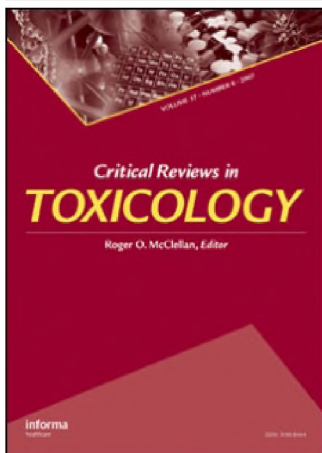


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On: 10 March 2008
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Publisher: Informa Healthcare
Informa Ltd Registered in England and Wales Registered Number: 1072954
Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Critical Reviews in Toxicology

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713401167>

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Online Publication Date: 01 March 2008

To cite this Article: Pierce, Jennifer S., McKinley, Meg A., Paustenbach, Dennis J. and Finley, Brent L. (2008) 'An Evaluation of Reported No-Effect Chrysotile Asbestos Exposures for Lung Cancer and Mesothelioma', Critical Reviews in Toxicology, 38:3, 191 - 214

To link to this article: DOI: 10.1080/10408440701845609

URL: <http://dx.doi.org/10.1080/10408440701845609>

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An Evaluation of Reported No-Effect Chrysotile Asbestos Exposures for Lung Cancer and Mesothelioma

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Numerous investigators have suggested that there is likely to be a cumulative chrysotile exposure below which there is negligible risk of asbestos-related diseases. However, to date, little research has been conducted to identify an actual “no-effect” exposure level for chrysotile-related lung cancer and mesothelioma. The purpose of this analysis is to summarize and present all of the cumulative exposure-response data reported for predominantly chrysotile-exposed cohorts in the published literature. Criteria for consideration in this analysis included stratification of relative risk or mortality ratio estimates by cumulative chrysotile exposure. Over 350 studies were initially evaluated and subsequently excluded from the analysis due primarily to lack of cumulative exposure information, lack of information on fiber type, and/or evidence of significant exposures to amphiboles. Fourteen studies meeting the inclusion criteria were found where lung cancer risk was stratified by cumulative chrysotile exposure; four such studies were found for mesothelioma. All of the studies involved cohorts exposed to high levels of chrysotile in mining or manufacturing settings. The preponderance of the cumulative “no-effects” exposure levels for lung cancer and mesothelioma fall in a range of approximately 25–1000 fibers per cubic centimeter per year (f/cc-yr) and 15–500 f/cc-yr, respectively, and a majority of the studies did not report an increased risk at the highest estimated exposure. Sources of uncertainty in these values include errors in the cumulative exposure estimates, conversion of dust counts to fiber data, and use of national age-adjusted mortality rates. Numerous potential biases also exist. For example, smoking was rarely controlled for and amphibole exposure did in fact occur in a majority of the studies, which would bias many of the reported “no-effect” exposure levels towards lower values. However, many of the studies likely lack sufficient power (e.g., due to small cohort size) to assess whether there could have been a significant increase in risk at the reported no-observed-adverse-effects level (NOAEL); additional statistical analyses are required to address this source of bias and the attendant influence on these values. The chrysotile NOAELs appear to be consistent with exposure-response information for certain cohorts with well-established industrial hygiene and epidemiology data. Specifically, the range of chrysotile NOAELs were found to be consistently higher than upper-bound cumulative chrysotile exposure estimates that have been published for pre-1980s automobile mechanics (e.g., 95th percentile of 2.0 f/cc-yr), an occupation that historically worked with chrysotile-containing friction products yet has been shown to have no increased risk of asbestos-related diseases. While the debate regarding chrysotile as a risk factor for mesothelioma will likely continue for some time, future research into nonlinear, threshold cancer risk models for chrysotile-related respiratory diseases appears to be warranted.

Keywords Asbestos, chrysotile, mechanics, threshold

INTRODUCTION

Over the past 30 years, there has been an increasing amount of research devoted to understanding the relative carcinogenic potencies of the various asbestos fiber types (i.e., serpentine chrysotile versus amphibole forms, such as amosite, tremolite,

and crocidolite). Wagner et al. (1965) were the first to note the apparent differences between crocidolite versus chrysotile potency when they reported that mesothelioma cases were quite common near crocidolite mines, but were absent in populations living and working near chrysotile mines. From the mid-1970s through the early 1990s, numerous epidemiology studies of asbestos-exposed cohorts described substantially higher disease rates in cohorts exposed to a mixture of fiber types (or predominantly amphiboles) versus those observed in cohorts

