk factors for canine mesothelioma are shown in Table 2. The findings were similar when mesothelioma patients were compared to either the cancer or noncancer control group. However, for 11 of the 14 risk factors studied, a stronger association with mesothelioma was noted in the analysis using the noncancer controls. Exposure of the owner to asbestos at work or through a hobby was found to be significantly associated with mesothelioma in the analysis using noncancer controls, (OR = 8.0, $CL_{95\%}$ 1.4-45.9); when cancer controls were used the odds ratio was 2.3, but was not significant (CL_{95} 0.6-8.7). The relative risk for mesothelioma with both control groups combined was 3.5 ($CL_{95\%}$ 1.1-11.0).

Information on the use of pesticides and insect repellents was obtained because talc may be contaminated with asbestos and other mineral fibers.[4] The relative risk for all forms of pesticides was elevated and was significant when any pesticide use was considered in comparison to noncancer controls (OR=11.0, $CL_{95\%}$ 1.5-82.1). The risk associated with any pesticide use when the control groups were combined was also significant (OR= 7.6, $CL_{95\%}$ 1.2-49.0). Preliminary microscopic observations of seven commercially available pet flea powders and sprays revealed large amounts of quartz, silicates, and silica, and small amounts of antigonite, a fiber closely related to chrysotile asbestos. While asbestos fibers were not specifically identified, exposure of humans to other mineral fibers has been associated with pulmonary disease (e.g., silicosis). Results of the lung tissue fiber analysis are presented in Table 3. The three dogs with mesothelioma had the highest levels of chrysotile fibers. The amphibole consisted of tremolite and actinolite, except in the case of control dog 1, where it was commercial amphibole in the form of amosite and crocidolite. The authors stated that the tremolite and actinolite were probably contaminants of the chrysotile.

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Methods: Ninety-six male and 96 female (barrier protected caesarian derived; Wistar strain) 6-8 week old rats were randomly allocated to one of the following groups:

(a) talc - Italian 00000 grade (92% talc mineral, 3% chlorite and 1% carbonate minerals; quartz was found in the powder at 0.5-1.0% level); no asbestos minerals of either tremolite or chrysotile varieties were detected;

(b) super fine chrysotile asbestos (SFA chrysotile);

(c) controls - no exposure to either material.

The animals were housed four to a cage except when in inhalation chambers (in a separate room) when there were 6 to a cage. Rats were fed on a proprietary brand of autoclaved cubes and water ad libitum; home cages were supplied with filtered air. There were sacrifices ten days after the end of each exposure period and at one year. The remaining animals were allowed to live until they died or appeared to be distressed. A full necropsy examination was carried out on all animals.

The dust clouds were generated for 7½ hours a day, 5 days a week. After 6 months' exposure half of the rats were removed and transferred to ordinary cages and were replaced by another 24 animals per dust. These rats were in turn removed and replaced after 3 months' exposure, and all exposure ceased after another 3 months (48 rats were exposed for 3 months, 24 for 6 months, and 24 for 12 months). The dosage was calculated as the product of concentration and time. The mean respirable dust concentration was 10.8 mg/m³ for each dust and the cumulative doses, i.e., the product of concentration and time, were approximately 4100, 8200, and 16400 mg/m³ hrs. for the 3-, 6-, and 12-month exposures.

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Results: Survival data were not presented. The amount of dust in the lungs was determined for the sacrificed rats. For talc, the mean amounts of dust in the lungs were 2.8, 4.5, and 12.3 mg per rat at the end of exposures of 3, 6, and 12 months, respectively. In contrast, the amount of SFA crysotile was close to the detection limit of the method and was estimated as only 0.6 mg/rat after 12 months' exposure.

An assessment was made of the severity of fibrosis in the lungs of rats sacrificed at the end of exposure and one year later (see Table 1 below).

TABLE 1. Inhalation Experiment - Mean Fibrosis at End of Exposure and One Year Later (Number of Rats)

Material	Time	Length of exposure		
		3 months	6 months	12 months
Italian talc	End of exposure	2 2 (8)	2 7 (6)	3 4 (6)
	1 year later	2 4 (8)	3 4 (4)	4 6 (4)
SFA chrysotile	End of exposure	2 8 (8)	3 0 (6)	3 2 (8)
	1 year later	2 2 (8)	3 2 (4)	4 2 (4)
Controls	End of exposure	1 8 (8)	1 9 (6)	1 3 (8)
	1 year later	1 6 (8)	1 5 (3)	1 9 (3)

The main features are that both Italian talc and SFA chrysotile produced fibrosis to a similar extent, and that there was some evidence of progression after exposure was discontinued in the longer exposed animals.

The number of rats with lung tumors are shown in Table 2. One adenoma occurred in the control group, two adenomata were observed in the rats exposed to talc, and 13 lung tumors, including one mesothelioma and 3 adenocarcinomata were observed in the SFA chrysotile group.

TABLE 2. Inhalation Experiment - Lung Tumors

Material	Exposure	Number at risk[1]	Adenomas	Number of lung tumors		
				Adenoma-losis	Adeno-carcinomas	Mesotheliomas
Italian Talc	3 months	39	0	0	0	0
	6 months	18	0	0	0	0
	12 months	24	2	0	0	0
SFA Chrysotile	3 months	40	0	0	0	1
	6 months	18	1	2	1	0
	12 months	22	3	3	2	0
Controls		71	1	0	0	0

[1]Number surviving at least 300 days from start of exposure

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Study No.	Type of Activity	Fiber Type	Exposure (how measured*)	No. in Cohort	Total Deaths (O/E) SMR	No. mesotheliomas	Lung Cancer Obs exp. SMR	Slope	Gastrointestinal Cancer obs exp SMR RR	Time since first exposure	Duration of Exposure	Type of Control	Analysis method
57	mining	chrysotile	mppcf low: 2.5-4.2 medium: 4.3-9.4 high: 14.4-23.6 very high: 46.8-82.6 (1)	10,939(M) 440(F)	4463(M) (1.06) 84(F) (0.9)	10(M) 1(F)	230 184 1.25	0.14 mppcf-yr	276 272.4 1.01	20+ years	At least one month	Quebec population	a,b
81	mining	chrysotile	10-36 f/ml (8)	544	178 (1.11)	1	28 11.1 2.5	mppcf-yr 0.30	10 9.5 1.05	20 yrs	20 yrs	Canadian death rates	
	mining	chrysotile	Cumulative exposure <100 f/y ≥100 f/y (2,3)	952	332 (1.55) 20 yrs (207) 20 yrs (137)	1	11 10.4 106 20 yrs: 1 1.7 59 20 yrs: 10 8.7 115	0.17 f/ml-yr	19 19.3 98 20 yrs: 4 4.8 83 20 yrs: 15 14.5 103	20 yrs 20 yrs	At least 30 days	National death rate (Italian)	a,c
65	friction materials	chrysotile crocidolite	Cumulative exposure (f-y/ml) (6) 0-9 10-49 50-99 100-356	13,460	M 1339 (0.9) F 299 (0.9)	M 8 F 2	M 151 139.5 1.09 F 8 11.3 0.71	f/ml-yrs 0.06	103 107 0.96 29 27 1.1		At least 10 yrs	National rates in U.K.	a,d
83	friction materials	chrysolite	mppcf (1) yrs level <1 2.28 1>5 2.06 5>20 .56 ≥20 1.06 Total 1.84	3641	1267	0	73 148.7	0.16	59 114.4	20 yrs	At least 1 month	Connecticut rates	e,f
73	textile	chrysolite crocidolite	1951- 10.8 f/cc 1972 - 2.9 f/cc (2,3)	822 (M) 284 (F)	293 (1.3) 24 (1.0)	9 1	51 23.8 2.1 F 3 0.9 3.3		16 15.7 1.02	From 10 to greater than 20 yrs	At least 10 yrs	National death rates	

Study No.	Type of Activity	Fiber Type	Exposure (how measured*)	No. in Cohort	Total deaths (O/E)	No. mesothel-iomas	Lung Cancer	Slope	Gastrointestinal Cancer				Time since first exposure	Duration of Exposure	Type of Control	Analysis method
									Obs	Exp	SMR	RR				
70	cement products	chrysotile crocido-lite	1-yr/ml (mean) (1) A - 44 B - 92 C - 180	328	125	11	37 5.6 6.6	f/ml-yr 4.82	8	5.4	1.48		20-33 yrs	at least 9 yrs	Ontario death rates	a
			P=production workers 18 yr-112.5f-yr/ml M=maintenance workers C=unexposed workers	186	58 (1.7)	10	20 3.3 6.1	R=0.067	4	2.5	1.6			18 yrs		
67	general manufac-turing	chrysotile crocidolite amosite	mppcf (1) cumulative dust exposure <125 (62) 125-249 (182) 250-499 (352) 500-749 (606) 750 + (976)	1075	781 (1.2)	5	19 197.9 9 180.0 19 327.6 9 450.0 7 777.8 63 270.0	0.658 mppcf-yr	55	39.9	1.4		retired workers	Avg. 25 yrs (3-51)	US male population	g
64	general manufac-turing (tex-tiles insula-tion materials)	chrysotile crocidolite amosite	f/ml 2 5-10 ≥20	4600 (M) 922 (f)	545 (1.74) 200 (1.69)	46 21	103 43.2 2.4 27 3.2 8.4		40 20	34 10.2	118 196		from 10-30 yrs	variable	national death rates of U.K.	
74	Insula-tors	chrysotile crocidolite amosite	(6) 4-12 f/ml	632	478	38	93 13.3 699		43	15.1	285		20+yrs		U.S. death	

Study No.	Type of Activity	Fiber Type	Exposure (how measured[a])	No. in Cohort	Total deaths (O/E)	No. mesotheliomas	Lung Cancer	Slope	Gastrointestinal Cancer				Time since first exposure	Duration of Exposure	Type of Control	Analysis method
									Obs	Exp	SMR	RR				
74	insula-tors	chrysotile amosite	4-12 f/ml (6)	17,800	2271 (1.4)	175	429 105.6 4.60	EPA .0107 1.01 (f/m/yr)	94	59.4	1.67		under 20 yrs over 20 years		U.S. death rates	
88	general manuf.	chrysotile crocidolite amosite	mppcf <125 125-249 250-400 500-749 750+	1348	754 (115)	not reported	58 21.7 267.3		53	41.8	126.8		20 yrs	ave. 25 yrs	urban popula-tion US males	
87	cement products	chrysotile crocidolite	total dust w/in 20 yrs initial exposure mppcf-yr (1) <10 11-50 51-100 101-200 >200	5645	601 (0.7)	2	<10 19 24.7 .77 11-50 8 11.4 .70 51-100 1 3.8 .26 101-200 9 3.1 2.90 >200 14 6.2 2.26 Total 51 49.2 1.0	mppcf-yr .44	10 10 3 0 2 Total 25	24.6 11.9 4.2 3 6.4 50.1	.41 .84 .71 - .31 0.5		>20 yrs	-	US and Louisiana death rates	(a)

Study No.	Type of Activity	Fiber Type	Exposure (how measured*)	No. in Cohort	Total deaths (O/E)	No. mesotheliomas	lung Cancer	Slope	Gastrointestinal Cancer Obs Exp SMR RR	Time since first exposure	Duration of Exposure	Type of Control	Analysis method
84	Textile	chrysotile crocidolite	cumulative exposure(1,5) (f/ml-yrs) 100-400+ 30f/ml (ave.)	679	201	7	28 18.6 1.5 / 12 4.65 2.6	1/ml-yr 1.0	14 17.6 1.1	10-30 yrs / 10-25 yrs	at least 10 yrs	national death rates	
85	Textile	chrysotile crocidolite	mpcf (ave. dust conc.) yrs level <1 2.11, 1,<5 1.86, 5,<20 1.67, ≥20 1.23, Total 1.8 (1)	2410	857 (1.27)	1	66 (not given) / 59 199.5	8.2 / mpcf.y 0.059	36 (not given) / 26 151.7	at least 10 yrs / 20 yrs	at least one month	S.Carolina rates	a,f
86	Textile	chrysotile amosite crocidolite	mpcf (ave. dust conc.) yrs level <1 2.60, 1,<5 2.40, 5,<20 2.73, ≥20 1.58, Total 2.32 (1)	4022	1392 (SMR=109)	14	70 / 53 105	mpcf.y 0.051	73 / 54 112.7	20 yrs	at least 1 month	Penna. rates	a,f

Analysis method used

(a)   man-years method-case
(b)   case-Lea-multiple controls analysis
(c)   McDonald & Liddell
(d)   case-control - Liddell
(e)   Mantel-Haenszel log-rank method
(f)   man-yrs life table method - Hill
(g)   modified lifetable method - Enterline

Exposure measurement procedure

(1)   midget impinger
(2)   membrane filter collection
(3)   phase contrast microscopy
(4)   thermal precipitator
(5)   static membrane filter
(6)   simulated conditions
(7)   actual conditions
(8)   NIOSH methods
(9)
(0) not stated

Exhibit B

Research & Engineering Center
August 11, 1971

MEMO FOR FILE:

FDA MEETING - ASBESTOS IN COSMETIC TALCS
AUGUST 3, 1971 - WASHINGTON, D.C.

The purpose and list of participants and discussants are given
in the attached two handouts from the meeting.

Summary

Dr. Romer (NYC Department of Air Resources) set the basis for
the meeting and reiterated his "demands" that the FDA:

1. specify lab procedures for evaluating talc;

2. evaluate cosmetic talcs;

3. decide on the acceptable limits of asbestos; and,

4. ban the sale of those cosmetic talcs which they deemed
   unacceptable.

Dr. Weissler (FDA) summarized at the end of the meeting by indi-
cating that FDA would decide which analytical techniques should
be used to evaluate cosmetic talcs, but would take no action
towards banning any talcs until they had secured competent advice
concerning the potential hazard of talcs containing small amounts
of asbestos. He will obtain specific written comments concerning
analytical techniques from the participants, specific health ad-
vice from various Government and other medical specialists, and
will issue a summary memorandum on the meeting, including FDA's
plans to evaluate cosmetic talcs. His outlook on the problem
seemed to be reasonable and he was, at least for the moment, not
stampeded by Romer's frequent interjections and demands for imme-
diate action by FDA.

The following briefly summarizes the comments by the various
speakers and associated discussion.

Dr. Malcolm Ross - U.S. Geological Survey

Described the genesis and geology of talc deposits, particularly
in the New England area. New York State talcs generally charac-
terized by high impurity contents of tremolite and quartz.

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FDA MEETING
ASBESTOS IN COSMETIC TALCS

Vermont talcs (source of J&J) generally relatively free of tremolite or other asbestos minerals.

Dr. Lewis J. Cralley - National Institute of Occupational
Safety and Health, Cincinnati, Ohio

Reviewed definition of "fiber" and related the hazard to respirability and time of total exposure. Introduced again the concept of heavy metal carcinogenesis. Reviewed his published study of fibers in talc and stated emphatically that he could detect only talc by X-rays. This reference to the probable presence of asbestos fiber in these talcs was, in fact, only a "probability" based on the known geology of talc deposits.

Dr. Irving J. Selikoff - Mt. Sinai School of Medicine

Gave his usual asbestos workers story following through to his study of chrysotile in lungs of New Yorkers. He stated "that lung cancer is not necessarily dose related", but in later discussion indicated that there might be a level below which it was not harmful. He alluded to the possibility that organic and other additives in talcum powder were potentially harmful.

He noted Kleinfeld's study of talc workers (Arch. Env. Health, Vol. 14:663, 1967) but stated it was not necessarily extrapolatable to community environment. He noted excess lung cancer in talc workers in the Gouverneur, New York district of tremolite talc. He emphasized the importance of smoking habits in asbestos worker's excess lung cancer, but not in mesothelioma.

Dr. Gavin Hildick-Smith - Johnson & Johnson

Estimated total integrated exposure of a baby to talc dust as less than six days and total exposure of a man using talc several times a day during entire life as only a few months. He described use benefits of talc in open heart surgery and other techniques to secure a desired fibrotic reaction and noted that not all talcs were equally good in this respect. He showed Dr. W. E. Smith's results on hamsters, which included one sample of a tremolitic talc with no carcinogenic effect. Incidentally, the data included three cases of carcinoma with exposure to diatomaceous earth

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Dr. Paul Gross - Industrial Health Foundation

Described animal experiments with talc (previously used on phy-
sicians' gloves) injected intentionally into bellies of animals.
These produced no granulomas. He described intertracheal in-
jections of hamsters with three types of talc (high nickel, low
nickel, and off-the-shelf cosmetic talc). No fibrosis after
two years, despite excessive amounts used. He noted Ian Webster's
conclusions that fibers must be at least 5 microns long to be
harmful.

Dr. Morris Kaplan - Consumers Union

Reiterated his interest in the safety of the consumer and that
any bias introduced in the evaluation and "banning" of talc
should be in the consumer's interest.

Dr. Raymond E. Barzilai - PDA

Described PDA's work on the use of particulates as drugs or as
adjuncts to rugs. His review of the use of particulates in bio-
medical research indicated: (1) the extreme paucity of animal
work, (2) no evidence or reference to mesothelioma, and (3) poor
characterization of the materials used in the research work.

Selikoff noted that talcs used to take off hulls from rice may
not always be removed from the rice and, in fact, talc with am-
phibole impurity had been noted in rice on the West Coast.

Dr. Herman F. Kraybill - FDA

Entered the political plea that FDA had indeed been active in
studying health problems and had met several times with Cralley
and Selikoff in 1967 and 1968. He introduced their previous
interest in the "asbestos in beer" situation. I clarified the
situation by noting that the beer with most asbestos in our
studies had never been filtered through asbestos and owed its
fiber content to water which originated in wells from the
Pennsylvania Serpentine Belt.

William V. Eisenberg - FDA

Reviewed FDA's optical microscopy competence in detecting asbestos.
He indicated one per cent was detectable. Nicholson introduced the

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subject of asbestos in injectable drugs and stated that more
than one-half of injectable drugs in a survey at the Mt. Sinai
Hospital Pharmacy contained asbestos in amounts up to 1 micro-
gram in a vial.

S. Speil - Johns-Manville

Reviewed asbestos technology and the importance of respirable
fraction vs total sample. Suggested separation into airborne
sample or use of "simulated tests" with personal samplers and
counting by ACGIH methods using recognized TLV with an "expo-
sure time" factor.

Nicholson objected to using present "high" TLV limits because
of "millions of people at risk" and Romer reintroduced "cloud
of fiber" scare.