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exposed to predominantly chrysotile (Enterline and Henderson, 1973; Meurman et al., 1974; McDonald and McDonald, 1977; Weiss, 1977; Acheson et al., 1981, 1982; Thomas et al., 1982; McDonald et al., 1983, 1984; Ohlson and Hogstedt, 1985; Gardner et al., 1986; Newhouse and Sullivan, 1989; Piolatto et al., 1990). In 1978 the American Conference of Governmental Industrial Hygienists (ACGIH) recommended threshold limit values of 0.2, 0.5, 0.5, 2 and 2 f/cc, for crocidolite, amosite, tremolite, chrysotile and "other forms" of asbestos, respectively (ACGIH, 1980). The more stringent recommendations for the amphiboles were "because of their greater potential for disease production" (p. 30). A U.S. Environmental Protection Agency (EPA) work group recently concluded that amphiboles are 4 times and 800 times as potent as chrysotile at inducing lung cancer and mesothelioma, respectively (Berman and Crump, 2003). Hodgson and Darnton (2000) of the United Kingdom (UK) Health and Safety Executive estimated that the risk of mesothelioma is in the ratio of 1:100:500 for chrysotile, amosite and crocidolite, respectively. In a more recent estimate of prospective mesothelioma incidence in the United Kingdom (based on import volumes of different asbestos fiber types), they assigned chrysotile a value of zero potency (Hodgson et al., 2005).

It has been suggested that differences in asbestos fiber type potency are due in part to differences in physicochemical properties that result in a much higher degree of biopersistence for amphibole fibers. Chrysotile fibers form large parallel sheets, while amphibole fibers are arranged in long linearly organized chains (Bernstein and Hoskins, 2006). The straight-chain structures are more biologically durable because they are more difficult to clear from the lung via macrophage engulfment or the mucociliary escalator. In addition, chrysotile fibers are easily depleted of critical components of their structure (e.g., magnesium and other cations) at low pH inside macrophages, thereby weakening the fibers, facilitating their destruction, and subsequently reducing their residence time in the lung (Jaurand et al., 1977; Roggli and Brody, 1984). Amphibole fibers are far more resistant to this type of leaching, and therefore have a much longer residence time (Jaurand et al., 1977; Roggli and Brody, 1984; Hesterberg et al., 1998). As such, the biological half-life of inhaled amphibole asbestos fiber types is in the range of years to decades, whereas the half-life of chrysotile is only days to weeks (de Klerk et al., 1996; Finklestein and Dufresne, 1999; Bernstein and Hoskins, 2006).

Chrysotile asbestos was historically used in hundreds of consumer products, including joint compound, floor tiles, brakes, manual clutches, automotive gaskets, mastic coatings, and welding rods. Although there are dozens of published epidemiological studies of asbestos-related diseases (i.e., lung cancer and mesothelioma) in occupational cohorts exposed to chrysotile during the manufacture or use of these products, to our knowledge there has been no systematic analysis of the available exposure-response information to identify a likely range of minimum cumulative chrysotile exposures necessary for increased

risk. Browne (1986) provides the only quantitative estimate of a "threshold" cumulative exposure for asbestos-related diseases. He examined the relative risk of lung cancer stratified by cumulative exposure to asbestos of mixed fiber types (chrysotile and amphiboles) in 10 different cohorts and concluded that "the threshold for increased risk of lung cancer appears to be somewhere in the range of 25–100 f/cc-years" (p. 558).

However, this assessment was not specific to chrysotile because studies with probable or known significant amphibole exposure were included (Enterline and Henderson, 1973; Seidman et al., 1979). Also, the Browne (1986) review did not address mesothelioma. Dunnigan (1986) also reviewed the available epidemiological and experimental data and concluded that "for chrysotile only exposures (without amphiboles), there is a threshold, below which no adverse health effects can be detected," but did not offer a quantitative estimate of the threshold dose (p. 41). Several others have since suggested that a threshold dose for chrysotile-induced disease may indeed exist (Ilgren and Browne, 1991; Meldrum, 1996; Churg, 1988; Hodgson and Darnton, 2000) but, like Dunnigan (1986), they have not posited an actual value or range of values.

Approximation of the cumulative chrysotile exposures associated with increased lung cancer and mesothelioma disease would aid in the health risk assessments of chrysotile-exposed occupations in several ways. First, it would aid in the analysis of occupations with well-established epidemiological and industrial hygiene assessments. For example, we recently determined that vehicle mechanics working with chrysotile-containing automotive friction products in the 1970s experienced median cumulative chrysotile exposures ranging from 0.16 to 0.41 f/cc-yr (Finley et al., 2007). Since it has been established that vehicle mechanics are not at an increased risk of developing lung cancer or mesothelioma, this estimated range of exposures should be below the chrysotile exposures necessary to cause lung cancer or mesothelioma. Second, a more informed understanding of the available chrysotile exposure-response data would improve the health risk assessments for occupations where chrysotile exposure information is available, but for which relevant epidemiological analyses do not exist and/or are difficult to obtain due to confounding exposures. For example, up until the 1980s, welders often used welding rods that contained low levels (<1% by weight) of chrysotile asbestos in the flux. Some epidemiological studies report elevated rates of mesothelioma in welders, yet it is known that welders often experienced direct and indirect exposure to amphibole-containing insulation (Danielsen et al., 1996; Moulin et al., 1993; Newhouse et al., 1985; Teta and Ott, 1988). Hence, the potential contribution of chrysotile-flux exposures to these disease endpoints cannot be determined directly from the epidemiological data. However, it should be possible to characterize estimated chrysotile-flux exposures via comparisons to the cumulative chrysotile exposure-response data and thereby reach a risk assessment conclusion for welders. In addition to these and other retrospective analyses, as recently noted by Yarborough (2006), there are emerging

nanotechnology research techniques involving the use of synthetic chrysotile in microelectronics, and it would therefore be beneficial to be able to accurately predict the magnitude of any potential health risks associated with the manufacture and use of these materials.

In this article, we assemble and summarize the published lung cancer and mesothelioma information for all chrysotile-exposed cohorts for which exposure and response data are available. Emphasis is placed on those studies where amphibole exposures are relatively low and stratified exposure-response results are reported by the authors. A range of cumulative "no-effect" exposure levels (highest estimated cumulative exposure at which no increased risk was reported) is identified from all studies that meet the criteria for inclusion (as defined in this analysis). Uncertainties that are likely to introduce bias are described in detail, and the upper-bound estimates of cumulative chrysotile asbestos exposure for U.S. brake mechanics are compared to the putative no-effect exposure levels to assess consistency with the brake mechanic epidemiological literature. We also discuss applications of this analysis to prospective occupational and consumer settings that might involve chrysotile exposures in the future.

METHODS

Study Selection Criteria

We performed a literature search for asbestos-exposed cohorts in multiple databases using a variety of search strategies and keyword combinations. To locate additional studies we systematically searched the reference lists of all studies identified by our search, as well as key review papers. We incorporated into our analysis all of the studies on occupational cohorts that met the following criteria:

1. Outcomes of interest included lung cancer (variously identified as "lung cancer," "respiratory cancer," "malignant respiratory neoplasms" or "malignant neoplasms of the lung") and/or mesothelioma.
2. The cohort was predominantly exposed to chrysotile asbestos (less than 10% of the potential asbestos exposures involved amphiboles).
3. There were no other known occupational exposures to respiratory carcinogens.
4. Relative risk or relative mortality estimates were provided or could be calculated and stratified by cumulative chrysotile exposure.
5. Cumulative chrysotile exposures were stratified into two or more exposure levels by the authors.

If multiple studies existed on a single cohort, the study with the most power (i.e., longer follow-up period, larger study population) was selected for the analysis. Wherever possible, we identify the following study elements for each cohort:

- Workplace description, type of industry, and location.
- Cohort demographics (age, duration of employment,

employment initiation date, smoking status, disease latency).

- Time period or decade(s) of exposure and follow-up.
- Diagnostic methods.
- Source of control population.
- Follow-up period.
- Quantity of chrysotile and amphiboles (if applicable) processed and best estimate of percent amphiboles used.
- Air sampling methods used and the method for calculating individual worker cumulative exposure.
- Stratified cumulative exposures for lung cancer and mesothelioma.

Due to the lack of available information regarding smoking habits and employment history in most studies, we were unable to control for smoking and previous occupational exposures to amphiboles (e.g., shipyard and insulation employment). We also did not attempt to differentially weight the studies, nor did we reinterpret any of the authors' findings.

No-observed-adverse-effect levels (NOAELs) were determined for each study as the highest exposure group at which there was no statistically significant increased risk for lung cancer and/or mesothelioma. If a risk metric (e.g., a mortality ratio or odds ratio) or confidence interval was not provided by the authors, when possible it and/or the 95% Fishers exact confidence interval was calculated based on the available data using OpenEpi software (available through Emory University School of Public Health; <http://www.sph.emory.edu/~cdckms/exact-midP-SMR.html>). To avoid confusion and for the sake of consistency, if the risk estimates were reported in the studies as a percentage, we reported the equivalent proportion in our analysis; this is noted in the text. If no increased incidence of cancer was reported in a cohort, the NOAEL was considered to be the highest exposure group in the study.

Cumulative exposure measurements reported in units other than fibers per cubic centimeter per year (f/cc-yr; equivalent to f/ml-yr) were converted to f/cc-yr using the conversion factor provided by the individual study authors. If cumulative exposure was reported in millions of particles per cubic foot per year (mppcf-yr) and a conversion factor was not provided, a conversion factor was determined based on published factors for plants with similar operations.

Throughout this article we use the term "cumulative exposure" in lieu of "cumulative dose" because the degree to which the airborne asbestos levels measured in these studies actually resulted in an inhaled "dose" is unknown. Also, we use the term "NOAEL" instead of "threshold" to emphasize that the highest minimum cumulative exposures at which no effects were observed are simply that, exposures without observed effects; whether or not these exposures truly represent "thresholds" below which effects do not occur cannot necessarily be discerned due to study limitations (as described in the Discussion).