Indicated 0.5 per cent amphibole was detectable by X-ray as
total but not specific amphiboles. Also that serpentine plus
chrysotile detectable by X-ray less than 1 per cent, with post-
acid treatment to distinguish between the two materials.

Emphasized need for examining for fibrous state if X-rays indi-
cated presence. Careful petrographic techniques could detect
amphiboles and chrysotile at 1 per cent limit. Downplayed use
of EM because of unknown biologic effect of this size, proba-
bility of finding tiny amounts probably not biologically sig-
nificant by this technique, and extreme cost. Reviewed possi-
bility of lower detection limits by concentration with heavy
liquids and a simple test for tremolite and actinolite by acid
leaching, followed by calcium oxide determination.

Dr. S. Lewin - New York University
              Consultant for Whittaker, Clark & Daniels

Suggested use of X-ray detection with 0.5 per cent detectable.
Indicated presence of "crocidolite" in one talc sample (probably
a different amphibole), but all other cosmetic talcs clean by
X-rays.

Dr. Art Langer - Mt. Sinai School of Medicine

Discussed techniques used at Mt. Sinai starting with light micro-
scopy through microprobe, where necessary, and finally electron

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microscopy. Indicated approximately one week work for com-
plete evaluation of a talc sample. Showed many slides indi-
cating presence of fibers by EM and "chrysotile" not verified
by electron diffraction. Still feels identification of chry-
sotile by shape 90 to 95 per cent certain.

Dr. Norwood - Chas. Pfizer & Company

Pfizer talc from Montana. X-ray indicated slight chlorite
impurity, but no amphiboles. Suggested X-ray followed by
petrographic and chemical analysis by X-ray emission. Agreed
that 8.4 Angstroms (amphibole) and 7.3 Angstroms (chrysotile
plus serpentine) were sensitive X-ray detectors for approxi-
mately 0.5 per cent.

Dr. Wilson Nashed of Johnson & Johnson introduced the following
group representing J&J interests.

W. T. Caneer - Colorado School of Mines Research Institute

Reviewed p__ographic and electron probe studies of J&J. Showed
clean fiber.

Dr. Gene Geiger - McCrone

Reviewed McCrone study of J&J cosmetic talc. Petrographic and
EM determination revealed no asbestos fibers. Fibrous material
identified as talc, both in the light microscope size range and
in the EM size range. All EM work very detailed. Looked at 50
grid squares with micrographs. 12 fibrous particles detected
corresponding to 0.03 per cent of sample. 11 fibers definitely
identified by microprobe as rolled talc platelets. One fiber
unidentifiable. Rolled talc fibrils often tend to unroll after
a long delay period.

Very important observation by Geiger indicates that electron
microprobe analysis of "chrysotile fibrils" may be necessary
except where there is a known exposure to chrysotile.

1. Sodium sesquicitrate has essentially the same diameter as a
    chrysotile fibril with a "hole" down the center. This is
    sometimes added as a conditioning agent to cosmetic talc.

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2. Hydromagnesite is fibrous in form. Diameter of 200 Angstroms with a "hole" down the center. Hydromagnesite is known to occur in some talc deposits. Geiger questions some of Art Langer's identification of chrysotile fibrils. This was a smoke screen, but a good counter offensive to Langer finding chrysotile everywhere.

Dr. F. D. Pooley - University of South Wales

Examined J&J talc by EM techniques, including heavy liquid density separation in a centrifuge. All fibrous constituents were identified as talc by electron diffraction.

Dr. R. F. Rolle - Johnson & Johnson

Showed beautiful electron micrographs of rolled up platelets of talc. Samples were made by replication using gold palladium plating.

Dr. W. F. Nicholson - Mt. Sinai School of Medicine

Sales pitch proposed a low level and high level study program for surveying cosmetic talcs. The low level technique would include polarized light microscopy and X-ray examination, and then possibly electron microscopy plus identification, if necessary. Langer questions whether 1 per cent chrysotile in fibrillar form could be detected and showed his studies of Spex milled chrysotile with no X-ray pattern visible after intensive grinding. I countered that this material was no longer chrysotile and, therefore, not pertinent.

Nicholson's more extensive program included, in addition to the initial survey:

1. air sampling tests and complete analysis from a selected gamut of samples after preliminary screening, as above;

2. statistical study of the Mt. Sinai lung survey samples of New York people to correlate fiber and talc content in the lungs with talc usage; and,

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Y. a complete epidemiological study of the workers mining and
    producing cosmetic talcs.

C. Maggiore - Mt. Sinai School of Medicine

Reported on Mt. Sinai exploratory work towards the development
of instrumentation for completely characterizing many and all
fibers and particles in a sample by shape, size, chemical
analysis, etc. He indicated the need for approximately $300,000
and 2 to 3 years for design and construction of a prototype unit.

S. SPEIL

SS/rs

Attachments (2)

cc:
W. P. Raines, DH
M. Swetonic, DH
C. H. Sheckler, DH
F. L. Pundsack
E. M. Fenner
J. P. Leineweber
File noted by:
    F. B. Hutto
    W. C. Streib

Exhibit F

EMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

F-620

: Dr. Robert M. Schaffner, Director
Office of Technology (BF-400)

DATE: July 31, 1973

)M : Dr. Alfred Weissler, Acting Director
Division of Color Technology (BF-430)

JECT: Summary and Comments on Prof. Lewin's Analytical Results for Asbestos
in Talc

1. The purposes of this memorandum are to present a summary of the
analytical results for asbestos in Cosmetic talcum-type powders obtained
by Prof. Seymour Z. Lewin of New York University in his role of consult-
ant to FDA; to compare his results with those obtained by other labora-
tories on some of the same samples; and to make some comments on the gen-
eral question of suitable techniques for the analysis of asbestos in talc.

2. I asked Dr. Lewin in December 1971 to undertake asbestos analyses in
100 samples of cosmetic powders; the scope was expanded on two subsequent
occasions, to include a total of 195 samples. I chose Dr. Lewin for this
work because he is an internationally-recognized expert on mineralogical
chemistry and because he is a member of the academic community and there-
fore likely to be impartial in a confrontation between industry and
government. Furthermore, his competence had previously been recognized
by industry (by virtue of their own use of him as a consultant) which
appeared to confer a desirable immunity against possible industry attacks
on the validity of the results.

3. Dr. Lewin's findings are shown in Table I; the key to the identities
of the numbered samples is given in Table IV. Please note also the ex-
planatory comments in Dr. Lewin's memo of July 10, 1973, which is an
Attachment to Table I. No varieties of asbestos other than chrysotile
(a serpentine) or tremolite (an amphibole) were found by Dr. Lewin in the
195 samples which he examined. As shown in Table I, Dr. Lewin found
definite indications of chrysotile in 17 of the samples (many of these
also had tremolite) and definite indications of tremolite but not chryso-
tile in an additional 18 of the samples. These results were obtained
primarily by means of X-Ray diffraction, supplemented in some cases by
optical microscopy and other techniques. However, Dr. Lewin points out
on page 2, paragraph 1 of the Table I Attachment that the chrysotile he
has identified in commercial products shows several significant dif-
ferences from "classical" chrysotile: in the location of its X-Ray dif-
fraction peaks, in its appearance under the microscope, in its reactivity
toward dilute acid, and in its behavior with respect to differential
thermal analysis.

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4. In Table II, I have compared Dr. Lewin's results for tremolite with those obtained for some of the same samples at FDA (by means of optical microscopy) and at the Pfizer Minerals, Pigments, and Metals Division (by means of X-Ray diffraction). This comparison, which was undertaken in order to obtain additional information on the samples, shows good semi-quantitative agreement among the three laboratories. Whatever quantitative differences exist in the amounts of tremolite found can be understood readily on the basis of such factors as (a) preferred orientation of plates and fibers in the packing of the X-Ray diffraction sample, and (b) inhomogeneities in sample composition, caused for example by air elutriation within the container when it is shaken.

5. In Table III, I have compared Dr. Lewin's results for chrysotile with those obtained for some of the same samples by four other laboratories; the additional two laboratories included in this part of the study are Columbia Scientific Industries of Austin, Texas (who sell the Stone apparatus for differential thermal analysis) and the Health Protection Branch of the Department of National Health and Welfare of the Canadian government in Ottawa. The agreement of results from different laboratories is much less satisfactory for chrysotile than that discussed above for tremolite. For example, samples 89 and 163 were found by Dr. Lewin to contain 5% and 10% of chrysotile, respectively, but chrysotile was not found in these samples by the other laboratories. Also, a preliminary finding of chrysotile in a sample of Johnson and Johnson Shower to Shower Body Powder has been disputed by the company, which claimed that their own analyses by several different techniques fail to show the presence of chrysotile. The explanation for these differences is attributable largely to Dr. Lewin's inclusion in the term "chrysotile" of mineral species which show significant differences from classical chrysotile, as discussed in paragraph 3 above.

6. The difficulties involved in analyzing talc and other samples for small amounts of asbestos have been pointed out by many investigators. It is not surprising that the results of different laboratories disagree sometimes, especially in the presence of transitional or altered mineralogical species. Moreover, with regard to the two varieties of asbestos of concern here, it is unfortunate that the one which is a clear inhalation hazard to man, namely chrysotile, poses an intrinsically more difficult analytical problem than the other, tremolite, which has not yet been shown to present a biological hazard. This is due in part to the less prominent X-ray diffraction peaks of chrysotile and to the fact that the fibers are often too small to be seen in the optical microscope.

7. In connection with a proposed new regulation on the safety of cosmetic talcum powders, we face the problem of specifying an analytical test for asbestos which must be satisfied by the powders if they are not to be considerated adulterated. On the basis of information available at present, I recommend consideration of the following procedure. The powders shall be examined first by X-ray diffraction, which has a sensitivity of the order of 1% for chrysotile and somewhat greater sensitivity

Page 3 - Dr. Robert M. Schaffner

for tremolite. If either species is found, confirmation that the species is present in fiber form is to be obtained by optical microscopy and electron microscopy. This is necessary because tremolite is known to occur in a non-fibrous form, and the X-ray diffraction pattern of chrysotile is the same as that of antigorite, a non-fibrous form of the same mineral. The sample is considered adulterated if the presence of fibrous tremolite or chrysotile is shown by the above procedure. An alternative procedure, based solely on optical microscopy (which is a less expensive and more widely available technique) might be proposed. However, the difficulty with optical microscopy alone is that it may completely miss the presence of chrysotile if the fibers are submicroscopic, which may well be the case in finely-milled talc; X-ray diffraction is not subject to this source of error.

Alfred Weissler, Ph.D.

Enclosures

FINAL REPORT

X-RAY POWDER DIFFRACTION ANALYSES OF COMMERCIAL COSMETIC POWDERS

Sample	Talc	Chlorite	Phlogo-pite	α-Quartz	Dolo-mite	Calcite	Trem-olite	Chryso-tile	Other Species
1	70%	3%	7%	n.d.	n.d.	n.d.	n.d.	n.d.	
2	100%	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	
3	99%	n.d.	1%	n.d.	n.d.	n.d.	n.d.	n.d.	
4	100%	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	
5	95%	2%	3%	n.d.	n.d.	n.d.	n.d.	n.d.	
6	80%	2%	5%	n.d.	n.d.	n.d.	n.d.	n.d.	CaUndecyl
7	86%	7%	2%	3%	2%	n.d.	n.d.	?	
8	95%	2%	3%	n.d.	n.d.	n.d.	n.d.	n.d.	
9	89%	7%	2%	2%	n.d.	n.d.	n.d.	n.d.	
10	93%	3%	2%	2%	n.d.	n.d.	n.d.	n.d.	
11	90%	2%	2%	4%	2%	n.d.	n.d.	n.d.	
12	100%	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	
13	60%	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	ZnUndecyl
14	31%	50%	2%	10%	7%	n.d.	n.d.	n.d.	
15	100%	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	
16	--	--	--	--	--	--	--	--	Kaolin, Starch
17	60%	30%	4%	n.d.	6%	n.d.	n.d.	n.d.	
18	90%	4%	2%	2%	2%	n.d.	n.d.	n.d.	
19	97%	1%	2%	n.d.	n.d.	n.d.	n.d.	n.d.	
20	35%	60%	1%	4%	n.d.	n.d.	n.d.	n.d.	
21	67%	25%	2%	3%	3%	n.d.	n.d.	n.d.	
22	59%	35%	1%	n.d.	5%	n.d.	n.d.	n.d.	
23	42%	50%	2%	3%	3%	n.d.	n.d.	?	
24	94%	1%	2%	3%	n.d.	n.d.	n.d.	n.d.	
25	95%	2%	3%	n.d.	n.d.	n.d.	n.d.	?	
26	95%	1%	4%	n.d.	n.d.	n.d.	n.d.	?	
27	78%	n.d.	2%	n.d.	20%	n.d.	n.d.	n.d.	
28	ca.20%	1%	n.d.	n.d.	n.d.	10%	n.d.	n.d.	Kaolin, Mica
29	ca.94%	n.d.	2%	n.d.	2%	n.d.	n.d.	n.d.	Kaolin
30	97%	1%	2%	n.d.	n.d.	n.d.	n.d.	n.d.	
31	47%	50%	2%	3%	8%	n.d.	n.d.	n.d.	
32	80%	7%	3%	2%	8%	n.d.	n.d.	n.d.	

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ample	Talc	Chlorite	Phlogo-pite	α-Quartz	Dolo-mite	Calcite	Trem-olite	Chryso-tile	Other Species
33	55%	40%	2%	n.d.	3%	n.d.	n.d.	n.d.	
34	78%	7%	4%	3%	8%	n.d.	n.d.	n.d.	
35	78%	5%	2%	10%	5%	n.d.	n.d.	n.d.	
36	ca.81%	4%	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	Mica
37	38%	50%	5%	n.d.	7%	n.d.	n.d.	n.d.	
38	87%	5%	4%	2%	2%	n.d.	n.d.	n.d.	
39	94%	3%	n.d.	3%	n.d.	n.d.	n.d.	n.d.	
40	67%	25%	n.d.	3%	5%	n.d.	n.d.	n.d.	
41	33%	8%	2%	2%	5%	n.d.	n.d.	n.d.	
42	89%	6%	n.d.	n.d.	3%	2%	n.d.	n.d.	
43	97%	n.d.	n.d.	3%	n.d.	n.d.	n.d.	n.d.	
44	--	--	--	--	--	--	--	--	ZnO, Kaolin
45	66%	30%	n.d.	n.d.	4%	n.d.	n.d.	n.d.	
46	48%	40%	n.d.	5%	7%	n.d.	n.d.	n.d.	
47	98%	n.d.	n.d.	n.d.	n.d.	2%	n.d.	n.d.	
48	88%	4%	2%	2%	4%	n.d.	n.d.	n.d.	
49	100%	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	
50	95%	5%	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	
51	100%	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	
52	87%	8%	2%	3%	n.d.	n.d.	n.d.	n.d.	
53	90%	4%	2%	2%	2%	n.d.	n.d.	n.d.	
54	ca.87%	3%	4%	n.d.	4%	n.d.	n.d.	?	
55	80%	15%	n.d.	5%	n.d.	n.d.	n.d.	n.d.	
56	90%	7%	n.d.	3%	n.d.	n.d.	n.d.	n.d.	
57	80%	15%	n.d.	n.d.	5%	n.d.	n.d.	n.d.	
58	96%	n.d.	n.d.	4%	n.d.	n.d.	n.d.	n.d.	
59	ca.90%	n.d.	n.d.	3%	n.d.	n.d.	n.d.	n.d.	Starch
60	ca.60%	30%	n.d.	n.d.	7%	2%	n.d.	n.d.	ZnStear.
61	38%	40%	n.d.	4%	18%	n.d.	n.d.	n.d.	
62	85%	2%	n.d.	3%	n.d.	10%	n.d.	n.d.	
63	87%	2%	2%	4%	n.d.	n.d.	5%	n.d.	
64	ca.80%	5%	3%	2%	3%	n.d.	n.d.	n.d.	ZnStear.
65	ca.78%	15%	n.d.	n.d.	4%	n.d.	n.d.	n.d.	ZnStear.
66	84%	5%	3%	3%	3%	n.d.	n.d.	2%	
67	78%	15%	n.d.	n.d.	5%	n.d.	2%	n.d.	
68	80%	15%	n.d.	n.d.	5%	n.d.	n.d.	n.d.	
69	97%	1%	n.d.	n.d.	n.d.	2%	n.d.	n.d.	

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ample	Talc	Chlorite	Phlogo- pite	α- Quartz	Dolo- mite	Calcite	Trem- olite	Chryso- tile	Other Species
70	28%	60%	n.d.	5%	7%	n.d.	n.d.	n.d.	
71	85%	10%	n.d.	2%	n.d.	n.d.	3%	n.d.	
72	86%	5%	3%	4%	n.d.	2%	n.d.	n.d.	
73	ca.80%	10%	n.d.	3%	5%	n.d.	n.d.	n.d.	ZnStear.
74	90%	n.d.	n.d.	n.d.	5%	5%	n.d.	n.d.	
75	75%	5%	n.d.	n.d.	15%	5%	n.d.	n.d.	
76	75%	n.d.	5%	5%	10%	n.d.	5%	n.d.	
77	91%	n.d.	4%	2%	n.d.	n.d.	3%	n.d.	
78	85%	2%	1%	4%	3%	n.d.	5%	n.d.	
79	81%	5%	4%	n.d.	2%	8%	n.d.	n.d.	
80	ca.50%	40%	n.d.	8%	n.d.	n.d.	n.d.	?	
81	ca.80%	7%	1%	6%	4%	n.d.	n.d.	?	
82	ca.78%	12%	2%	4%	3%	n.d.	n.d.	?	
83	ca.84%	6%	5%	n.d.	4%	n.d.	n.d.	?	
84	ca.92%	4%	n.d.	n.d.	3%	n.d.	n.d.	?	
85	ca.86%	5%	n.d.	n.d.	8%	n.d.	n.d.	?	
86	85%	4%	2%	4%	4%	n.d.	n.d.	?	
87	ca.30%	50%	n.d.	4%	12%	3%	n.d.	?	
88	61%	n.d.	n.d.	5%	25%	n.d.	4%	5%	
89	68%	1%	3%	8%	10%	n.d.	5%	5%	
90	55%	n.d.	3%	7%	25%	2%	3%	5%	
91	ca.50%	1%	n.d.	n.d.	3%	5%	n.d.	5%	Mica
92	64%	n.d.	n.d.	6%	20%	n.d.	5%	5%	
93	55%	1%	4%	6%	25%	n.d.	5%	4%	
94	ca.46%	4%	3%	6%	35%	n.d.	4%	?	
95	86%	n.d.	n.d.	5%	4%	n.d.	2%	3%	
96	28%	n.d.	3%	6%	45%	n.d.	8%	10%	
97	31%	1%	1%	5%	35%	n.d.	12%	15%	
98	ca.40%	n.d.	3%	n.d.	6%	2%	n.d.	n.d.	Kaolin, Mica
99	ca.40%	n.d.	3%	n.d.	6%	2%	n.d.	n.d.	Kaolin, Mica
00	ca.80	10%	4%	n.d.	2%	n.d.	n.d.	n.d.	ZnStear.
01	63%	8%	3%	7%	4%	n.d.	15%	n.d.	
02	63%	2%	n.d.	3%	15%	n.d.	10%	7%	
03	93%	3%	n.d.	n.d.	4%	n.d.	n.d.	n.d.	
104	91%	3%	1%	2%	3%	n.d.	n.d.	n.d.	