RESULTS

Cohort/Exposure Study Identification and Determination of No-Effect Exposures

During our review, over 350 studies were initially evaluated and subsequently excluded from the analysis. Reasons for study exclusion were primarily lack of cumulative exposure information, lack of information on fiber type, and/or evidence of significant exposures to amphiboles. The following studies met the inclusion criteria: Albin et al. (1990), Berry and Newhouse (1983), Brown et al. (1994), Dement and Brown (1994), Dement et al. (1994), Hughes et al. (1987), Lacquet et al. (1980), Liddell and Armstrong (2002), McDonald et al. (1983a, 1984, 1993), Neuberger and Kundi (1990), Peto et al. (1985), and Piolatto et al. (1990). These studies examined cohorts exposed to chrysotile asbestos during asbestos mining and milling or the manufacture of asbestos-containing cement, friction, and textile products.

No-effect cumulative exposure levels for lung cancer and mesothelioma for the studies just listed are presented in Tables 1 and 2. When possible, we provided best estimates of the fraction of amphiboles present, as reported in Berman and Crump (2003). In addition, if the NOAEL was in the highest or the lowest exposure group, and the NOAEL was reported as ">" or "<," respectively, the mean and median cumulative exposure of the NOAEL group was reported in Table 1 or 2 if this information was provided by the authors.

Asbestos Cement Products Manufacturing

Belgium

Lacquet et al. (1980) is a follow-up to Van den Voorde (1967), and presents x-ray results and updated mortality data for workers in a Belgian cement factory. The factory processed about 39,000 tons of asbestos annually, consisting of 90% chrysotile, 8% crocidolite, and 2% amosite, which were used in the manufacture of building materials and pipes (Berman and Crump, 2003; p. A.29).

The cohort was comprised of male workers who worked in the factory for at least 12 months within the 15-yr period of 1963 through 1977 (the size of the cohort is not presented). Specific demographic information for each individual, such as employment duration, job classification, smoking history, average age at employment initiation, and latency were not provided. All causes of death were determined by family doctors and/or social workers who visited the relatives (Belgian authorities do not release individual information from death certificates). Expected mortalities by age group were calculated based on the yearly rates for Belgium for the years 1965 to 1975; rates for other years were estimated by the authors.

Fiber counts measured using the membrane filter method were available from 1970 through 1976; dust concentrations for the previous years were estimated by the authors using a logistic decay model with an inflection point at 1960. Fiber concentrations were estimated from 1928 onward, and were thought by

the authors to be much higher than the actual levels measured post-1970. Lacquet et al. (1980) considered their estimates to be accurate to within one order of magnitude of the actual concentrations in the factory. Individual exposures were calculated based on the duration of time spent at each of the five general areas of the plant: Area 4 involved handling of raw asbestos fibers, milling, and mixing of asbestos cement; Area 3 involved the finishing of cement products by sawing, drilling, filing, etc.; Area 2, which was situated between the previous two areas, was where asbestos-cement pipes and sheets were molded, pressed, dried, and lifted off the mold; Area 1 represented nonmanufacturing locations with very low asbestos concentrations, such as offices; and Area 0 represented work outside the asbestos industry, with negligible dust levels. The asbestos concentrations in Areas 4, 3, 2, and 1 were estimated to be 100, 24, 16, and 0.4 fibers/cc, respectively. The authors did not present the individual time-weighted average concentrations or exposure estimates.

Lacquet et al. (1980) segregated the cohort into seven exposure groups, with a total of 29,366 man-years of observation, and stated that there were no statistically significant increases in respiratory cancer deaths in any exposure group, including those in the highest estimated cumulative exposures of 1600–3200 fiber/cc-yr. To address the possible influence of the "healthy-worker effect," an internal case-control study was also performed, in which 4 control subjects were selected at random per case. The authors reaffirmed that dust exposure did not significantly affect mortality due to respiratory cancer. Standardized mortality ratios (SMRs)* and confidence intervals for the different exposure groups were calculated by us for respiratory cancer, based on the number of observed and expected respiratory cancer deaths provided by the authors (see Table 8, p. 790). One death due to pleural mesothelioma was reported in the highest exposure group (1600–3200 fiber/cc-yr); however, the expected number of mesothelioma deaths based on the background incidence in Belgium was not provided. For the purposes of our evaluation, it was assumed that this single case represented a true increase in mesothelioma risk for that exposure group. The NOAELs for nonmesothelioma respiratory cancer and mesothelioma in this study therefore were 1600–3200 f/cc-yr and 800–1599 f/cc-yr, respectively.

New Orleans

A prospective cohort study was conducted among workers in two cement manufacturing plants in New Orleans that were in operation since the 1920s (Hughes et al., 1987; Weill et al., 1973, 1979). Chrysotile was the primary fiber type used in both plants. Plant 1 consisted of one building in which flat shingles and corrugated sheets were produced. Amosite was used in corrugated

*The standardized mortality ratio (SMR) is used to compare the mortality experience of a study population with a standard population, and is calculated as observed deaths divided by expected deaths. It is an estimate of the relative risk.

TABLE 1
Studies of Lung Cancer in Chrysotile Cohorts

Authors	Year	Industry	Fraction Amphiboles ^a Best Estimate (%) (Range (%))	Disease Classification	Minimum Latency (Years)	Total Number of Cases (# of Cases Associated with NOAEL)	Risk Estimate for Exposures at the NOAEL (95%CI)	NOAEL (f/cc-years)
Lacquet et al.	1980	Cement Manufacturing: (Belgium)	~10 (NA)	Respiratory cancer	Not Specified	21(0)	—	1,600–3,200 ^d
Berry & Newhouse	1983	Friction Materials Manufacturing: (United Kingdom)	0.5 (0–2)	Lung cancer	10	105(5)	OR = 0.88 (0.24–2.72)	100–356 ^d
McDonald et al.	1983	Textiles: (Pennsylvania)	8(3–15)	Malignant neoplasms respiratory	20	53(6)	SMR = 1.60 (0.59–3.48)	120–240 ^e
McDonald et al.	1984	Friction Materials Manufacturing: (Connecticut)	0.5 (0–2)	Malignant neoplasms respiratory	20	73(1)	SMR = 0.55 (0.01–3.08)	≥112 ^{d,e,f}
Peto et al.	1985	Textiles: (Rochdale)	5(2–15)	Lung cancer	20	93(6)	SMR = 1.06 (0.39–2.31)	85.7–114.3
Hughes et al.	1987	Cement Manufacturing: Plant 1 (New Orleans)	1(0–2)	Respiratory malignancies	20	22(5)	SMR = 1.23 (0.40–2.85)	≥140 ^{d,e} (mean = 256.2)
Hughes et al.	1987	Cement Manufacturing: Plant 2 (New Orleans)	5(2–15)	Respiratory malignancies	20	42(4)	SMR = 1.56 (0.42–3.94)	≥70 ^{d,e}
Albin et al.	1990	Cement Manufacturing: (Sweden)	3 (0–6)	Malignant respiratory disease except mesothelioma	20	27 (NA)	RR = 1.9 (0.5–7.1)	≥40 ^d (mean = 67, median = 88.2)

(Continued on next page)

TABLE 1
Studies of Lung Cancer in Chrysotile Cohorts (*Continued*)

Authors	Year	Industry	Fraction Amphiboles ^a Best Estimate (%) (Range %)	Disease Classification	Minimum Latency (Years)	Total Number of Cases (# of Cases Associated with NOAEL)	Risk Estimate for Exposures at the NOAEL (95%CI)	NOAEL (f/cc-years)
Neuberger & Kundi	1990	Cement Manu- facturing: (Austria)	NA (NA)	Lung cancer	Not Specified ^b	49 (24)	SMR = 0.96 (0.64–1.43)	>25 ^{d,g}
Piolatto et al.	1990	Mining and Milling: (Italy)	0.3(0.1–0.5)	Lung cancer	Not Specified ^c	22(10)	SMR = 1.1 (0.55–2.11)	>400 ^d
McDonald et al.	1993	Mining and Milling: Asbestos Mine and Mill (Quebec)	1(0–4)	Malignant neoplasms of the lung	20	133(22)	SMR = 1.55 (0.97–2.35)	≥942 ^{d,e}
McDonald et al.	1993	Mining and Milling: Thetford Mines (Quebec)	1(0–4)	Malignant neoplasms of the lung	20	155(28)	SMR = 1.05 (0.70–1.52)	314–942 ^e
Liddell & Armstrong	2002	Mining and Milling: (Quebec)	1(0–4)	Lung cancer	20	44(8)	SMR = 1.12 (0.48–2.21)	≥1,884 ^{d,e,g,h} (mean = 3,832)
Brown et al.	1994	Textiles: (South Carolina)	0.5 (0–2)	Lung cancer	15	124(7)	SMR = 0.65 (0.28–1.43)	1.4–2.7 ^e

^a = Source: Berman and Crump, 2003; ^b = In a further investigation on lung cancer mortality, the authors excluded all persons with less than 15 years latency. They reported that the results did not differ substantially from that provided for the whole cohort, however risk estimates stratified by cumulative exposure were not provided (p. 618); ^c = Although there was not a requisite minimum latency, Piolatto et al. reported that 3 deaths due to lung cancer occurred in individuals with less than 20 years from their first exposure to asbestos, 7 with between 20 and 30 years, and 12 with over 30 years since their first asbestos exposure; ^d = Indicates that this was the highest exposure group in the study; ^e = Converted units to f/cc-years; ^f = Lack of apparent dose-response; marginally significant increase observed in lowest exposure group, however, no statistically significant increase observed in higher exposure groups; ^g = Adjusted for smoking; ^h = Same principal cohort as McDonald et al. 1993.

NA = Not available.

– = Zero cases reported.