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ample	Talc	Chlorite	Phlego-pite	α-Quartz	Dolo-mite	Calcite	Trem-olite	Chryso-tile	Other Species
05	92%	3%	1%	2%	2%	n.d.	n.d.	n.d.	
.06	91%	3%	1%	3%	2%	n.d.	n.d.	n.d.	
.07	87%	5%	2%	n.d.	6%	n.d.	n.d.	n.d.	
.08	81%	10%	2%	2%	3%	n.d.	2%	n.d.	
.09	74%	15%	3%	3%	3%	n.d.	2%	?	Kaolin
.10	99%	n.d.	1%	n.d.	n.d.	n.d.	n.d.	n.d.	
.11	42%	40%	2%	n.d.	15%	n.d.	1%	n.d.	
.12	ca.60%	n.d.	n.d.	4%	n.d.	10%	n.d.	n.d.	Salicylic A., Boric
.13	75%	15%	n.d.	3%	7%	n.d.	n.d.	n.d.	
14	53%	40%	n.d.	3%	4%	n.d.	n.d.	n.d.	
15	53%	40%	n.d.	3%	4%	n.d.	n.d.	n.d.	
.16	53%	40%	n.d.	3%	4%	n.d.	n.d.	n.d.	
17	42%	35%	n.d.	15%	4%	2%	n.d.	?	
18	53%	40%	n.d.	3%	4%	n.d.	n.d.	n.d.	
19	49%	40%	n.d.	6%	5%	n.d.	n.d.	n.d.	
20	46%	40%	n.d.	8%	4%	n.d.	n.d.	?	
.21	87%	8%	2%	n.d.	3%	n.d.	n.d.	n.d.	
.22	56%	35%	n.d.	5%	4%	n.d.	n.d.	?	
.23	51%	40%	n.d.	3%	4%	n.d.	n.d.	?	
.24	54%	40%	n.d.	3%	3%	n.d.	n.d.	?	
.25	55%	40%	n.d.	2%	3%	n.d.	n.d.	?	
.26	75%	10%	3%	4%	8%	n.d.	n.d.	n.d.	
.27	85%	n.d.	n.d.	4%	n.d.	n.d.	n.d.	n.d.	Boric Acid
.28	60%	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	CaUndecyl.
.29	97%	n.d.	n.d.	n.d.	3%	n.d.	n.d.	n.d.	
.30	ca.88%	7%	n.d.	2%	3%	n.d.	trace	trace	
.31	ca.92	3%	3%	n.d.	2%	n.d.	trace	n.d.	
.32	95%	3%	2%	n.d.	n.d.	n.d.	n.d.	n.d.	
.33	94%	2%	4%	n.d.	n.d.	n.d.	n.d.	n.d.	
.34	93%	3%	2%	n.d.	2%	n.d.	n.d.	n.d.	
.35	93%	2%	3%	n.d.	2%	n.d.	n.d.	n.d.	
.36	89%	4%	3%	2%	2%	n.d.	n.d.	n.d.	
.37	91%	4%	n.d.	3%	2%	n.d.	n.d.	n.d.	
.38	85%	7%	3%	2%	3%	n.d.	n.d.	n.d.	
.39	ca.85%	n.d.	n.d.	2%	n.d.	n.d.	n.d.	n.d.	ZnStear. MgCO$_3$
.40	ca.85%	n.d.	n.d.	2%	1%	n.d.	n.d.	n.d.	ZnStear. MgCO$_3$

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Sample	Talc	Chlorite	Phlogo-pite	α-Quartz	Dolo-mite	Calcite	Trem-olite	Chryso-tile	Other Species
141	80%	n.d.	n.d.	2%	1%	n.d.	n.d.	n.d.	ZnStear, MgCO$_3$
142	79%	7%	5%	4%	5%	n.d.	n.d.	n.d.	
143	55%	2%	n.d.	3%	25%	n.d.	5%	10%	
144	ca.70%	10%	n.d.	6%	n.d.	n.d.	5%	?	ZnStear. Kaolin
145	ca.70%	3%	n.d.	n.d.	3%	n.d.	n.d.	2%	ZnStear. Kaolin, ZnO
146	ca.85%	n.d.	n.d.	4%	n.d.	5%	n.d.	n.d.	ZnStear.
147	ca.85%	n.d.	n.d.	n.d.	n.d.	5%	n.d.	n.d.	Kaolin
148	ca,45%	40%	n.d.	n.d.	8%	n.d.	2%	n.d.	ZnStear.
149	ca.50%	10%	n.d.	10%	12%	n.d.	8%	?	Kaolin
150	80%	2%	n.d.	5%	n.d.	5%	n.d.	n.d.	Kaolin
151	63%	25%	n.d.	2%	10%	n.d.	n.d.	n.d.	
152	ca.70%	2%	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	Pyrophyllite
153	ca.80%	2%	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	ZnO, Boric Acid
154	ca.70%	10%	4%	4%	2%	n.d.	2%	n.d.	ZnO
155	ca.84%	10%	n.d.	4%	2%	n.d.	n.d.	?	
156	79%	10%	n.d.	6%	3%	n.d.	2%	n.d.	
157	63%	2%	n.d.	3%	18%	n.d.	6%	8%	
158	78%	7%	n.d.	3%	2%	10%	n.d.	n.d.	
159	ca.74%	10%	2%	n.d.	4%	10%	n.d.	?	
160	60%	25%	n.d.	n.d.	4%	10%	n.d.	trace	
161	59%	25%	n.d.	2%	4%	10%	n.d.	n.d.	
162	50%	25%	n.d.	2%	5%	10%	n.d.	n.d.	
163	55%	2%	n.d.	3%	20%	n.d.	10%	10%	
164	92%	3%	2%	n.d.	2%	n.d.	n.d.	1%	
165	92%	5%	n.d.	n.d.	2%	n.d.	n.d.	?	
166	ca.50%	40%	n.d.	2%	8%	n.d.	n.d.	?	
167	76%	10%	n.d.	n.d.	12%	n.d.	2%	n.d.	
168	--	--	--	--	--	--	--	--	Gypsum
169	--	--	--	--	--	ca.80%	--	--	
170	52%	n.d.	n.d.	5%	25%	n.d.	n.d.	8%	
171	70%	10%	n.d.	5%	15%	n.d.	n.d.	n.d.	
172	43%	50%	n.d.	n.d.	5%	n.d.	2%	n.d.	
173	ca.99%	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	?	
174	ca.60%	1%	2%	15%	n.d.	n.d.	n.d.	n.d.	Kaolin, Mica

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Sample	Talc	Chlorite	Phlogo-pite	α-Quartz	Dolo-mite	Calcite	Trem-olite	Chryso-tile	Other Species
175	ca.86%	3%	n.d.	10%	n.d.	n.d.	n.d.	?	
176	ca.79%	3%	2%	15%	n.d.	n.d.	n.d.	?	
177	84%	10%	4%	2%	n.d.	n.d.	n.d.	n.d.	
178	ca.50%	20%	2%	5%	4%	n.d.	n.d.	?	Kaolin
179	97%	n.d.	n.d.	3%	n.d.	n.d.	n.d.	n.d.	
180	88%	n.d.	n.d.	n.d.	12%	n.d.	n.d.	n.d.	
181	ca.70%	n.d.	n.d.	n.d.	n.d.	10%	n.d.	n.d.	Kaolin
182	ca.40%	25%	15%	n.d.	n.d.	n.d.	n.d.	?	ZnO
183	ca.76%	10%	n.d.	n.d.	2%	10%	1%	?	
184	93%	2%	n.d.	2%	n.d.	n.d.	3%	n.d.	
185	ca.50%	8%	n.d.	n.d.	n.d.	25%	n.d.	n.d.	ZnO
186	ca.50%	5%	n.d.	n.d.	n.d.	25%	n.d.	?	ZnO
187	ca.85%	5%	n.d.	2%	n.d.	5%	2%	n.d	
188	70%	15%	2%	3%	4%	5%	1%	?	
189	72%	12%	n.d.	3%	2%	5%	1%	n.d.	
190	ca.82%	12%	2%	n.d.	3%	n.d.	n.d.	?	
191	96%	2%	n.d.	n.d.	2%	n.d.	n.d.	n.d.	
192	100%	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	
193	ca.93%	2%	n.d.	2%	2%	n.d.	n.d.	?	ZnStear.
194	ca.94%	2%	n.d.	n.d.	3%	3%	n.d.	?	
195	97%	n.d.	n.d.	n.d.	3%	n.d.	n.d.	n.d.	

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ATTACHMENT TO TABLE I

Memorandum to: Dr. George Thompson
Food and Drug Administration

From: S. Z. Lewin
Chemistry Department, New York University

Re: Determination of Asbestos Contents of Commercial Talcum Powders.

This will serve to summarize the main points of our discussion on this date of July 10, 1973 with respect to the factors involved in the detection and estimation of asbestos in talc, and the status of the tabulation of results of the analyses of commercially available consumer products containing talcum powder.

My research group has been engaged in studies of talc and its accessory minerals continuously since July 1971, and we are continuing to work in this field. We have undertaken to investigate the following problems:

A. Tabulation of the x-ray diffraction data for talc and all solid phases (whether naturally occurring, or added in the course of processing) encountered with talc in mineral, industrial, cosmetic and pharmaceutical products.

B. Elucidation of the x-ray diffraction spectrum (i.e., precise locations and relative intensities of peaks and variability thereof) of chrysotile. Assignment of the diffraction peaks to the crystal planes responsible for them, and interpretation in terms of crystallogra phy of the effects of grinding, orientation, and sample preparation.

C. Investigation of the chemical properties of chrysotile, antigorite, chlorite, tremolite, and talc; specifically, measurement of the rates of hydrolytic and ion replacement reactions.

D. Microscopy, both optical and electron, of chrysotile and of talcs containing various accessory minerals, including chrysotile and tremolite.

E. Measurement of the degree of enrichment, due to air elutriation, of asbestos in the lightest fractions of the dust from commercial

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F. Development of a method based on the combination of x-ray diffraction, chemical reactivity, and microscopy for the estimation of the chrysotile and tremolite contents of consumer products (these two being the only asbestiform minerals encountered in all the American products examined so far, with only one possible exception), and application of the method to the analysis of about 200 standard store-purchased specimens.

G. Investigation of alternative analytical methods, viz., differential thermal analysis and density gradient centrifugation, as alternative or supportive techniques.

Our results to date support the following conclusions:

1. The chrysotile that is found in commercial talcs is generally different in significant respects from the chrysotile that occurs as massive, fibrous growths in veins in serpentine rocks. That is, the former has diffraction peaks that may differ from the latter by as much as 0.2 A (at 7.3 A); it is more reactive toward dilute acids; it shows a different appearance under the microscope; and its DTA endotherms and exotherm are shifted relative to those of the latter (and apparently diminished).

2. The presence of chrysotile as a minor constituent in talc may be established with reasonable certainty on the basis of (a) the presence of x-ray diffraction peaks in the vicinity of 7.23 to 7.43 A and 3.59 to 3.65 A, (b) the pronounced weakening or complete disappearance of these peaks upon treatment upon treatment of the specimen with 1 M HCl at 80°C for 1 hour, (c) the presence of fiber bundles of visible size under 250X or higher magnification in the optical microscope which show a refractive index of about 1.54 (these fiber bundles may be short and straight, and may be coated with a bumpy encrustation of $MgCO_3$, or may be embedded in talc or other particles), and (d) the presence of fibers under the electron microscope which yield an electron diffraction pattern that corresponds in d-values to those found in the x-ray diffraction pattern (these fibers typically do not have a hollow central capillary running through them).

3. The concentration of chrysotile in a talc may be estimated by measuring the area under the x-ray diffraction peak at about 7.3 A
     . . . .   that of an internal standard. The best internal standard

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is calcium oxalate monohydrate (peak at 5.83 A).

4. The quantitative results are conditioned by the fact that segregation effects in talc powders are considerable; the analytical method gives a reproducibility of ±2 to 3% average deviation in replicate determinations on the same sample, but different samples from the same bulk container are found to vary by as much as 200%.

5. The quantitative results are further complicated by the fact that antigorite gives an x-ray pattern that is indistinguishable from that of chrysotile. The HCl treatment specified above does not affect ground antigorite, but it is not yet known whether antigorite, if it occurs in talc, has the same chemical reactivity as the ground material from massive antigorite, or whether (like chrysotile) its properties may be variable depending upon the rock matrix in which it is found.

6. Subject to the qualifications inherent in the above, we have obtained quantitative estimates of the chrysotile contents of about 200 commercial talcum powder specimens. We have also determined the contents of the other minerals in these products, including tremolite, quartz, chlorite, dolomite, and others. There is no ambiguity in the identification of these latter species, but the quantitative results for these are also affected by the segregation problem, which is most serious for those constituents present in the smallest amounts.

7. Most of the commercial talcs tested are free of any detectable amount of any of the asbestiform minerals, according to the criteria enumerated above. Thus, there appears to be an adequate supply of talc for which there is no ambiguity about the absence of chrysotile or tremolite. In about 10% of the samples tested, there appear to be definitely detectable amounts of either chrysotile or tremolite present.

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TABLE II

INTERLABORATORY COMPARISON OF ANALYTICAL RESULTS FOR TREMOLITE
IN COSMETIC TALCUM-TYPE POWDERS

SAMPLE NO.	N.Y.U. (X-RAY DIFFRACTION)	FDA[a] (OPTICAL MICROSCOPY)	PFIZER[b] (X-RAY DIFFRACTION)
	RESULTS		
1	n.d. (not detected)		
2	n.d.		
3	n.d.		
4	n.d.		
5	n.d.		
6	n.d.		
7	n.d.		
8	n.d.		
9	n.d.		
10	n.d.		
11	n.d.		
12	n.d.		
13	n.d.		
14	n.d.		
15	n.d.		
16	--[c]		
17	n.d.		
18	n.d.		
19	n.d.		
20	n.d.		
21	n.d.		
22	n.d.		

SAMPLE NO.	N.Y.U. (X-RAY DIFFRACTION)	FDA (OPTICAL MICROSCOPY)	PFIZER (X-RAY DIFFRACTION)	
23	n.d.			
24	n.d.			
25	n.d.			
26	n.d.			
27	n.d.			
28	n.d.			
29	n.d.			
30	n.d.			
31	n.d.			
32	n.d.			
33	n.d.			
34	n.d.			
35	n.d.			
36	n.d.			
37	n.d.			
38	n.d.			
39	n.d.			
40	n.d.			
41	n.d.			
42	n.d.			
43	n.d.			
44	--			
45	n.d.			
46	n.d.			
47	n.d.			
48	n.d.			

RESULTS

SAMPLE NO.	N.Y.U. (X-RAY DIFFRACTION)	FDA (OPTICAL MICROSCOPY)	PFIZER (X-RAY DIFFRACTION)
49	n.d.		
50	n.d.		
51	n.d.		
52	n.d.		
53	n.d.		
54	n.d.		
55	n.d.		
56	n.d.		
57	n.d.		
58	n.d.	n.d.	
59	n.d.		
60	n.d.	n.d.	
61	n.d.	n.d.	
62	n.d.		
63	5%	moderate amount	
64	n.d.		
65	n.d.		
66	n.d.		
67	2%		
68	n.d.		
69	n.d.		
70	n.d.	small amount	
71	3%	n.d.	
72	n.d.	n.d.	
73	n.d.		
74	n.d.	small amount	

SAMPLE NO.	N.Y.U. (X-RAY DIFFRACTION)	FDA (OPTICAL MICROSCOPY)	PFIZER (X-RAY DIFFRACTION)
75	n.d.		
76	5%		
77	3%	small amount	
78	5%	moderate amount	
79	n.d.		
80	n.d.	n.d.	
81	n.d.		
82	n.d.		
83	n.d.		
84	n.d.		
85	n.d.	n.d.	
86	n.d.		
87	n.d.	n.d.	
88	4%	large amount	
89	5%	large amount	1.6%
90	3%	large amount	
91	n.d.		
92	5%	large amount	
93	5%	large amount	
94	4%	large amount	1.9%
95	2%		
96	8%	moderate amount	0.7%
97	12%	large amount	8.1%
98	n.d.		
99	n.d.	n.d.	
100	n.d.	very small amount	

RESULTS

SAMPLE NO.	N.Y.U. (X-RAY DIFFRACTION)	FDA (OPTICAL MICROSCOPY)	PFIZER (X-RAY DIFFRACTION)
101	15%	large amount	10 to 15%
102	10%	large amount	
103	n.d.		
104	n.d.		
105	n.d.		
106	n.d.		
107	n.d.	n.d.	
108	2%		
109	2%		
110	n.d.		
111	1%		
112	n.d.		
113	n.d.		
114	n.d.		
115	n.d.		
116	n.d.		
117	n.d.		
118	n.d.		
119	n.d.		
120	n.d.		
121	n.d.		
122	n.d.		
123	n.d.		
124	n.d.		
125	n.d.		
126	n.d.		

RESULTS

SAMPLE NO.	N.Y.U. (X-RAY DIFFRACTION)	FDA (OPTICAL MICROSCOPY)	PFIZER (X-RAY DIFFRACTION)
127	n.d.		
128	n.d.		
129	n.d.		
130	trace		
131	trace		
132	n.d.		
133	n.d.		
134	n.d.		
135	n.d.		
136	n.d.		
137	n.d.		
138	n.d.		
139	n.d.		
140	n.d.		
141	n.d.		
142	n.d.		
143	5%		
144	5%		
145	n.d.		
146	n.d.		
147	n.d.		
148	2%	small amount	
149	8%	present	
150	n.d.		
151	n.d.		
152	n.d.	n.d.	

SAMPLE NO.	N.Y.U. (X-RAY DIFFRACTION)	FDA (OPTICAL MICROSCOPY)	PFIZER (X-RAY DIFFRACTION)
		RESULTS	
153	n.d.		
154	2%	small amount	approx. 0.5%
155	n.d.		
156	2%		
157	6%		
158	n.d.		
159	n.d.		
160	n.d.		
161	n.d.		
162	n.d.		
163	10%	large amount	3.8%
164	n.d.	n.d.	
165	n.d.		
166	n.d.		
167	2%		
168	-c		
169	--		
170	n.d.		
171	n.d.		
172	2%		
173	n.d.		
174	n.d.		
175	n.d.		
176	n.d.		
177	n.d.		
178	n.d.		

RESULTS

SAMPLE NO.	N.Y.U. (X-RAY DIFFRACTION)	FDA (OPTICAL MICROSCOPY)	PFIZER (X-RAY DIFFRACTION)
179	n.d.		
180	n.d.		
181	n.d.		
182	n.d.		
183	1%		
184	3%		
185	n.d.		
186	n.d.		
187	2%		
188	1%		
189	1%		
190	n.d.		
191	n.d.		
192	n.d.		
193	n.d.		
194	n.d.		
195	n.d.		

Footnotes:

a. Work done by Mr. Arnold E. Schulze, Division of Microbiology. (See Appendix A)
b. Pfizer, Inc.; Minerals, Pigments, and Metals Division, Easton, Pa.
c. The use of a dash means that the powder does not contain talc and therefore is not expected to contain tremolite or chrysotile as contaminants. No asbestos was found.

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TABLE III

INTERLABORATORY COMPARISON OF ANALYTICAL RESULTS FOR CHRYSOTILE IN COSMETIC TALCUM-TYPE POWDERS

SAMPLE NO.	N.Y.U. (X-RAY DIFF.)	FDA (OPT. MICR.)	PFIZER[a] (X-RAY DIFF.)	COLUMBIA SCIENTIFIC[b]	HPB[c]
1	n.d. (not detected)				
2	n.d.				
3	n.d.				
4	n.d.				
5	n.d.				
6	n.d.				
7	?				
8	n.d.				
9	n.d.				
10	n.d.				
11	n.d.				
12	n.d.				
13	n.d.				
14	n.d.				
15	n.d.				
16	--				
17	n.d.				
18	n.d.				
19	n.d.				
20	n.d.				
21	n.d.				
22	n.d.				

RESULTS

AMPLE NO.	N.Y.U. (X-RAY DIFF.)	FDA (OPT. MICR.)	PFIZER[a] (X-RAY DIFF.)	COLUMBIA SCIENTIFIC[b]	HPB[c]
23	?				
24	n.d.				
25	?				
26	?				
27	n.d.				
28	n.d.				
29	n.d.				
30	n.d.				
31	n.d.				
32	n.d.				
33	n.d.				
34	n.d.				
35	n.d.				
36	n.d.				
37	n.d.				
38	n.d.				
39	n.d.				
40	n.d.				
41	n.d.				
42	n.d.				
43	n.d.				
44	--				
45	n.d.				
46	n.d.				
47	n.d.				
48	n.d.				

RESULTS

SAMPLE NO.	N.Y.U. (X-RAY DIFF.)	FDA (OPT. MICR.)	PFIZER[a] (X-RAY DIFF.)	COLUMBIA SCIENTIFIC[b]	HPB[c]
49	n.d.				
50	n.d.				
51	n.d.				
52	n.d.				
53	n.d.				
54	?				
55	n.d.				
56	n.d.				
57	n.d.				
58	n.d.	n.d.			
59	n.d.				
60	n.d.	n.d.			
61	n.d.	n.d.			
62	n.d.				
63	n.d.	n.d.			
64	n.d.				
65	n.d.				
66	2%				
67	n.d.				
68	n.d.				
69	n.d.				
70	n.d.	n.d.			
71	n.d.	n.d.			
72	n.d.	n.d.			
73	n.d.				
74	n.d.	n.d.			

SAMPLE NO.	N.Y.U. (X-RAY DIFF.)	FDA (OPT. MICR.)	PFIZER[a] (X-RAY DIFF.)	COLUMBIA SCIENTIFIC[b]	HPB[c]
			RESULTS		
75	n.d.				
76	n.d.				
77	n.d.	n.d.			
78	n.d.	n.d.			
79	n.d.				
80	?	n.d.			
81	?				
82	?				
83	?				
84	?				
85	?	n.d.			
86	?				
87	?	n.d.			
88	5%	n.d.			
89	5%	n.d.	n.d.	inconclusive	
90	5%	possible, in talc grains			
91	5%				
92	5%	possible, in talc grains			
93	4%				
94	?	much antigorite[d] ?	n.d.	inconclusive	
95	3%				
96	10%	possible, in talc grains	n.d.	inconclusive	<0.1%
97	15%	moderate antigorite?	n.d.	inconclusive	

AMPLE NO.	N.Y.U. (X-RAY DIFF.)	FDA (OPT. MICR.)	PFIZER[a] (X-RAY DIFF.)	COLUMBIA SCIENTIFIC[b]	HPB[c]
98	n.d.				
99	n.d.	n.d.			
100	n.d.	possible, in talc grains			
101	n.d.	much antigorite?	n.d.	n.d.	
102	7%	n.d.			
103	n.d.				
104	n.d.				
105	n.d.				
106	n.d.				
107	n.d.	n.d.			
108	n.d.				
109	?				
110	n.d.				
111	n.d.				
112	n.d.				
113	n.d.				
114	n.d.				
115	n.d.				
116	n.d.				
117	?				
118	n.d.				
119	n.d.				
120	?				
121	n.d.				
122	?				

RESULTS

RESULTS

AMPLE NO.	N.Y.U. (X-RAY DIFF.)	FDA (OPT. MICR.)	PFIZER[a] (X-RAY DIFF.)	COLUMBIA SCIENTIFIC[b]	HPB[c]
123	?				
124	?				
125	?				
126	n.d.				
127	n.d.				
128	n.d.				
129	n.d.				
130	Trace				
131	n.d.				
132	n.d.				
133	n.d.				
134	n.d.				
135	n.d.				
136	n.d.				
137	n.d.				
138	n.d.				
139	n.d.				
140	n.d.				
141	n.d.				
142	n.d.				
143	10%				
144	?				
145	2%				
146	n.d.				
147	n.d.				
148	n.d.	n.d.			

RESULTS

AMPLE NO.	N.Y.U. (X-RAY DIFF.)	FDA (OPT. MICR.)	PFIZER[a] (X-RAY DIFF.)	COLUMBIA SCIENTIFIC[b]	HPB[c]
149	?	n.d.			
150	n.d.				
151	n.d.				
152	n.d.	n.d.			
153	n.d.				
154	n.d.	n.d.	$0.1\%^{e}$	n.d.	
155	?				
156	n.d.				
157	8%				
158	n.d.				
159	?				
160	trace				
161	n.d.				
162	n.d.				
163	10%	n.d.	n.d.	inconclusive	n.d.
164	1%	possible, in talc grains			
165	?				
166	?				
167	n.d.				
168	--				
169	--				
170	8%				
171	n.d.				
172	n.d.				
173	?				
174	n.d.				

RESULTS

SAMPLE NO.	N.Y.U. (X-RAY DIFF.)	FDA (OPT. MICR.)	PFIZER[a] (X-RAY Diff.)	COLUMBIA SCIENTIFIC[b]	HPB[c]
175	?				
176	?				
177	n.d.				
178	?				
179	n.d.				
180	n.d.				
181	n.d.				
182	?				
183	?				
184	n.d.				
185	n.d.				
186	?				
187	n.d.				
188	?				
189	n.d.				
190	?				
191	n.d.				
192	n.d.				
193	?				
194	?				
195	n.d.				

Footnotes:
- Pfizer, Inc., Minerals, Pigments, and Metals Division, Easton, Pa.
- Columbia Scientific Industries, Austin, Texas, using Differential Thermal Analysis.
- Health Protection Branch of Canadian Government, Ottawa, by electron microscopy, oral communication by Drs. Pontefract and Cunningham.
- Antigorite is a non-fibrous form of the same mineral as chrysotile.
- By transmission electron microscopy.

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TABLE IV

KEY TO SAMPLE NUMBERS OF COSMETIC TALCUM-TYPE POWDERS

SAMPLE NO.	PRODUCT NAME	FURTHER IDENTIFICATION
1	Ammens Powder, Medicated	Bristol-Myers (No. IF25)
2	Amolin Deodorant Powder	Norwich
3.	Aquamarine Cooling Spray Bath Powder	Revlon (143)
4	Bagatelle Amber Dusting Powder	Corand (DCH)
5	Bourjois Bath Powder	
6	Caldesene Medicated Powder	Pennwalt (5274)
7	Cashmere Bouquet Body Powder	Colgate-Palmolive
8	Chanel No. 5 Bath Powder	
9	Countess Rocheau Cake Dusting Powder	Jergens
10	Crepe De Chine Dusting Powder, Millot	House of Fragrance (L1132)
11	Crepe De Chine Poudre Mist, Millot	House of Fragrance
12	Cuticura Talcum Powder	Purex (07170)
13	Desenex	WTS-Pharmacraft
14	Desitin Baby Powder	Pfizer (1139Z) (3/29/72)
15	Desitin Baby Powder	Pfizer (115A) (5/10/72)
16	Diaparene Baby Powder	Breon (E1030)
17	Dorothy Gray "Secret Of The Sea" Dusting Powder	
18	Emeraude Talcum Powder	Coty (355-4010)
19	English Leather	Mem
20	Faberge "Music" Dusting Powder	(2891)
21	Friendship Garden Dusting Powder	Shulton (3/27/72)
22	Friendship Garden Dusting Powder	Shulton (5/9/72)
23	Friendship Garden Dusting Powder	Shulton (7/13/72)

PLE O.	PRODUCT NAME	FURTHER IDENTIFICATION
4	Heaven Sent Aerosol Bath Powder Mist	Rubinstein
5	Heaven Sent Bath Powder	Rubinstein
!6	Helen Pressl "Little Lady"	
?7	Importa, Spain Mens' Talc	
28	Isis Floral Talcum Powder	
29	Johnson's Baby Powder	(028Q)
30	Johnson and Johnson Medicated Powder	(3612)
31	Koscot Beauty Dust--Oil of Mink	
32	Lanvin Arpege Dusting Powder	(1288)
33	Lanvin Arpege Powdered Mist	
34	Lanvin Arpege Talc	
35	Lewis Baby Powder	
36	Loves Fresh Lemon Glossy Powder	Manley & James
37	Macy's Scented Borated Talcum	
38	Macy's Talcum, Apple	(2K4)
39	Marcelle Dusting Powder, Hypo-Allergenic	
40	Mary Chess Perfumed Dusting Powder	
41	Mennen Baby Magic Powder	(B112)
42	Mennen Quinsana Foot Powder	(H202)
43	Merck Talc, Product No. 6460, Lot No. 6460)	(8039301)
44	Mexsana 2387-D Medicated Powder	Plough
45	Old Spice Body Talcum	Shulton
46	Persian Lilac Deluxe Dusting Powder	April Showers (LFN)
47	Persian Lilac Spray Bath Powder	April Showers (B200B)
48	Pond's Perfumed Talc Body Deodorant Dream Flower	(115B)
49	Prince Matchabelli Beloved Spray Powder	

MPLE NO.	PRODUCT NAME	FURTHER IDENTIFICATION
50	Quest Deodorant Powder	
51	Replique Spray Bath Powder	Parfums Raphael (004)
52	Riviana Foods - Italian Stearin Talc	For Rice
53	September Morn By Pond's	(19B)
54	Seven Winds After Bath Talc	DuBarry (021085)
55	U S P Talc	
56	Vaseline Intensive Care Baby Powder	(I 209)
57	Yves Saint Laurent Rive Gauche Spray Talc	
58	Z B T Baby Powder	(F1021)
59	Zeasorb Super Absorbent Medicated Powder	Stiefel
60	Ambush-Dana Dusting Powder	
61	April Showers	(9884)
62	Avon Unforgettable Perfumed Talc	
63	Beloved Perfumed Dusting Powder, Prince Matchabelli	
64	Coty Face Powder Rachel	
65	Desert Flower Spray Bath Powder	Shulton (E 1 BKI)
66	Emeraude Dusting Powder	Coty
67	Emeraude Spray Dusting Powder	Coty (1 AEY)
68	Fabergé Flambeau Deodorant Spray Powder	(37 WBF)
69	Jean Naté Spray Bath Powder	(1 N 247)
70	Jeris Talc, Flesh	
71	Jolie Madame Dusting Powder, Balmain	
72	Lady Esther Face Powder, Rachel	
73	Max Factor Face Powder, Rachelle	
74	Medicated Comfort Powder	Parke-Davis
75	OH! de London Talc	Yardley (498)

MPLE NO.	PRODUCT NAME	FURTHER IDENTIFICATION
76	To Know Me Is To Love Me - Tinkerbell	Tom Fields, Ltd.
77	Touch And Glow Face Powder, Creamy Peach	Revlon
78	Toujours Moi Bath Powder	Corday
79	Yardley April Violets	(4908)
80	Chantilly Dusting Powder	Houbigant (11F)
81	Cashmere Bouquet	
82	Jean Naté Talc	(on 345)
83	Mennen Shave Talc	(B 81)
84	Shower To Shower Body Powder	Johnson & Johnson (5507BG)
85	Pure Baby Powder, Dart Drug	(K 11C)
86	Pond's Dream Flower Perfumed Talc	(O 13D)
87	Almay Hypo-Allergenic Face Powder	
88	Constance Carroll, Bouquet Talc	
89	Djer-Kiss Talcum	Kerkoff
90	Flamingo Dusting Powder, Tussy	(L1047)
91	Lander Lilacs And Roses Talc	
92	Mavis Talcum	Vivaudou
93	Mavis Body Powder	Vivaudou
94	Tangee	Luft-Tangee
95	ZBT Baby Powder	(B0048)
96	Blanchard's Dusting Powder	
97	Born Wild Dusting Powder	Del Labs
98	Lander Gardenia And Sweet Pea Talc	
99	Lander Lilacs And Roses Deodorant Body Talc	
100	Miss Dior Dusting Powder	
101	Tai Winds Spray Talc	(Avon (DCC 1272 2-14-72,HWS)

4PLE NO.	PRODUCT NAME	FURTHER IDENTIFICATION
02	Tosca Dusting Powder	
03	Coty L'Aimant Talcum Powder	(1JJ)
04	Coty Emeraude Talcum Powder	(01A)
05	Coty L'Aimant Dusting Powder	(1M)
06	Coty Imprévu Dusting Powder	(1DE)
07	Coty Muguet des Bois Dusting Powder	(2DO)
08	Revlon Intimate Perfumed Bath Powder	(241)
109	Jean Naté Bath Powder	Lanvin - Charles of the Ritz (2137)
110	Jean Naté Spray Bath Powder	Lanvin - Charles of the Ritz (2103)
111	Old Spice Body Talc	Shulton, Inc. (MFO)
112	Dr. Scholl's Foot Powder	(20517)
113	Faberge Xanadu Luxury Bath Powder Spray	(Y1)
114	Faberge Zizanie de Fragonard	(2132) Ref. 61159-019
115	Faberge Tigress Bath Powder	Ref. 2052-003
116	Faberge Woodhue for Men	Ref. 5027 (0252)
117	Faberge Brut for Men Shower Buff All-Over Body Powder	Ref. 5400
118	Faberge Talc	(raw material: from France)
119	Faberge Aphrodesia Bath Powder	Ref. 2052 (2172)
120	Faberge Straw Hat Bath Powder	
121	Faberge Aphrodesia for Men Shower Buff	Ref. 5027
122	Faberge Xanadu de Luxe Bath Powder	Ref. 1244-028 (2342)
123	Faberge Woodhue Bath Powder	Ref. 2052-002
124	Faberge Music Dusting Powder	Ref. 0714-018 (3121)
125	Faberge Flambeau Bath Powder	Ref. 2052 (3471)

SAMPLE NO.	PRODUCT NAME	FURTHER IDENTIFICATION
126	Mennen Baby Magic	
127	Walgreen's Crib Age	
128	Caldesene Medicated Powder	
129	Desiten	
130	Vaseline Intensive Care	
131	Johnson and Johnson Medicated Powder	
132	Johnson Baby Powder	
133	Johnson's Baby Powder	(108T)
134	Johnson's Baby Powder	(109T)
135	Johnson and Johnson Medicated Powder	(0452K)
136	Johnson and Johnson Shower to Shower Body Powder	(C 512Z)
137	Johnson and Johnson Shower to Shower Body Powder	(0709X1)
138	Johnson and Johnson Shower to Shower Body Powder	(0872K)
139	Avon Brocade Spray	(31602)
140	Avon Bird of Paradise Spray	(B1652)
141	Avon Tai Winds Spray Talc	(4065)
142	Mennen Bath Talc	(A308)
143	Pin-Zow Talque	Perfection Beauty Products, Inc., Pearl River, N.Y.
144	Overton's "High-Brown" Face Powder	
145	Softee Face Powder	
146	Westport Face Powder	
147	Hazel Bishop Pressed Powder	
148	Lady Wayne Face Powder	
149	Solitaire Cake Makeup	
150	Dreamglo Pressed Powder	

SAMPLE NO.	PRODUCT NAME	FURTHER IDENTIFICATION
151	Early American Old Spice Talcum Powder	
152	Corsage Dusting Powder	Lander
153	Ammens Powder, Medicated	
154	Bismoline Medicated Powder	
155	Rite Aid Pure Baby Powder	
156	Warner Pure Baby Powder	
157	Mavis Imported Talcum	
158	Avon Brocade Perfumed Talc	
159	Avon Blue Lotus Perfumed Talc	
160	Avon Beauty Dust Refill - Charisma	
161	Avon Elusive Beauty Dust Refill	
162	Avon Régence Perfumed Talc	
163	Pinaud Clubman Talc	
164	Grand Union Baby Powder	(101672)
165	Cashmere Bouquet	(4212DX) (Supplied by Mfgr.)
166	Almay Face Powder, Soft Beige	(List No. 719, Lot 201, Supplied by Mfgr.)
167	Tawny Tone Body Talc From Black Heritage	(Beauty Mistus, Inc. Greenwich, Conn.)
168	Colgate Tooth Powder	
169	Dr. Lyon's Tooth Powder	
170	"C" Bouquet Talc.	(Winarick, Inc. Distr. by F. W. Woolworth)(2662)
171	Tangee Dusting Powder	(George W. Luft Co.)(2762)
172	Jeris Talc	(Winarick) (2732)
173	Corsage Dusting Powder	(Lander Co.)
174	Lander Gardenia & Sweet Pea Deodorant Body Talc	

AMPLE NO.	PRODUCT NAME	FURTHER IDENTIFICATION
175	Lander Baby Powder	
176	Lander Lilac & Roses Body Talc	
177	Beloved Perfumed Dusting Powder	Prince Matchabelli (235A)
178	Jean Naté Talc No. 60	(2264)
179	Jean Naté Spray Bath Powder	(2101)
180	Tinkerbell Body Talc	(Tom Fields, Ltd., Div. of MEM)
181	Yardley Sigh Shadow Brush-On Eye Shadow	Ref. No. 721
182	Max Factor Face Powder, Rachelle	(Supplied by Mfgr.)
183	Tweed Bath Powder, Lentheric	(Yardley)(44)
184	Yardley Next to Nature Sheer Pressed Powder	(A2)
185	Yardley April Violets Dusting Powder	(162)
186	Yardley Red Roses Dusting Powder	(165)
187	Yardley Springflowers Talc	(260)
188	Yardley White Lavender Talc	(271)
189	Yardley Red Roses Talc	(214)
190	April Showers Deodorant Talc	Ref. No. 9882
191	Chantilly Houbigant Dusting Powder	(2JBB)
192	Tinkerbell Dusting Powder	(Tom Fields, Ltd.)
193	Tinkerbell Powder Mitt	(Tom Fields, Ltd.)
194	Tinkerbell Dusting Powder	(Tom Fields, Ltd.)
195	Tinkerbell Body Talc	(Tom Fields, Ltd.)