TABLE 2
Studies of Pleural Mesothelioma in Chrysotile Cohorts

Authors	Year	Industry	Fraction Amphiboles ^a Best Estimate (%) (Range (%))	Disease Classification	Minimum Latency (Years)	Total Number of Cases (# of Cases Associated with NOAEL)	Risk Estimate for Exposures at the NOAEL (95%CI)	NOAEL (f/cc-years)
Lacquet et al.	1980	Cement Manufacturing: (Belgium)	10 (NA)	Mesothelioma	Not Specified	1(0)	—	800–1,599 ^d
McDonald et al.	1984	Friction Materials Manufacturing: (Connecticut)	0.5 (0–2)	Mesothelioma	20	0(0)	—	≥112 ^{b,c}
Albin et al.	1990	Cement Manufacturing: (Sweden)	3(0–6)	Mesothelioma	20	12(NA)	RR = 1.9 (0.2–21.3)	<15 (mean = 3.1, median = 1.4)
Piolatto et al.	1990	Mining and Milling: (Italy)	0.3 (0.1–0.5)	Cancer of the pleura	20	2(1)	SMR = 10 (0.25–55.7)	>400 ^b

^a = Source: Berman and Crump, 2003; ^b = Indicates that this was the highest exposure group in the study; ^c = Converted units to f/cc-years; ^d = Only one death due to mesothelioma was reported; however, authors did not indicate the expected number of deaths due to mesothelioma. Thus, we conservatively assumed that this case represented a statistically significant increase in mesothelioma.

NA = Not available.

— = Zero cases reported.

siding from the early 1940s through the late 1960s, and crocidolite was used occasionally for approximately 10 years beginning in 1962. Plant 2 consisted of 4 buildings, each manufacturing different products. Shingles were the first product manufactured by the plant, followed by roofing materials, pipes, and asphalt flooring products. Pipe production, which commenced in 1946, used crocidolite and chrysotile. All other areas used only chrysotile. Berman and Crump (2003) estimated, based on the plant history provided in Hughes et al. (1987), that amphiboles accounted for roughly 1% of the total asbestos used at plant 1 (range 0–2%) (see Table 7–16). For plant 2 the best estimate was 5%, with a range of 2–15%.

The cohort included all men who had been employed for at least one month before 1970, and for whom a valid Social Security number was available from company records. The total number of men in the study population was 6931, of whom 2565 were employed at plant 1 and 4366 at plant 2. Sixty-one percent of plant 1 workers initiated employment between 1942 and 1949, and 74% of plant 2 employees started working during the period 1937 through 1949 (Hughes et al., 1987; see Table 3, p. 163). The mean durations of employment for plants 1 and 2 were both less than 4 years, with median employments of less than one year. On average, age upon hiring was higher in plant 1 (31.7 years) than in plant 2 (26.8 years), and was particularly high in plant 1 during the Second World War (39.0 years). Although smoking was not controlled for, based on the results of a cross sectional study of over 95% of the workers employed in these plants in 1968, the authors indicated that there was a comparable smoking prevalence between the two plants (Weill et al., 1973, 1975). In addition, they reported that the smoking rates calculated for the two plants were only slightly less than the estimate for all United States men in 1969.

Follow-up continued until 1982 or to age 80, whichever was reached first, and over 96% of the population was traced. Of the deceased ($n = 2143$), death certificates were obtained for 2014 (94%). Deaths for which certificates were not acquired were assigned to categories of causes of death in the same proportion as those with certificates. The mortality experience of this cohort was compared to Louisiana rates obtained from the State of Louisiana Department of Health and from Marsh and Preininger (1980). The authors noted that age-adjusted lung cancer rates in Louisiana for the period of 1960–1979 were 29% higher for Caucasians and 9% higher for African Americans than rates reported for the country as a whole (Riggan et al., 1983).

Beginning in 1952, air sampling data were collected in both plants by industry, insurance companies, and government personnel using the midjet impinger. A total of 100 samples were taken in plant 1 prior to 1970 and 1664 in plant 2. Membrane filter sampling began in 1969. The estimated exposure concentrations for the years prior to 1952 were based on both air sampling data and anecdotal information from company management and long-term employees. Individual exposures were estimated using the midjet impinger data; the authors do not provide details, but this was presumably done by job classification and duration.

The relatively recent exposures (up to 10–15 years previously) were not included in calculating the cumulative exposure for each worker.