October 19, 2012

Submitted via mail and also via email to cirinfo@cir-safety.org

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<div align="center">

Initial Comments on CIR draft Scientific Literature Review
For "Talc as Used in Cosmetics"
(posted by CIR Aug. 22, 2012)

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Dear Dr. Andersen,

We commend CIR staff for the thoroughness of the draft SLR. We do have a number of comments aimed at improving the evaluation. Most of our comments pertain to the extensive ovarian and endometrial cancer epidemiology, since we agree with the draft that the non-epidemiologic evidence indicates lack of talc carcinogenicity (*e.g*., the use of talc in pleurodesis and pharmaceuticals and the fairly extensive *in vitro* and *in vivo* experiments).

The Center for Regulatory Effectiveness is not representing a particular company or industry segment in filing these comments. CRE operates independently and these comments are solely its own. CRE has become involved in this issue because it could impact not just the cosmetics industry, but also many other diverse and important industries that use talc in their products. If further support for the notion that talc causes cancer (irrespective of target organ) emerges, even in the form of a CIR evaluation of the data as insufficient to determine safety, it could put pressure on companies to find substitutes. It appears that this has already happened to a large extent in the cosmetics industry, where many companies now advertise that their products are talc-free, apparently due to a plethora of Internet comments that talc causes cancer and earlier publicity about the various epidemiologic studies and discovery of asbestos contamination in some brands of talcum powder during the 1970s.

To start, a significant issue is whether the subjects in the epidemiologic studies could have been exposed to brands of body powder contaminated with asbestos, thereby distorting the results as they would pertain to cosmetically pure talc as defined in the U.S. since 1976.

Potential exposure of study subjects to talcum powder contaminated with asbestos prior to about 1976

The very first paragraph of the draft SLR recognizes the possibility that some brands of talc were contaminated with asbestos prior to about 1976, and it states that therefore "studies

before that date are likely of uncertain relevance to talc as currently used in cosmetics." But this is not the point that should be made. The issue is not whether <u>studies</u> prior to 1976 are relevant; the issue is whether subjects in the epidemiologic studies were significantly exposed to pre-1976 talc.

In examining this issue it should first be recognized that ovarian cancer is primarily a late-age cancer. From 2005-2009, the median age at diagnosis for cancer of the ovary was 63 years of age.[1] The following graph shows the age-specific incidence rates most recently reported by SEER (the NCI Surveillance Epidemiology and End Results program). This graph was created by us from tools on the SEER website.[2] As can be seen, the rates per 100,000 population continue to rise substantially from the median of 63 until age 84.

Age-Specific (Crude) SEER Incidence Rates By Cancer Site All Ages, All Races, Female 2000-2009
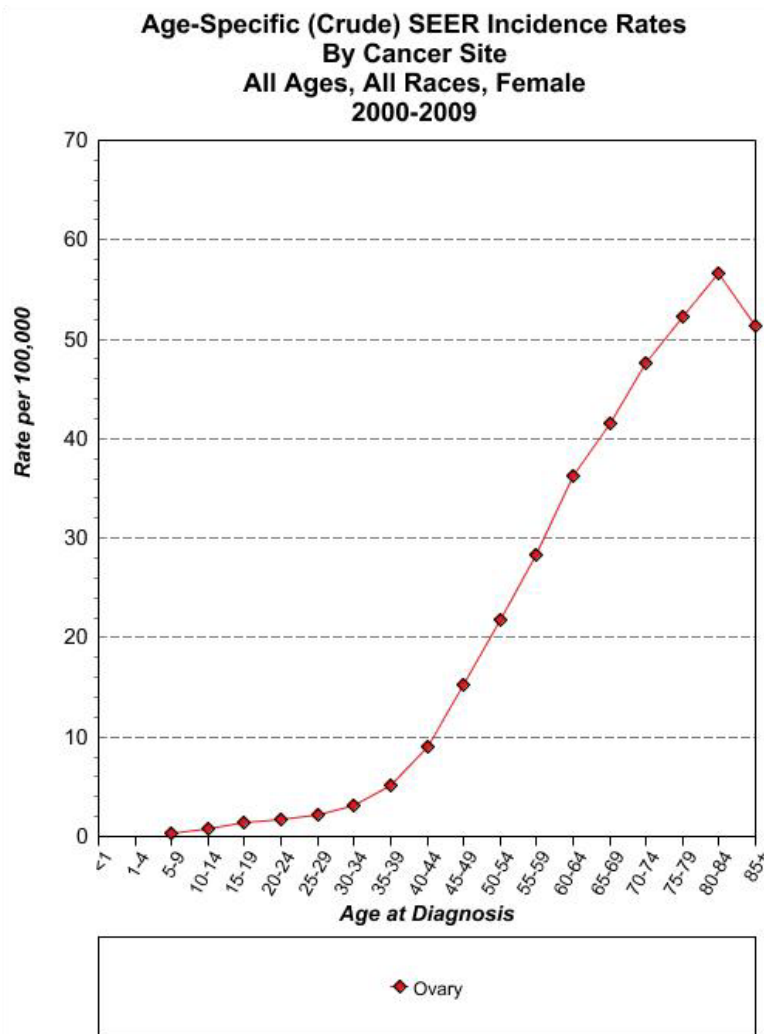
Cancer sites include invasive cases only unless otherwise noted.
Incidence source: SEER 18 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana, New Jersey and Georgia excluding ATL/RG).
Rates are per 100,000.
Ovary excludes borderline cases or histologies 8442, 8451, 8462, 8472, and 8473.
Datapoints were not shown for rates that were based on less than 16 cases.

Thus, for example, if we assume that many subjects first began using talcum powder at about the age of 20 (which might be conservative given the data on first use at <20 in Rosenblatt *et al.* 2011 and in Harlow *et al.* 1992), that would mean that, applying the SEER 63 yr. median, a large portion of the ovarian cancer cases in the studies started using talcum powder 43 years before the time they were interviewed about use (or perhaps close to the time of diagnosis). That would mean that even a case interviewed in 2005 (apparently the latest interview year in the epidemiology), for example, could well have begun using talcum powder in 1962 or thereabouts, far before the 1976 "cut-off" suggested in the first paragraph of the draft SLR and at a time when there could have been a high likelihood of exposure to asbestos in some brands of powder.

A review of the full spectrum of individual epidemiologic studies confirms the likelihood of substantial pre-1976 exposure in the subjects. The CRE Table 1 below shows dates of interview or diagnosis and the reported ages of the subjects. (Note that many of the studies reported a mean age, whereas the SEER data above are based on median age.) For example, note that a number of studies used the 1982 Nurses Health Study ("NHS") questionnaire (1982 was the only year in which the questionnaire contained a question on talc use), which would have meant that presumably most of the subjects responding to the relevant question in 1982 would have used predominantly pre-1976 talcum powder.

Table 1. Potential exposure of subjects to asbestos contamination prior to about 1976

Study (chronolog.)	Study yr(s)/yr(s) Subjects questioned (or date of diagnosis)	Case subject age range (median or mean) at diag. or interview	Study location/comments
Cramer et al. 1982	1978-81	18-80 (mean 53.2)	U.S. (Greater Boston area)
Hartge et al. 1983	1974-77	No info.	U.S. (Wash., DC area)
Whittemore et al. 1988	(diag.1983-85)	18-74	U.S. (San Francisco area)
Booth et al 1989	1978-83	20-64 (mean 52.4)	England (London, Oxford)
Harlow & Weiss 1989	(diag. 1980-85)	20-79	U.S. (western Wash. State)
Harlow et al. 1992	(diag. 1984-87)	18-76 (59% ≥50)	U.S. (Boston area)
Rosenblatt et al. 1992	(diag. 1981-85)	Most 40-69	U.S. (Baltimore hospital)
Hankinson et al. 1993	1982 (NHS)	36-61	U.S. (NHS --prospective, but small numbers – n. not given)
Tzonou et al. 1993	(diag. 1989-91)	No info.	Greece (only 6 exp. cases)
Purdie et al. 1995	(diag. 1990-93)	18-79 (most >40)	Australia
Shushan et al. 1996	1990-93	36-64	Israel – fertility drug study
Chang & Risch 1997	(diag. 1989-92)	35-79 (57.2- mean?)	Canada (Toronto area)
Cook et al 1997	(diag. 1986-88)	20-79 (majority 55-79)	U.S. (western Wash. State)
Green et al. 1997	(diag. 1990-93)	18-79	Australia
Godard et al. 1998	(diag. 1995-96)	26-85 (53.7 mean at diag.)	Canada (Montreal)
Cramer et al. 1999	(diag. 1992-97)	maj. >50	U.S. (E. Mass. & NH)
Wong et al. 1999	(diag. 1982-95)	54.9 mean	U.S. (Buffalo, NY- Roswell)

Gertig et al. 2000	1982 (NHS)	36-61	U.S. (NHS prosp. cohort)
Ness et al. 2000	1994-98	20-69	U.S. (PA, NJ, DE)
Mills et al. 2004	2000-2001	<40 - ≥70 (mean 56.6)	U.S. (Central California)
Cramer et al. 2005	1998-2003	<35 - ≥65 (subst. ≥65)	U.S. (E. Mass & NH)
Jordan et al. 2007	(diag. 2002-05)	no info.	Australia
Gates et al. 2008	1982 (NHS), 1992-97, 1998-2003 (NECC)	NECC mean 52, NHS mean 61	U.S. (NHS and NECC – E. Mass. & NH)
Merritt et al. 2008	(diag. 2002-05)	<50 - ≥70	Australia
Moorman et al. 2009	1999-2008	20-74 (predom. >50)	U.S. (N. Car.)
Wu et al. 2009	(diag. 1998-2002)	18-74 (predom. >45)	U.S. (Los Angeles County)
Karageorgi et al. 2010	1982 (NHS)	36-61 (48 mean?)	U.S. (NHS, endom. cancer)
Rosenblatt et al. 2011	(diag. 2002-05)	35-74 (subst. no. reported First use at <15 and sig. no. before 1959 or 1970)	U.S. (western Wash. State)
Vitonis et al. 2011	(diag. 1998-2008 – NECC)	Mean 52? (see Gates et al.)	U.S. (NECC - E. Mass. & NH)
Kurta et al. 2012	(diag. 2003-08)	<30-≥70	U.S. (Buffalo, Cleveland, Pittsburgh)
Neill et al. 2012	2005-2007	Mean 61.3 (sig. no. used >40-60 yrs.)	Australia (endom. cancer – contradicts Karageorgi et al.)

Other Indefiniteness of Substance(s) Exposures in the Epidemiologic Studies

In 2000, the United States National Toxicology Program ("NTP") began a review of a nomination of talc for inclusion in the Report on Carcinogens ("RoC"). (The three core Federal agencies of the NTP are NIH/NIEHS, FDA, and NIOSH/CDC, with other agencies such as EPA, CPSC, and DoD participating through the NTP Executive Committee). In 2000, after the NTP RoC Subcommittee of its Board of Scientific Counselors voted 8-2 against listing in the RoC, NTP decided to defer the talc nomination pending further review. After that internal review, in 2005, NTP announced that it was withdrawing both talc nominations (cosmetic talc and occupational exposure to talc) because, it explained: "It has become evident that the literature on both forms of talc, with a few exceptions, provides an inadequate characterization of the actual materials under study to enable one to reach definitive conclusions concerning the specific substances responsible for the range of adverse health outcomes reported." Although the withdrawal was not accompanied by any further explanation or analysis, a careful review of the epidemiologic studies on talc and ovarian and endometrial cancer shows that, in addition to the asbestos issue discussed above, many of the studies raise obvious questions about the actual exposure that was being studied.

CRE Table 2 below shows that many of the studies were based on questioning of subjects not just about talc, but about any kind perineal exposure to various powders or sprays.

In addition many of the studies did not quote or characterize the exposure question(s) asked, and they could similarly have been indefinite with regard to talc.

Table 2. Substance studied

Study (chronolog.)	Exposure question to subjects	Comments
Cramer et al. 1982	Exact question not given or characterized.	
Hartge et al. 1983	Exact question not given. Refers to "talc," but also refers to "body powder" near end.	
Whittemore et al. 1988	Exact question not given or characterized.	
Booth et al 1989	Exact question not given or characterized.	
Harlow & Weiss 1989	Exact question not given, but states that women were asked what type(s) of "powders" (also referred to as "talc") they applied to perineum after bathing. Article then states that the responses were then categorized (apparently by the investigators) into one or more of three categories of "talc-containing powders" – baby powder, deodorizing powder, or other or unspecified talcum or dusting powders, or cornstarch.	The study found lack of associations for exclusive use of "baby powder," "combined use," or "talc, unspecified." But in women who used deodorizing powder either alone or in combination with baby powder the RR was significantly higher: 2.8 (1.1-11.7) (n=14).
Harlow et al. 1992	Exact question(s) not given. Article refers consistently to "talc." However, Table 2 refers to use of "generic baby powder" and notes that 7 cases reported use of "combinations of more than one brand," 20 cases Reported use of generic baby powder, and 14 cases reported use of "scented powder."	Compared exclusive use pre-1960 with exclusive use post-1960. Pre- was 1.6 (1.1-2.5) (n=75); post- was 1.1 (0.6.2.1) (n=29). Conceded that the study was unable to answer the key question of whether the risk pertains to all cosmetic talcs or only to certain preparations likely to be contaminated with asbestos, and that the difference in risk among pre-1960 and post-1960 users might support the view that purity is the issue.
Rosenblatt et al. 1992	Subjects asked about use of "talc" or "talcum powder"	
Hankinson et al. 1993	Subjects were given 1982 questionnaire for Nurses Health Study ("NHS"), which asked (Q. 29): "Have you ever commonly used talcum, baby powder or deodorizing power" on the perineum or sanitary napkins, daily, 1-6 times per week, or less than once a week.	No statistically significant association found between "talc use" and ovarian cancer, but there were relatively few cases (n not given).
Tzonou et al. 1993	Exact question not given or characterized.	
Purdie et al. 1995	Exact question not given or characterized.	
Chang & Risch 1997	Exact question not given, but article states that subjects were asked about both talc and cornstarch use.	The article also states that "commercial talc substitutes often replace talc with cornstarch."
Cook et al 1996	Exact question not given. Subjects were asked about any or only use of various powders: talcum, cornstarch, baby, deodorizing, scented bath/body, or unspecified. Only 16 of the 99 exposed cases who stated that they used one type of powder exclusively stated that the powder they used exclusively was talcum powder. On the other hand, the vast majority of exposed cases (159) reported use of some powder other than talcum powder or multiple kinds of powders. (Table 4).	Subjects were asked to identify the type of powder they used, and talcum powder was only a small proportion of the different types of "powders." Only 16 out of 99 stated they used talcum powder exclusively; 33 out of 193 (including multiple powder usage) used talcum powder at some time. (See Table 4). Note also that the highest RR was for deodorant spray, which would have raised the overall RR for "powders." Yet, only a few subjects reported using cornstarch-based powder.
Green et al. 1997	Exact question not given or characterized, except for "ever" use of talc.	Article as a whole simply refers to "talc" exposure.

Godard et al. 1998	Exact question not given or characterized	
Cramer et al. 1999	Subjects were asked whether they "had regularly used talc, baby, or deodorizing powders dusted or sprayed …."	Article states that only a few subjects reported using cornstarch-based powder.
Wong et al. 1999	Exact question not given or characterized.	
Gertig et al. 2000	Used NHS questionnaire from 1982 (see Hankinson et al. 1993 *supra*.)	
Ness et al. 2000	"As an adult and prior to [reference date] did you ever use talc, baby or deodorizing powder, at least [frequency and mode]."	Article as a whole refers only to "talc" exposure.
Mills et al. 2004	Exact question(s) not given. Article refers consistently to use of "talc" and "talcum powder." However, the article also states: "Our study was not able to differentiate between use of perineal powders containing talc and those containing cornstarch …."	
Cramer et al. 2005	Exact question not given, but this second phase of the New England case-control study ("NECC") presumably used the same question as the first phase (Cramer et al. 1999, *supra*), which asked subjects whether they "had regularly used talc, baby, or deodorizing powders dusted or sprayed …."	
Jordan et al. 2007	Exact question not given.	
Gates et al. 2008	Exact question not given, but subject population was comprised of the NHS and the first two phases of the NECC. All three studies asked whether the subjects had regularly used "talc, baby, or deodorizing powder, dusted or sprayed."	
Merritt et al. 2008	Exact question not given, but article states that subjects were asked whether they had ever used "powder or talc" in the genital area.	Article consistently refers to "talc" exposure.
Wu et al. 2008	Subjects asked about "talc use" prior to and after 1975. Exact question(s) not given.	Only pre-1975 use showed an association. Article noted that this was inconsistent with some other studies.
Moorman et al. 2009	Exact question not given.	
Karageorgi et al. 2010	Used 1982 NHS questionnaire. See Hankinson et al. 1993 *supra*.	Study of endometrial cancer.
Rosenblatt et al. 2011	Subjects asked about use of "powders," including "talcum, baby, cornstarch, deodorant, body/bath, and other or unknown" prior to and after 1975. But a breakdown by type of powder was not reported, and article narrative states that reporting of use of pure cornstarch powder was "quite uncommon"	"The most frequently reported category of product used after bathing was baby powder (not shown); few women reported exclusive use of talcum powder or of cornstarch (a product that does not contain talcum powder). Within limits of precision, findings regarding ovarian cancer risk among women who reported the use of talcum powder were similar to those presented for all types of powders combined …." "The validity of all of these studies, including ours, may be influenced by the level of non-response among cases and controls, and by the potential for misclassification (differential and non-differential) of exposure status. The latter derives not just from errors in the recall of the use of genital powder, but from the fact that the presence or concentration of talc can vary from brand to brand and even within one brand of powder over time. Therefore, even when

		respondents are asked specifically about perineal exposure to powders that contain talc (as in our study), they may be unable to provide accurate information." "Data from additional cohort studies would be welcome, but without details concerning the composition of the powders used by cohort members—details that many participants may not be able to provide— the results of such studies may similarly be ambiguous in their interpretation."
Vitonis et al. 2011	This study involved all three phases of the NECC study, so even though the question(s) asked were not given, it can be presumed that the question(s) in the 3d phase were the same as in the first two phases, in which the question(s) was whether subjects had regularly used "talc, baby, or deodorizing powder, dusted or sprayed." See Cramer et al. 1999 and Cramer et al. 2005, *supra*.	Article states that subjects were asked about "long term genital talc use."
Neill et al. 2012	Subjects asked whether they had "ever used any sort of powder or talc in the genital area …"	Endometrial cancer study.

Out of the 23 studies listed in draft SLR Tables 10 and 11 (pp. 73-74), 8 were studies in which the exposure questions, as indicated above, were clearly not specific to talc or talcum powder (Harlow 1992, Ness 2000, Harlow 1989, Cook 1997, Cramer 1999, Cramer 2005, Mills 2004, Merritt 2008). More importantly, out of the 10 studies shown in those tables as reporting weak but statistically significant risk numbers, 5 were ones for which the exposure questions were clearly not specific to talc or talcum powder (Ness 2000, Cook 1997, Cramer 1999, Mills 2004, Merritt 2008). In view of this, the specification in Table 9 (1st col.) that the exposure substance in most of the studies was "talc" could be misleading.

One could also well question whether women asked about use of talc or talcum powder really understood that they were being asked about a body powder comprised mainly of the specific mineral talc, rather than simply any smooth, white powder. One is reminded of the days when any photocopying was often referred to as "xeroxing," even after there were many copying machine brands on the market other than Xerox. This could explain the disconnects in the Cook 1997 study with only a small proportion of subjects reporting exclusive use of talcum powder, but few reporting use of cornstarch-based powder, and the Cramer 1999 study reporting little use of cornstarch-based powders. In view of what appears to have been a clear increase in the marketing of cornstarch or other talc-free powders and sprays starting in the 1980s, and a decline in sales of talc-based powders, such low numbers of exposure to cornstarch or other talc-free powders appear very unlikely. In a 1986 commentary, Natow noted that in the wake of the asbestos-in-talc scare in the 1970s, "[m]any consumers switched to powders that were talc-free and contained mainly corn starch."[3] The quoted comments from Rosenblatt 2011 in the above table appear very pertinent. While CRE does not have data on respective market share of various powder compositions, or when compositions changed, and consumer knowledge of constituents, the Personal Care Products Council or its members might be able to provide such data. However, it is apparent from even casual Internet searches since 2000 that there is a great variety of body powders that are being marketed as "talc-free," with many of them noting that they are talc-free due to concerns regarding the potential carcinogenicity of talc.

Lack of Evidence Supporting Translocation from Perineum to Ovaries

A key issue with regard to the epidemiologic studies is whether powder applied externally to the perineum can enter the female reproductive system and translocate to the ovaries (or uterus). If it cannot plausibly do so, there is no basis for assuming exposure of the ovaries to talc, and the epidemiologic studies showing a positive association due to perineal dusting should be disregarded.

A review of the epidemiologic studies shows that many either assumed that translocation can occur (based on statements from other studies), or they relied on several human or animal experiments supposedly showing translocation, detection of talc of talc-like particles in sections of excised human ovarian tissue or ovarian tumors, or reduction in ovarian cancer risk indicated in some studies of women who had undergone tubal ligation or hysterectomy.

<u>Experimental Studies of Translocation</u>

None of the experimental studies of particulate translocation, either human and animal, with the exception of the Boorman & Seely NTP rodent study,[4] involved deposition of talc or other dry particulate matter on the perineal skin. The draft SLR does not note this. These studies, summarized below, virtually all involved deposition of <u>solutions</u> containing particulate matter <u>inside</u> the reproductive tract. The Boorman & Seely study was a follow-up to the NTP inhalation rodent bioassay, and the rodents were completely covered with aerosolized talc powder for the duration of the experiment, and no translocation was found (although the anatomy of the rodent reproductive system differs somewhat from that in humans). As discussed in the next section (on anatomic and physiologic barriers), bypassing of the labia minora and most of the vagina is a significant distortion. The administration of oxytocin and anesthesia and elevation of the pelvis were also likely significant distortions of real-world powder application conditions. Use of a solution also likely distorted the experiments, especially those in which a patient had her pelvis elevated. Injection or application via aerosol spray could also have created false conditions. Anesthesia during surgery would likely have impeded muscular peristalsis and ciliatic movement. Administration of oxytocin could induce altered (upward) uterine contractions and anti-paristalsis in the oviducts.

Table 3. Human and animal experiments in translocation

Study/experiment	Species	Exposure substance, other conditions	Exposure site	Results
DeBoer 1972	Humans	India ink ("a colloidal suspension of carbon"), 0.2 ml, injected into 159 patients about to undergo abdominal surgery. Cyntocinon (synthetic oxytocin) was administered to some. Patients were in Trendelenberg position and placed under anesthesia.	Vagina, cervical canal, or uterus	Patients examined during surgery. Translocation from uterus to fallopian tubes or peritoneum in sign. number; no translocation from cervical canal or vagina, and backflow from uterus. Translocation from vagina to uterus in 2 out of 37.
Egli & Newton 1961	Humans	Suspension of carbon particles in Dextran and bone black, 3-4 ml,	Vaginal posterior fornix	Carbon particles were found in the fallopian

|				
		placed in the vaginal posterior fornix by speculum. Three patients were undergoing hysterectomy, and the suspension was introduced after anesthesia and oxytocin and with pelvis elevated 15 degrees. After introduction of the suspension, the patients were returned to a supine position.		tubes of 2 out of the 3 women.
Sjösten 2004	Humans	Patients scheduled for hysterectomy Examined with either cornstarch powdered or non-powdered gloves either 1 or 4 days pre-operatively. Tissue removed during surgery was examined for starch particles.	Vagina	Starch particles found in cervical canal, uterus, fallopian tubes, and peritoneal fluid. Ovaries not mentioned.
Venter & Iturralde 1979	Humans	Radio-labeled human albumin micro-spheres in solution deposited in patient a day before gyn. surgery. Patients had pelvis elevated for about 2 hr. Count was performed on tissue removed in surgery.	Vaginal posterior fornix	In 9 of 21 cases, radioactivity was detected in the fallopian tubes and ovaries. In 5 there was severe tubal occlusion.
Zervomanolakis 2007	Humans	Deposition of radio-labeled human serum albumin into 1000 patients, followed by administration of oxytocin.	Vaginal posterior fornix	Radioactivity was detected in a large proportion of subjects in the fallopian tubes. Oxytocim greatly increased transport in the follicular phase. The oxytocin apparently assisted peristalsis in the uterus and fallopian tubes.
Boorman & Seely 1994	Rats	Follow-up to NTP inhalation study, in which rodents were exposed to aerosolized talc 6hr/day for <2 yr, resulting in full-body dermal exposure and inhalation	Perineal and pulmonary	No translocation found.
Edelstam 1997	Rabbits	Biosorb[TM] starch powder deposited intra-vaginally while rabbits were anesthetized and ovulation was induced. Control rabbits used.	Vagina	There was not a statistically significant difference in numbers of particles in all portions of the reproductive tract (excluding ovaries) and the peritoneum. And no adhesions or granulomas were observed. But the authors concluded that translocation ("retrograde migration") could not be excluded.
Henderson 1986	Rats	Talc in saline solution injected into the uterus at the end of the cervical canal in one group, and intra-vaginally in another group	Uterus and vagina	Talc found in ovaries of both groups. Apparently there were no controls, and study is described as a "pilot study."
Keskin 2009	Rats	Talc in saline solution was applied as an aerosol every day for three months to two groups. One group was said to have received intra-vaginal applications, and the other was said to have received perineal applications,	Vagina and perineum(?)	Foreign body reactions, "infections," and increased number of inflammatory cells were found in all portions of the reproductive system. No

		however the manner in which the "perineal" applications were made via aerosol was not described. Talc in "dust form" was not applied.		neoplastic changes were found. (Translation from Turkish – there appear to be some translation problems -- e.g. statement that the aerosol application "can be optimally intravaginal.") Contradicted by Boorman & Seely, *supra*.
Phillips 1978	Rabbits	Radio-labeled talc in an aqueous glycerol jelly suspension was injected intra-vaginally into six rabbits (3 for 3 days, 3 for six days, then 3 days to sacrifice)	Vagina	No translocation found in the first group of 3; in the second group, a small amount of radioactivity was found in the cervix and fallopian tubes, but not in the ovaries.
Whener 1985	Monkeys	Neutron-activated talc in water deposited once in posterior fornix of vagina with pelvis elevated 15%. Oxytocin was administered. Animals were sacrificed 1 hr. and 72 hr. after exposure.	Vagina	No translocation found beyond site of deposition. Described as a pilot study. Also used a bone-black solution, but found what seemed to be contamination issues.
Whener 1986	Monkeys	Neutron-activated talc in saline solution injected into the posterior fornix of six monkeys with pelvis elevated 20-25% for 30 workdays. Oxytocin administered 1x/wk.	Vagina	No translocation detected beyond vagina-cervix (dissected as single unit) near site of injection.

Anatomic and Physiologic Barriers to Translocation

Although the draft SLR discusses many of the above translocation experiments, it does not discuss the anatomic and physiologic features of the female reproductive system that are likely to operate as barriers or impediments to intrusion and upward migration (*i.e*., translocation or retrograde migration) of inanimate particulate matter such as talc from the external perineal skin to the ovaries. The purpose of this section is to discuss those apparent barriers in order to show the lack of biological plausibility for translocation.[5]

The graphic below depicts the complete female reproductive organ system. (The graphic is derived from others in texts noted in the References, since most graphics show only portions of the full system.)
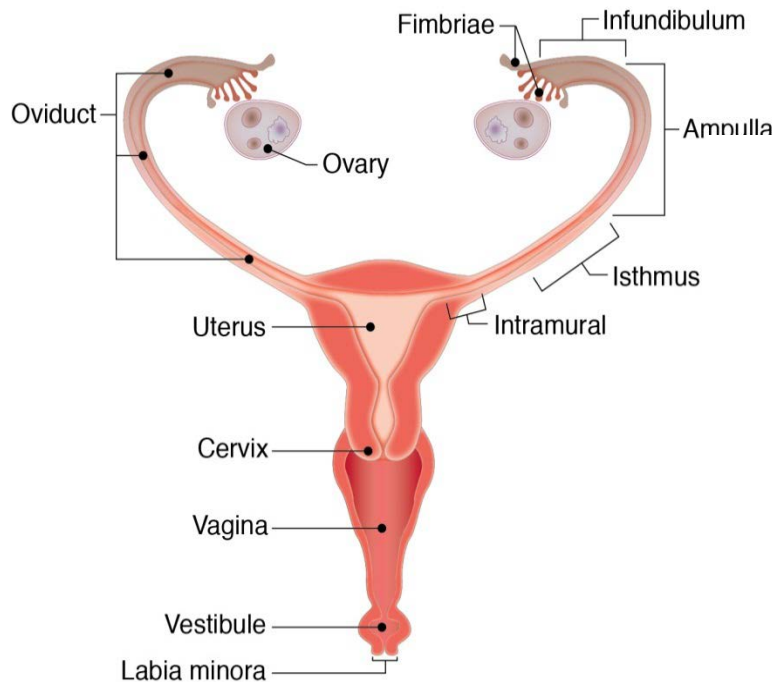
The first thing to consider is that it is not by accident that spermatozoa have a self-contained propulsion system. They have multiple barriers or impediments to overcome. In addition, spermatozoa have, as discussed below, a substantial "headstart" over particulate matter that might be deposited in the external genital area. Spermatazoa are deposited in the vagina, much of it in or near the upper portions of the vagina and the cervical os (mainly in the posterior fornix of the vagina). Such depositions of spermatozoa therefore bypass the labia minora and much of the vagina and its exudates. They are then able to "swim" through the cervical canal (for a short period near ovulation), the uterus, and much of the fallopian tubes. However, even with this means of propulsion, out of the millions or hundreds of millions of spermatozoa normally deposited in the vagina during intercourse, it has been estimated that only roughly several dozen reach the ampulla section of the fallopian tubes where fertilization of an oocyte can usually occur.[6] It is not established whether any spermatozoa travel past the ampulla section of the oviducts and the fimbriae and either enter the peritoneal space or contact the ovaries, except possibly under abnormal conditions. (Note that there is no direct connection between the fallopian tubes and the ovaries – there is open peritoneal space between the fimbriae and the ovaries.)

Ovulation and fertilization occur when a follicle with its included oocyte grows within the ovaries and eventually protrudes through the wall of the ovary and develops into an ovum, and then the ovum breaches the surface of the ovary and escapes along with follicular fluid.[7] (See the depiction of this below.[8]) Note that there is no direct tubal connection between the oviducts and the ovaries that would allow any material to be transported into the ovaries. (The ovaries are attached to the uterus by an ovarian ligament, while another ligament caries the arterial and venous blood.) Through a mechanism that is still unclear (but perhaps signaling by the follicular fluid escaping along with the ovum), the fimbriae sense the ovum and accompanying follicular material when they escape from the ovary and move closer to the

ovaries and sweep up the oocyte into the fallopian tube where it is propelled by muscular contractions and fluid flowing towards the uterus under the influence of cilia to the ampullary section of the tube, where it can encounter spermatozoa and be fertilized. If an ovum is fertilized, the egg is then propelled towards and into the uterus by tubal peristalsis and oviductal fluid under the influence of the oviductal cilia.[9]
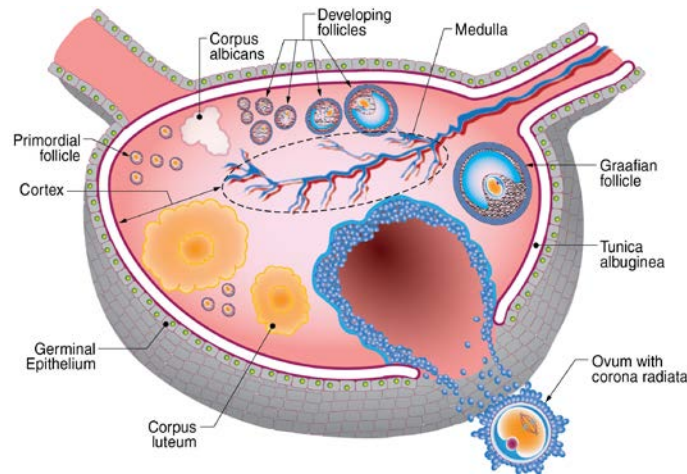
If there is no implantation of the egg into the uterus, the uterine endometrium is regularly sloughed off (approximately every 28 days) and escapes through the cervical canal and vagina as menses.

As should be apparent from this description of the initial phases of reproduction, the movement of reproductive material and fluids is normally away from the ovaries and towards the perineum. All of this movement must be overcome by the propulsive movements of the spermatozoa, with perhaps a temporary assist induced by oxytocin immediately after coitus.

In recent years, evidence has emerged that indicates that during coitus there can be release of oxytocin, and that the oxytocin can temporarily induce reverse peristalisis in the uterus and oviducts in order to assist spermatozoa in reaching the ampulla section of the tubes;[10] however, it is unclear whether this "anti-peristalsis" operates beyond the ampulla region and whether it is sufficiently strong to propel inanimate particulates especially into and past the oviducts. But even if that could happen, the particulate matter would mainly exit into the peritoneal space. And the effectiveness of such a temporary assistive mechanism would depend on the particulate matter initially being present in the uterus. There is also the phenomenon of retrograde menstruation, which could carry particulate matter through the oviducts into the peritoneum, but that also assumes initially the presence of particulate matter in the uterus or oviducts. The transport of uterine endometrium material into the peritoneal cavity can also result in endometriosis.[11]

Following is a list and description of the barriers/impediments to translocation of inanimate particulate matter from the perineum into and through the female reproductive tract to the ovaries under normal conditions.