Plant 1 employees were classified into the following cumulative exposure groups: <6, 6–24, 25–49, 50–99, and ≥ 100 mppcf-yr. The mean cumulative exposure for each of the exposure categories was 4, 13, 35, 74, and 183 mppcf-yr, respectively. Hughes et al. (1987) did not observe a statistically significant increase in deaths due to respiratory cancer in plant 1 employee, 20 years or more after their initial employment in any exposure category. For the highest cumulative exposure group (≥ 100 mppcf-yr), an SMR of 1.23 was reported (a confidence interval was not provided). Plant 2 employees with a lapse of 20 years or more since their initial employment were divided into two groups, one that included chrysotile-only exposed individuals, and the other with both chrysotile and crocidolite exposure. Plant 2 employees with chrysotile-only exposure were divided into the following cumulative exposure groups: <3, 3–5, 6–24, 25–49, and ≥ 50 mppcf-yr. No increase in death from lung cancer was reported in any of the exposure groups. An SMR of 1.56 (a confidence interval was not provided) was reported for the highest exposure category (≥ 50 mppcf-yr); the authors indicated that this was not significant at the 0.05 level. It is also important to note that the authors indicate that as a whole, there is an observed excess in lung cancer in Plant 2 workers. However, based on the results provided, this increased risk appears to be localized to employees with exposure to both crocidolite and chrysotile.

Hammad et al. (1979) developed a particle-to-fiber conversion factor based on comparative midjet impinger and membrane filter samples collected in various areas of one of the plants. The authors approximated that 1.4 f/ml was roughly equivalent to 1 mppcf. We applied this conversion factor to the aforementioned exposures which yielded cumulative respiratory cancer NOAELs for plant 1 and plant 2 employees of ≥ 140 f/cc-yr (mean cumulative exposure for this group was 256.2 f/cc-yr) and ≥ 70 f/cc-yr (mean cumulative dose for this exposure group was not provided), respectively.

Nine pleural mesothelioma deaths occurred in this cohort. Seven of these deaths occurred in plant 2 workers, and six of these deaths occurred in workers who had previously been employed in the pipe production area where they had known exposure to crocidolite asbestos (Hughes et al., 1987; see Table 12, p. 169). Cumulative exposure levels for these workers were not provided, and therefore a mesothelioma NOAEL was not reported in this study.

Sweden

Albin and colleagues (1990, 1996) performed a cohort mortality study among Swedish cement factory workers, as well as a nested case control study of the workers with mesothelioma. The asbestos that was handled was mainly chrysotile (>95%), with smaller amounts of crocidolite or amosite. Crocidolite was used only in sheet production performed prior to 1966. The amounts used from 1953 were less than 1%, and purportedly did not

exceed 3 to 4% of the total amount of asbestos used. Amosite (maximum <18% total use) was used for a few years during the 1950s. Extrapolating from the plant history, Berman and Crump (2003) estimated that the percentage of amphiboles used in this plant ranged from 0–6%; they reported a best estimate of 3% (see Table 7–16).

The exposed cohort consisted of all male employees registered in the company personnel records from 1907 through 1977 who were employed for at least 3 months ($n = 2898$). Follow up continued until December 31, 1986 (Albin et al., 1990). The referent cohort was comprised of 1552 men employed in five different industries in the region (fertilizer production, slaughter house, wool and polyester textile, sugar refinery, and metal industries) that were not known to have processed asbestos, and who fulfilled the same requirements as the asbestos workers. Additionally, the referents with suspected previous occupational exposure to asbestos were excluded from the analysis, resulting in a referent group comprised of 1233 subjects. Information regarding the demographics and smoking status of the exposed cohort and referent group was not provided.

Death certificates were obtained and recoded according to the International Classification of Diseases 8 (ICD-8) by the National Swedish Central Bureau of Statistics. Regional (1958–1986) and National (1958–1984) cancer registries were searched, and all available histopathological information was reviewed for cases of respiratory cancer. Mesothelioma cases were confirmed using light microscopy and immunohistochemical staining. A minimum latency of 20 years since start of employment was applied to both cohorts.

Dust measurements existed for the time period from 1956 through 1977; prior to 1969 impinger or gravimetric measurements were available, and after 1969 the membrane filter method was used. Albin et al. (1990) estimated average dust exposures for different jobs and periods using data on dust concentrations, production, and dust control measures. The estimates for the period 1947 to 1951 were used by the authors for the entire period before 1942 based on the assumption that the production process was mainly the same. The authors indicated that the actual exposure levels before 1942 may have been greatly underestimated for some tasks, but explained that workers engaged in these operations only accounted for 5–10% of the total cohort.

Individual exposures were calculated, presumably based on individual job classifications and work histories (details were not provided), for 1503 (78%) of the 1929 Swedish workers. Albin et al. (1990) developed three cumulative exposure groups, <15 f/cc-yr, 15–39 f/cc-yr, and ≥ 40 f/cc-yr, with a total of 17028 man-years of observation, and noted no statistically significant increase in death due to respiratory cancer (excluding mesothelioma) in any group, even those in the highest cumulative exposure group. The authors indicated that the relative risk estimate was adjusted for possible confounding by age and calendar year. A statistically significant increase in deaths ascribed to pleural mesothelioma

was observed in the two highest exposure groups, 15–39 and ≥ 40 f/cc-yr, and the authors reported a relative risk of 21.2 (95% CI 2.5–178) and 22.8 (95% CI 2.4–212), for the groups, respectively. For the purposes of our analysis, the no-effect level identified for lung cancer was ≥ 40 f/cc-yr (mean cumulative exposure for this group was 67 f/cc-yr, median cumulative exposure was 88.2 f/cc-yr), and for mesothelioma was <15 f/cc-yr (mean cumulative exposure for this group was 3.1 f/cc-yr, median cumulative exposure was 1.4 f/cc-yr).