1. <u>Closure of the labia minora</u>: Under normal conditions (*i.e.*, not coitus or childbirth), the labia minora are firmly closed by the bulbospongiosus (also known as the bulbocavernosus) sphincter muscles[12] and not even water can enter, much less particulate matter (just like the lips to the oral cavity).[13]

2. <u>Collapsed vagina</u>: Virtually all diagrams of the female reproductive system (even the one above) depict the vagina as an open tube. This is not anatomically accurate. Under normal conditions the vagina is collapsed inward such that it would be seen in cross-section roughly like an H or W (in other words, a potential, rather than actual, space).[14]

3. <u>Vaginal and cervical mucus and exudate</u>: The walls of the vagina and cervix exude mucus and other fluids, which flow downward, with the amount and viscosity varying with menstrual status and age.[15] The Office of Women's Health at the U.S. Dept. of Health and Human Services advises against douching because, as it states on its website, the vagina cleans itself with those secretions.[16]

4. <u>Closed cervical os</u>: Most of the time during the menstrual cycle the entrance to the cervical canal is closed off, much like the vaginal os is closed off by the labia minora.[17]

5. <u>Hostile cervical mucus</u>: During most of the menstrual period the cervical canal is filled with a mucus that is impenetrable even to spermatozoa. For several days during the periovulatory period of the menstrual cycle this mucus becomes more fluid, but it only allows material such as spermatozoa (about 5 microns), and possibly only if it is motile, to pass through.[18]

6. <u>Cervix-to-oviduct length of passage</u>: If material can travel through the cervical canal into the uterus, it still would have to travel some distance to the top of the uterus in order to enter the small openings into the oviducts. The entrance to the oviducts in the uterus is less than a millimeter in diameter.[19]

7. <u>Menses</u>: At the end of each menstrual period (about 28 days), the endometrial surface of the uterus sloughs off and flows out the vagina. This flow likely flushes out with it anything in the way of foreign material in the uterus, cervical canal, or vagina.

8. <u>Oviductal peristalsis</u>: If an ovum is fertilized in the ampulla section of an oviduct, oviductal peristalsis and fluid, assisted by the cilia in the oviducts, move it into the uterus.[20]

9. <u>Fimbrial-ovarian gap</u>: If particulate matter were somehow to travel to the fimbrial section of the oviducts, it would exit into the perineal cavity. At that point, it could go in many different directions and land on the surface of the peritoneum, different organs, including the surface of the ovaries, or the peritoneal lining. If that happened, the particulate matter would immediately be subject to phagocytosis.

10. <u>Ovarian follicular exudate</u>: As follicles develop in the ovaries, they displace fluid from within the ovaries and it exudes from the ovaries into the peritoneal space when ovulation occurs.[21]

11. <u>Ovarian bursa (or tunica)</u>: Beneath the epithelial surface of the ovaries, where most tumors develop, there is a dense layer of bursa or tunica that would be very difficult for any particulate to penetrate.[22] Thus, if a study indicates that particulates were found deep within the ovarian tissue it should be considered suspect.

Use of talc on diaphragms, cervical caps, or a partner's condoms would bypass the labia minora and most of the vagina and deposit talc near the cervical os. However, the epidemiologic studies that have investigated these particular exposures have almost uniformly found no association, and more recent studies have dismissed a possible association based on those studies.

In summary, spermatozoa require self-contained propulsion (via their flagellae or tails) in order to ascend to the ampullary section of the oviducts. Even then, only a very tiny percentage of them arrive there. And spermatozoa are deposited near the opening to the cervix, and therefore escape the barriers created by the labia minora, collapsed vagina, and downward flow of vaginal and cervical mucus/exudate and menses. It is highly unlikely that inanimate particles deposited outside the vagina on the perineal skin could travel not only to the ampulla section of the oviducts, but completely through the oviducts and past the fimbriae. Even if they could, they would then have to travel across the peritoneal space between the fimbriae and the ovaries and attach to the surface of the ovaries (it being presumably nearly impossible for them to actually penetrate the ovaries) and escape phagocytosis. Thus, the hypothetical pre-condition to talc causing ovarian cancer – exposure of the ovaries to perineally-applied talc -- has not been established and appears to conflict with known anatomy and physiological processes in the female reproductive tract.

This subject was discussed at the two-day 1994 workshop sponsored jointly by FDA, CTFA, and ISRTP. (The workshop was attended by 110 individuals from government agencies, academia, industry, consulting, and the consumer sector.) In the consensus summary of the workshop it is stated that "[f]ollowing a presentation by Dr. Brown (University of Wisconsin), the discussion made it clear that available histologic and physiological studies provide no basis to conclude that talc can migrate to the ovaries from the perineal region."[23]

The 2006 IARC review (published in 2010) that resulted in an evaluation of "possibly carcinogenic to humans" (with several dissents) (for "talc-based body powder," not talc) found that the evidence for translocation was "weak."[24] But the IARC reviewers did not consider the anatomical/physiological aspects of the translocation issue, and there were no gynecologists on the working group or participating as invited experts. In reality, as can be seen, the literature evidence for translocation from the <u>perineum</u> would be better characterized as non-existent, and taking into account anatomic and physiologic factors, the overall evidence would probably be best characterized as indicating that translocation of particulate matter from the perineum is very implausible .

Lack of Evidence of Granulomas, Inflammation, or Adhesions in the Reproductive Tract of Powder Users

Talc is known to cause inflammation, foreign-body granulomas, and scarring or adhesions when introduced into the thoracic or peritoneal cavities, or into wounds or surgical

incisions. The medical community generally stopped using talc-powdered surgical and examination gloves (as well as cornstarch-powdered gloves) for just this reason many years ago. Yet, despite talcum powder having been actively marketed and widely used by consumers for at least well over a century, there have never to our knowledge been published reports of inflammation, granulomas, or adhesions in the female reproductive system associated with perineal dusting with talcum powder (or cornstarch or other powder constituents). How can this be if talc is able to enter, and remain in, the reproductive system following use? The presence of talc particles in or on reproductive organs would cause inflammation, granulomas, and adhesions. Simply as a matter of common experience and societal knowledge, women would not use talcum powder as extensively as they have (in the range of forty percent in the United States) if they experienced inflammation, scarring, and granulomas. Medically, talcum powder usage has not been associated with tubal occlusion, pelvic inflammatory disease, or vaginitis. One would think that such an association would be easily discoverable in the pathology lab, by laparoscopy, or even visually during a gynecologic examination. And reports of talc found in or on ovarian tissue samples do not show typical signs of inflammation and granuloma formation. Because granulomas and adhesions form around particulate matter, and inflammation responses are detectable, the cause of any such abnormalities should be easy to diagnose if due to particulate matter.   Note the findings of granulomas and "infections" in the Keskin et al. translocation study on rats.[25] Yet tissue samples purportedly showing particulates on or embedded in them have not been reported to show these typical signs, which seems to indicate that the presence of particulates occurred after the tissue was removed from the body and was due to contamination, either from ambient dust or surface dust.

Lack of Consistency in the Risk Estimates in the Epidemiologic Studies

The draft SLR indicates at p.18 that the epidemiologic studies have shown "a fairly consistent association between perineal dusting with talc powders and ovarian cancers." (Citation omitted).   The body of epidemiology presents a semblance of consistently positive (though mainly statistically non-significant) weak associations; however, it should be noted that, as discussed above, many of the studies, particularly many showing a statistically positive association, did not specifically study talc (as opposed to other types of powders or sprays) as an exposure; and most of the studies, when examined from the viewpoint of types of exposure or frequency/duration categories, show associations that are either not statistically significant or negative (see Table 9 of the draft SLR).

In a significant number of studies (13), exposure via sanitary pads or underwear is broken out separately – and such "indirect" exposure should result in just as much direct exposure to the perineum as "direct" dusting of the perineum. Table 4 lists RRs/ORs from all of the studies that broke out exposure via sanitary pads and/or underwear separately.

Table 4: Exposure via sanitary pads or underwear

Study (alphabetical)	RR/OR
Chang & Risch 1997	1.26 (0.81-0.96)
Cook 1997	0.9 (0.5-1.5)
Cramer 1982	1.52 (0.98-2.47)

Cramer 1999	san. pd. 1.45 (0.68-3.09) undwr. 1.21 (0.40-2.8)
Gertig 2000	0.89 (0.61-1.28)
Harlow 1992	1.1 (0.4-2.8)
Karageorgi 2010	0.98 (0.75-1.27)
Ness 2000	san. pd. 1.6 (1.1-2.3) undwr. 1.7 (1.2-2.4)
Rosenblatt 1992	4.8 (1.3-17.8)
Rosenblatt 2011	0.82 (0.58-1.16)
Whittemore 1988	0.62 (0.21-1.80)
Wong 1999	0.9 (0.4-2.0)
Wu 2009	san. pd. 1.61 (0.93-2.78) undwr. 1.71 (0.99-2.97)

While the number of subjects exposed via these modes was relatively small in many of the above studies (as indicated by the confidence intervals), it appears that a pooling or meta-analysis would yield a considerably lower RR/OR than the 1.3 or 1.4 generally attributed to "perineal" exposure as a whole.

As has been frequently noted in the studies themselves, the overall body of epidemiology studies is very inconsistent with regard to dose-response, with many showing a lack of a consistent positive dose-response, and some even indicating an inverse dose-response. This is inconsistent with basic principles of toxicology.

It should also be noted that a number of all the studies were "ever/never" studies, which is a crude study design, especially since it might be more susceptible to recall bias (discussed below).

Basis for Recall Bias

It is generally recognized that case-control epidemiologic studies are particularly susceptible to recall bias by cases. This is because cases (*i.e.*, women diagnosed with cancer) have a tendency to search out, or recall more frequently, exposures that they believe, or that others believe, might have caused their cancer. Cases might conduct library or Internet searches or discuss their disease with friends and support groups. *Zota et al.*[26] recently investigated possible recall bias among women with breast cancer in a case-control study examining possible association with home cleaning, air-freshener, and insecticide products. They found that RRs were weakly elevated (about 2.0) for association with cleaning and air-freshener products (and very weakly for some insecticide products) among women who believed that chemicals and air pollution contribute "a lot" to breast cancer as compared with cases who did not have such a belief. This study appears uniquely analogous to the case-control studies here because it involved a female reproductive system cancer and similarly weak RRs.

The IARC working group recognized the susceptibility of case-control studies to recall bias, but tended to discount it on the basis that the largest flurry of publicity concerning cancer and talc-based body powders occurred in the mid-1970's, and possibly very close to early 2006 (when the working group met), and in between those times "it was the opinion of the Working Group that there had not been widespread public concern about this issue …."[27] This seems like

odd reasoning because the study cohorts ages spanned the 1970s and because, while the working group or IARC staff apparently did not conduct research on the subject, there appears to have been, in fact, wide reporting of both the asbestos-in-powders cancer issue in the 1970s and subsequent case-control studies through the 1980s and 1990s. A search of the ProQuest database of newspaper and periodicals articles from 1976 to very recently turned up hundreds of stories of this sort.[28] Some examples from major U.S. newspapers (and there are many more from smaller newspapers and other English-speaking countries such as England, Canada, and Australia where epidemiologic studies were conducted) include the following, copies of which are attached:

"Asbestos Fibers Found in Baby Powder," The Washington Post, Mar. 8, 1976, p. A1.

"Study finds asbestos in 9 body powders," The Boston Globe, Mar. 8, 1976, p. 2.

"10 of 19 talc powders found to have asbestos," Baltimore Sun, Mar. 9, 1976, p. A3.

"Asbestos Found in Baby Powders," Los Angeles Times, Mar. 8, 1976, p. A7.

"Asbestos Found in Ten Powders," New York Times, Mar. 10, 1976, p. 43.

"Study links talcum powder use to ovarian cancer," Associated Press - Baltimore Sun, Aug. 6, 1982, p. A3. (Article on Cramer *et al*. 1982 study.) (Note that AP stories are distributed to thousands of daily newspapers and other media outlets both nationally and internationally. Just in the U.S., about 1,400 daily papers are AP subscribers.)

"Hospital Study Ties Talc Use to Ovarian Cancer," Associated Press - The Hartford Courant, Aug. 6, 1982, p. A3. (Article on Cramer et al. 1982 study.)

CNN transcript for story regarding release of Cancer Prevention Coalition and Nader group's "dirty dozen" list, which included talcum powder, Sept. 21,1995 (10 pm news).

"The Perils of Powders," Time, Inc. Health, Sept. 1996, p. 17. (ProQuest abstract of article on Cook *et al*. 1997 study (advance release 1996).)

"Genital powders linked to cancer use tied to ovarian cancer, reports study by Hutchinson Center," Associated Press – Seattle Post-Intelligencer, Mar. 5, 1997, p. B1 (ProQuest abstract of article on Cook *et al*. 1997 study.)

"Study links ovarian cancer, use of feminine products …," Orlando Sentinel, Mar. 5, 1997, p. A15. (ProQuest abstract of article on *Cook et al*. 1997 study.)

"Ovarian cancer risk linked to powder, sprays," Associated Press - Denver Post, Mar. 5, 1997, p. A7. (ProQuest abstract of article on Cook *et al.* 1997 study.)

Perhaps more important than the above hard-copy publications for relevance to recall bias is the development, since roughly the mid- to late-1990s, of an individual's ability to easily search the Internet for pertinent materials, whether health literature, news articles, or non-expert advice/advertisements. Internet use began to explode in the mid-1990s along with new search

engine capabilities. PubMed became widely available in about 1999-2000,[29] allowing women to access all the epidemiologic studies cited herein. For many years the Internet has provided access to a multitude of articles and advertisements with advice to use "talc-free" body powders because talc is linked to cancer and is similar to asbestos. For example, a current Internet search on Google for "ovarian cancer baby powder" will turn up about 236,000 (not a typo) results. Regardless of the content of the postings, an ovarian cancer patient picked for a case-control study could be sensitized by such materials to the talc-ovarian cancer hypothesis and be more primed to recall use of any sort of powder applied to the perineum.

Conclusions

- Talcum powder and cosmetics containing talc have been used by consumers for well over a century with no reports of adverse effects or discomfort unless used inappropriately or accidentally inhaled in large quantities.

- There is convincing evidence that talc is not carcinogenic. The notion that talc is similar to asbestos has been shown to be unsupported. Talc is non-genotoxic and non-tumorigenic *in vitro* and in animal experiments, and has been proven non-carcinogenic through its widespread use in medical pleurodesis and pharmaceuticals, and occupationally by millers. A number of experiments have even indicated that talc has cancer-inhibiting properties (anti-angiogenic and promoting apoptosis).

- The numerous case-control studies -- allegedly of exposure to "talc," but often actually based on exposure to various powders or sprays of unknown composition – and ovarian cancer are far too problematic to raise significant doubts regarding talc safety. Serious problems with the ovarian epidemiologic studies include the following (not necessarily in order of importance):

  1. There is no evidence that powder applied externally to the perineum is able to translocate to the ovaries. Basic anatomic and physiologic knowledge concerning the female reproductive system indicates strongly that it is not possible for talc ordinarily to gain entrance to the system, and if it does, to move through the vagina, cervical canal, uterus, and oviducts, and across the peritoneal space from the oviducts to the ovaries and escape phagocytosis. Analyses of the results of studies asking about use of talc on diaphragms, cervical caps, or condoms, which would deposit talc farther inside the reproductive tract, have not shown a positive association. This knowledge is augmented strongly by very long practical consumer and gynecologic experience in which perineal powders that should cause inflammation, granulomas, scarring, and adhesions if particles entered the reproductive system have not been reported to be associated with such lesions. Because talc (as well as some other particulates resembling talc, such as zeolite) is ubiquitous in dust due to its many common uses, and because particles supposedly talc found on ovarian tissue specimens do not show surrounding typical signs of inflammation or granulomatous formation, it is likely that any such findings are due to ordinary dust contamination after surgical removal.

2. All of the epidemiologic study cohorts have age ranges overlapping the period prior to 1976 when asbestos was supposedly detected in significant quantities in some brands of body powders.

3. Many of the epidemiologic studies were studies of exposure to various types of powders or sprays in addition to talcum powder. Most other studies do not provide the actual question(s) asked of subjects regarding exposures. Moreover, it is not clear that many consumers (or study subjects) recognize talcum powder as a type of powder distinct from talc-free powders.

4. As a body, the majority of studies show very weak RRs or ORs that are not statistically significant. In particular, studies reporting risks from exposure via sanitary pads or underwear (in addition to those reporting on use of talc on diaphragms and condoms) appear to be either negative or extremely weak.

5. The majority of studies do not show a positive biological gradient (increasing risk with increasing exposure), which is one of the hallmarks of toxicity.

6. Case-control studies are recognized as susceptible to recall bias, and it can be shown that the talc-cancer hypothesis has received widespread publicity since at least 1976 (when asbestos contamination was reported in some brands of body powders), and particularly since Internet access by the general public became more available and popular beginning towards the end of the twentieth century.

7. The only prospective cohort study was essentially non-positive.

We look forward to Expert Panel review and discussion of this matter.

Respectfully,

/s/

William G. Kelly, Jr.
Center for Regulatory Effectiveness

Attachments (news articles and abstracts)

References

[1] SEER Stat Fact Sheets: Ovary. http://seer.cancer.gov/statfacts/html/ovary.html.

[2] http://seer.cancer.gov/faststats/selections.php?#Output.

[3] Natow AJ. 1986. Talc: Need we beware? *Cutis* 37(5):328-29.

[4] Boorman GA and Seely JC. 1995. The lack of an ovarian effect of lifetime talc exposure in F344/N rats and B6C3F1 mice. *Regul Toxicol Pharmacol* 21:242-43.

[5] Graphic below based on various graphics and photos in Mescher AL, **Junquiera's Basic Histology, Text and Atlas**, 12th ed., McGraw-Hill 2010, chapter 22.

[6] Jones RE, **Human Reproductive Biology**, 2d ed., Academic Press 1997, pp. 165-66.

[7] Mescher, *supra* , p. 393.

[8] Graphic based on graphics in Mescher, *supra*, p. 390.

[9] See Jones, *supra*, at 40.

[10] Zervomanolakis I *et al*. 2007. Physiology of upward transport in the human female genital tract, Part I: Nonpregnant uterine peristalsis, In: *Reproductive biomechanics*. *Annals NY Academy of Sc* 1101:1-20; Jones, *supra*, at 166.

[11] See Jones RE, *supra*, p. 43.

[12] Crafts RC, **A Textbook Of Human Anatomy**, 2d ed., John Willey & Sons 1979, pp. 310, 315; Alexander NJ *et al*. 2004. Why consider vaginal drug administration? *Fertil Steril* 82(1):1-12; Jones RE, *supra*, p. 48.

[13] Siegel P. 1960. Does bath water enter the vagina? *Obstet Gynecol* 15:660-61.

[14] Barnhart KT *et al*. 2006. Baseline dimensions of the human vagina. *Human Reproduction* 21(6): 1618–226; Crafts, *supra*, at 298.

[15] Hussain A and Ahsan F. 2005. The vagina as a route for systemic drug delivery. *J Controlled Release* 103:301-13; Alexander NJ *et al*. 2004. Why consider vaginal drug administration? *Fertil Steril* 82(1):1-12; Lai SK *et al*. 2009. Micro- and macrorheology of mucus. *Adv Drug Deliv Rev* 61(2):86-100.

[16] U.S. Dept. of Health and Human Serv., Nat'l Women's Health Inform. Ctr., Office of Women's Health. 2011. *Frequently Asked Questions* ("Most doctors say that it is best to let your vagina clean itself. The vagina cleans itself naturally by producing mucous.") (available at http://www.womenshealth.gov/publications/our-publications/fact-sheet/douching.cfm#f).

[17] Fuchs A and Westman A. 1945. Studies on the functional sphincter in the cervix uteri. *Acta Physiol Scand* 10(3-4):350-54.

[18] See Jones RE, *supra*, pp. 41, 165-66.

[19] Page EW *et al.*, **Human Reproduction**, 2d ed., W. B. Sauders Co. 1976, p. 37.

[20] Mescher, *supra*, p. 395. See also Page EW et al., *supra*, p. 37.

[21] Mescher, supra, p. 393.

[22] Mescher, *supra*, p. 388.

[23] Carr CJ. 1995. Executive summary to Talc: Consumer uses and health perspectives. *Reg Tox Pharm* 21:211-15.

[24] IARC monograph 93 (2010) at 411.

[25] Keskin N *et al.* 2009. Does long-term talc exposure have a carcinogenic effect on the female genital system of rats? An experimental pilot study. *Arch Gynecol Obstet* 280(6):925-31.

[26] Zota AR *et al*. 2010. Self-reported chemicals exposure, beliefs about disease causation and risk of breast cancer in the Cape Cod Breast Cancer and Environment Study: a case control study. *Environ Health* 9:40.

[27] IARC monograph 93, *supra*, at 409.

[28] Personal search done by W. Kelly (signatory of these comments) at Library of Congress. The ProQuest database covers over 2500 newspapers and periodicals and other media; however, full text copies of articles are available for only about half the entries, with abstracts provided for the other entries. The ProQuest database tends to focus on major media. A more comprehensive search, and one that returns full-text articles, could probably be conducted through the Readers Guide to Periodical Literature with copies of entries retrieved from microfilm. Such a search would be somewhat time-consuming. The ProQuest search reflected in these comments was conducted in less than a day.

[29] See "PubMed Celebrates its 10th Anniversary!" National Library of Medicine technical bulletin posted Oct. 5, 2006. Available at http://www.nlm.nih.gov/pubs/techbull/so06/so06_pm_10.html.

October 19, 2012

F. Alan Andersen, Ph.D.
Director
Cosmetic Ingredient Review
Suite 412
1101 17th Street, NW
Washington, DC 20036-4702

RE: Scientific Literature Review: Talc as Used in Cosmetics

Dear Dr. Andersen:

The Talc/Wollastonite Section of the Industrial Minerals Association – North America (IMA-NA) and EUROTALC are pleased to file these joint comments on the Cosmetic Ingredient Review's (CIR) Scientific Literature Review: *Talc as Used in Cosmetics* (SLR), dated August 15, 2012. The IMA-NA is an industrial trade association representing producers of industrial minerals, including talc, in North America. EUROTALC is an industrial trade association representing producers of talc in the European Union.

At the outset, IMA-NA and EUROTALC wish to compliment the CIR staff responsible for documenting the SLR. Their work is a thorough and comprehensive examination of talc used in cosmetics from chemical, toxicokinetic, toxicological, genotoxic, carcinogenic, irritation and sensitization perspectives. Overall, we believe that the SLR supports a determination that talc used in cosmetics is safe under its intended conditions of use.

However, as producers of talc, including talc used in cosmetics, IMA-NA and EUROTALC member companies would like to submit specific comments on the SLR. These comments will focus on topics and issues with which we are most familiar and have particular expertise, namely on chemistry, mineralogy, production, occupational exposure, and toxicology. We believe that the comments we offer below may be useful and help improve the SLR accuracy.

Please note that IMA-NA and EUROTALC are available to make a presentation at a public hearing of the Expert Panel should the Chairman or Expert Panel determine that IMA-NA's and EUROTALC's participation might help inform the Expert Panel on particular matters within the associations' expertise.

Specific Comments

IMA-NA's and EUROTALCS specific comments will either identify a section of the SLR upon which we wish to comment and then address that section specifically or we will offer more general comments on a specific topic.

Page 1

Introduction

Statement:

"Therefore, this report will only address non-asbestiform talc."

Comment:

      We recommend the following revised wording:

      "Therefore, this report will only address talc that does not contain asbestos."

Chemistry

Comment:

      We recommend this section be titled "Mineralogy and Chemistry."

Definition and Structure

Statement:

"Pure talc has the formula $Mg_3Si_4O_{10}(OH)_2$ and a chemical composition of 31.88% by weight (wt) magnesium oxide (MgO), 63.37% silicon dioxide (SiO_2), and 4.75% water (H_2O)."

Comment:

      We recommend the following revised wording:

      "The mineral talc has the formula $Mg_3Si_4O_{10}(OH)_2$ and a theoretical chemical composition, expressed as oxides, of 31.7% by weight (wt) magnesium oxide (MgO), 63.5% silicon dioxide (SiO_2), and 4.8% hydrogen dioxide (H_2O)."

Statement:

"Talc belongs to the silicate subclass phyllosilicates and the clay group montmorillonite/smectite and is a sheet silicate."

Comment:

This definition is partly true: talc belongs to a type (dioctahedral or trioctahedral) of phyllosilicates. The montmorillonite/smectite group belongs to the same type. Talc does not belong to the montmorillonite /smectite group.

We recommend the following revised wording:

"Talc belongs to the silicate subclass phyllosilicates."

Statement:

"Some elements, such as nickel and iron, may be embedded in the talc particle lattice, but they are bound within the particle and do not exert any biological action. Small amounts of aluminum can substitute for silicon in the tetrahedral positions and small to moderate amounts of aluminum, iron (Fe(III), Fe(II)) and manganese can substitute for magnesium in the octahedral positions."

Comment:

We recommend the following revised wording:

"Small amounts of aluminum and iron(III) can substitute for silicon in tetrahedral sites. Trace amounts of nickel and small to moderate amounts of iron(II), iron(III), aluminum, and/or manganese can substitute for magnesium in octahedral sites. Such substitutions are bound within the crystal lattice and therefore do not exert any biological action. The replacement of hydroxyl groups (OH-) by fluorine may also occur."

Page 2

Physical and Chemical Properties

Statement:

"Talc can be tabular, granular, fibrous, or platy, but it is usually crystalline, flexible, and soft. The physical form of talc dust is directly related to the source of the talc and to the minerals found in the ore. Talc particles in cosmetic-grade talc are flat and plate-like. The size of an individual talc platelet can vary from 1 μm to over 100 μm, depending on the formation of the deposit, and the platelet size determines lamellarity. Highly lamellar talc (i.e. macrocrystalline talc) has large individual platelets, while microcrystalline talc has small platelets. Talc deposits are (informally) characterized by the natural crystallinity of

the ore as "macro-crystalline" talc (large, well-defined platelets) and "micro-crystalline" talc (small, randomly oriented platelets)."

Comment:

It should be emphasized that these are <u>bulk texture rock attributes</u>, *not* necessarily particle morphology attributes of talc. Talc is dominantly platy.

We recommend the following revised wording:

"The mineral talc is predominantly platy, with adjacent layers very weakly bonded by Van der Waals forces. This allows talc to be easily sheared along the plane and gives it its natural slippery feel as well as its softness. Talc is the softest mineral with a hardness of 1 on a Mohs' scale of 1 to 10.

The physical form of talc rock is related to the source and geological conditions during formation of the deposit. Talc's platelet size determines its lamellarity, which, in turn, is related to the genesis of talc deposits. Highly lamellar talc (informally classified as macrorystalline talc) has large individual platelets, while microcrystalline talc has small, randomly oriented platelets."

Statement:

"The particle size of talc powder depends on the process used to make the powder. Cosmetic talcs commonly have particle sizes ranging between 0.3 to 50 μm, with only minor fractions consisting of particles considered respirable."

Comment:

We recommend the following revised wording:

"The particle size of talc powder depends on the process used to make the powder. Typical cosmetic talcs have average particle sizes ranging between 4 and 15 μm when measured by sedimentation method, with only minor fractions consisting of particles considered respirable."

Statement:

"Another source recites … 400-mesh [74, 44, 37 μm, respectively] screen, respectively, when wet-out …."

Comment:

We recommend the following revised wording:

"Another source recites … 400-mesh [74, 44, 37 μm, respectively] when wet-out …."

Constituents/Impurities

Statement:

"Non-talc minerals associated with commercial talc vary from deposit to deposit. The most common minerals found in talc include chlorite, magnesite, dolomite, tremolite, amthophyllite, serpentine, and quartz. Naturally occurring talcs can have small amounts of fluorine (up to 0.5% by wt), titanium dioxide (up to 0.10%), alumina (up to 3%), ferrous oxide (up to 3%), ferric oxide (up to 2%), and calcium oxide (up to 1.5%), and sometimes traces of manganous oxide and sodium monoxide., and naturally occurring talc also may contain calcite, kaolin, and phlogopite."

Comment:

This paragraph mixes mineralogical and chemical information. A part of the third sentence above relates to the chemical composition of the talc product and the remainder of sentence relates to the mineral composition. For the uninitiated reader, it may seem that talc products include the mentioned minerals plus the chemical oxides listed. In fact, the chemical composition is directly linked to the mineralogical composition.

To better understand the relationship between generally recognized mineral phases and chemical composition, we have attached Appendix A to our comments, which provides mineral names and chemical formulae.

We recommend the following revised wording:

"Associated minerals found in commercial talc products vary from deposit to deposit depending on the conditions of formation of the deposit. The most common minerals associated with talc are chlorite, magnesite, dolomite, calcite, mica, quartz, and fluorapatite. Amphiboles and serpentine are associated with certain specific talc deposits. These deposits are rare and historically were used for low-grade industrial applications due to the impurities present"

Analytical Methods

Statement:

"The absence of asbestiform amphibole minerals in cosmetic talc is determined using the generally accepted method of x-ray diffraction and optical microscopy and dispersion-staining. Other methods for the detection of fibrous amphibole, such as transmission electron microscopy with selected area diffraction and electron microprobe, were considered but were not adopted by the cosmetics industry trade association."

Comment:

> We recommend the following revised wording:
>
> "The absence of asbestiform amphibole minerals in cosmetic talc is determined using the generally accepted method of x-ray diffraction and optical microscopy with dispersion-staining. Other methods for the detection of asbestiform amphiboles and serpentine, such as transmission electron microscopy with selected area diffraction, were considered but were not adopted by the cosmetics industry trade association. USP is considering incorporating transmission and/or scanning electron microscopy as part of its Talc Monograph modernization effort."

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Statement:

"Free crystalline silica (quartz) in talc can be detected using differential thermal analysis, which permits detection at a 0.5 – 1.0% w/w minimum detectable level, or by x-ray diffraction."

Comment:

> We recommend the following revised wording
>
> "Crystalline silica (quartz) in talc can be detected using x-ray diffraction or infrared spectrometry, which permit detection at a 0.1% w/w minimum detection level. Differential thermal analyses also can be used."

Production

Statement:

"Talc is sorted (beneficiated) from other non-talc minerals, and the processing can be wet or dry. Wet beneficiation processing may be utilized in the production of high-purity talcs, such as those required for cosmetics. The talc ore is crushed and ground (in a wet or dry state) to a fineness that liberates it from other non-talc minerals."

Comment:

> We recommend the following revised wording:
>
> "Crude talc ore can be sorted (beneficiated) to improve purity of commercial products by either dry or wet processing. In either case, the talc ore is crushed and ground to a fineness suitable for specific end-uses."

Statement:

"Cosmetic talc is typically sterilized by gamma irradiation."

Comment:

> Cosmetic and pharmaceutical talcs are no longer sterilized by gamma treatment.
>
> We recommend the following revised wording:
>
> "Cosmetic talc is typically sterilized by heat treatment."

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Occupational Exposure

Statement:

"Human pulmonary effects of chronic occupational inhalation of talc include diffuse interstitial fibrosis and progressive massive fibrosis (often called complicated pneumoconiosis). Depending on the composition and contaminants of talc, three forms of talc-related pulmonary effects have been described: pure talcosis, produced by exposure to talc that is free of silica and asbestiform minerals; talco-asbestosis, produced by the inhalation of talc with asbestiform fibers; and talco-silicosis, produced by exposure to talc associated with silica and other non-asbestiform fibers. A fourth talc-related disease, stemming from i.v. administration of talc, is not related to occupational exposure, but instead is usually associated with abuse of oral medications. Each form has a distinctly different radiographic appearance. The radiographic abnormalities associated with pure talcosis consist of small nodules that are usually seen in the lower pulmonary fields. Reticulations may occur, but this is less common. Pure talcosis results in pulmonary function test results that are consistent with restrictive pulmonary disease."

Comment:

> According to a recent study commissioned by the industry association EUROTALC, although early epidemiological work suggested a relationship between talc exposures and pneumoconiosis, this work did not take into account confounding factors, notably smoking as the main confounder. No reliable study establishing a clear link between exclusive talc exposure and pneumoconiosis has been identified. Furthermore, the more recent studies with state-of-the-art correction for confounding factors did not find an association between pneumoconiosis and current industrial talc exposure (Wild et al., 2008) limited to a maximal talc dust concentration of 2 mg/m^3 air. Any observed effects are non-specific particle effects rather than a specific intrinsic fibrogenic activity of talc (*Talc {Asbestos-Free}, Evaluation of the Carcinogenic Potential and Potential Target Organ Toxicity in Humans Expert Statement*, Bjarte Furnes and Christian Strupp, April 2010, Harlan Laboratories Ltd., Switzerland, unpublished report). For these reasons, in

case of co-exposure with crystalline silica and in absence of talc lung overload it is correct to define the cases of pneumoconiosis observed as pure silicosis and not as silico-talcosis. Similarly in case of co-exposure with asbestos the cases of pneumoconiosis observed should be considered as asbestosis and not talco-asbestosis. The cases of talc pneumoconiosis described in the past were the consequences of talc dust lung overload. There is no data supporting a specific fibrogenic interaction between talc and silica or asbestos.

Statement:

"As given in Table 5, statistically significantly elevated standardized mortality ratios (SMRs) for silicosis and silicotuberculosis were observed in an early study of talc miners and millers in the Italian Piedmont region. The miners were employed for at least one year and the millers for at least two years in their respective occupations. Talc in this region reportedly contained no fibrous material, except for tremolite micro-inclusions. This study also found statistically significantly reduced SMRs for malignant neoplasms, including lung, bronchial and tracheal cancers. Updates of this study reported similar results, including statistically significant increases in mortality, which were attributable primarily to non-malignant respiratory diseases among the miners, no increases in SMRs for cancer, including lung cancer, and no mesothelioma cases."

Comment:

> Note that there were no statistically significant increases in mortality in millers attributable primarily to non-malignant respiratory disease. The excess mortality observed in miners is attributable to silica exposure. This means that the exposure to talc in the absence of lung overload does not cause excess non-malignant respiratory diseases.

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Co-carcinogenicity

Statement

"The effects of instillation of B[a]P alone were not investigated in this study, but the researchers noted that B[a]P does not initiate respiratory tumors. Therefore, it appears that talc had a co-carcinogenic effect in inducing respiratory tumors in hamsters when instilled intratracheally with B[a]P."

Comment:

> The BaP is a genotoxic carcinogen and consequently is considered to be able to initiate respiratory tumours. The absence of investigation on the effects of instillation of BaP alone is a bias and limits the weight of the results of the study, which cannot support the hypothesis that talc has a co-carcinogenic effect.

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References

Comment:

We recommend adding the following reference:

McCarthy, E.F., Genco, N.A., and Reade, E.H., Jr., 2006, Talc, in Kogel, J.E., Trivedi, N.C., Barker, J.M., and Krukowski, S.T., eds., Industrial minerals and rocks (7th edition): Littleton, Colorado, Society for Mining, Metallurgy, and Exploration, Inc., p. 971–986.

Conclusion

The Talc/Wollastonite Section of IMA-NA and EUROTALC are pleased to file these joint comments on the Cosmetic Ingredient Review's Scientific Literature Review: *Talc as Used in Cosmetics*. As producers of talc, including talc used in cosmetics, IMA-NA and EUROTALC member companies have focused their comments on topics and issues with which they are most familiar and have particular expertise that should be of use to the CIR Expert Panel, namely on mineralogy and chemistry, and occupational exposure. We compliment the CIR staff responsible for documenting the SLR and we also believe that it supports a determination that talc used in cosmetics is safe under its intended conditions of use. We hope that the SLR can be improved by incorporating the specific comments we have offered.

Please remember that IMA-NA and EUROTALC are available to make a presentation at a public hearing of the Expert Panel should the Chairman or Expert Panel determine that IMA-NA's and EUROTALC's participation might help inform the Expert Panel on particular matters within the associations' expertise.

Should you have any questions, comments or suggestions regarding these written comments, please contact either Mark Ellis at +1 202 457 0200 or Dr. Michelle Wyart-Remy at +32 2 210 44 10. Alternatively, they can be reached via e-mail at markellis@ima-na.org or m.wyart@ima-europe.eu.

Sincerely,

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Appendix A

Generalized Mineral Phases

Talc	$(Mg,Fe)_3Si_4O_{10}(OH,F)_2$
Chlorite/Clinochlore	$(Mg,Fe,Al)_6(Si,Al)_4O_{10}(OH,F)_8$
Calcite	$CaCO_3$
Dolomite	$CaMg(CO_3)_2$
Magnesite	$MgCO_3$
Quartz	$\alpha\text{-}SiO_2$
Tremolite	$Ca_2Mg_5Si_8O_{22}(OH)_2$
Anthophyllite	$(Mg,Fe)_7Si_8O_{22}(OH)_2$
Serpentine	$(Mg,Al,Fe)_3(Si,Al)_2O_5(OH)_4$
Fluorapatite/Hydroxyapatite	$Ca_{10}(PO_4)_6F_2/Ca_{10}(PO_4)_6(OH)_2$
Pyrite	FeS_2
Magnetite	Fe_3O_4
Hematite	$\alpha\text{-}Fe_2O_3$