Vöcklabruck

Neuberger and Kundi (1990) conducted a cohort study among workers of the oldest cement factory in the world, located in Vöcklabruck (upper Austria). From 1895 forward, chrysotile was the predominant fiber type used in the facility. From 1920 to 1977 crocidolite was also used in the pipe factory. Up to 33% of the asbestos used in pipe production was crocidolite, which amounted to roughly 4% of the total amount of asbestos used at the facility (Neuberger, 2006). Amosite (up to 3%) was also used in certain products from 1970 to 1986; however, according to the authors, this usage did not contribute to the overall exposure of this cohort.

The cohort included all persons employed for at least 3 years from 1950 to 1981. It was comprised of 2816 people, 82% of whom were employed before 1969, when the dust conditions had yet to significantly improve. Smoking information was obtained via interview for cohort members who had left the plant after 1950 and were still alive in 1982. Lung cancer deaths were initially determined by review of death certificates; a further analysis of the best available information was performed using results gathered from hospital, pathological institute and social insurance records. Information on mean age at initial employment, start date, duration of employment, and mean disease latency was not provided.

Individual cumulative exposures were estimated from personal records on duration of exposure at different workplaces, estimations of dust concentrations until 1965, and dust measurements (mainly by the conimeter method until 1975, and by personal air samples and membrane filter methods thereafter). The cohort was subsequently divided into two cumulative exposure groups, ≤ 25 f/cc-yr and > 25 f/cc-yr.

The authors observed an overall increased risk for lung cancer (SMR = 1.7), when compared to the age- and sex-specific mortality rate for lung cancer in upper Austria. However, after controlling for smoking, the authors reported no increased risk in mortality from lung cancer in either of the two cumulative exposure groups. For the cumulative asbestos exposures of ≤ 25 f/cc-yr, an SMR of 1.26 was calculated (95% CI 0.83–1.95); and for > 25 f/cc-yr cumulative exposure an SMR of 0.96 (95% CI 0.64–1.43) was calculated. The cumulative lung cancer NOAEL for this cohort was therefore > 25 f/cc-yr.

Five mesothelioma cases were reported; however, the relative risk of mesothelioma stratified by cumulative exposure was not reported, and therefore a mesothelioma NOAEL could not

be determined from the information provided. It is worth noting that in a subsequent nested case-control study (Neuberger and Kundi, 1990), the authors found that the mesothelioma cases had significantly higher crocidolite exposure than the controls.

Friction Products Manufacturing

United Kingdom

A retrospective cohort mortality study was conducted on workers in a factory producing friction materials in the United Kingdom (Berry and Newhouse, 1983; Newhouse et al., 1982; Newhouse and Sullivan, 1989). The plant, founded in 1898, manufactured a variety of friction materials, such as brake blocks, and brake and clutch linings. Chrysotile was the only fiber type used in the facility, with the exception of brief periods from 1929 to 1933 and from 1939 to 1944 during which crocidolite was used to manufacture railway blocks. During both of these time periods, the blocks were made in a well-defined area of one of the workshops, and only a minority of the workforce was exposed. Small amounts of crocidolite were also used sporadically in an experimental workshop. Berman and Crump (2003) estimated that 0.5% (range 0–2) of the total asbestos used in this plant was amphiboles (see Table 7–16).

The initial study group consisted of individuals whose employment began in 1941 through 1979 who were identified by factory personnel files, resulting in 13460 subjects, of whom about two-thirds were men. Over two-thirds of the population began employment by 1960, and less than 6% of the cohort began work prior to 1941 (Berry and Newhouse, 1983). The follow up period was later extended to 1986 (Newhouse and Sullivan, 1989). The duration of employment ranged from less than 1 year to over 30 years. Approximately one-third of the men and women left before completing one year of service, but 27% of the men and 14% of the women remained at the factory for 10 years or more. Overall cohort mortality information was obtained from death certificates from the National Health Service Central Registrar and the Department of Health and Social Security, and was restricted to the period following 10 years after first employment in the factory.

Beginning in 1967, regular measurements of airborne dust levels were taken throughout the factory using the membrane filter method; personal sampling began in 1968. Airborne fiber concentrations in the earlier years were approximated by the authors by simulating earlier working conditions, using detailed knowledge of when processes were changed and exhaust ventilation introduced. Based on knowledge of the historical industrial hygiene practices and for purposes of quantifying asbestos concentrations, the authors divided the factory into four exposure periods: (1) pre-1931: before the Asbestos Regulations and when all operations were carried out in an open-plan area; (2) 1932–1950: when exhaust ventilation was implemented in most machining operations and there was increased separation between the stages of production; (3) 1951–1969: gradual improvement

in air quality and application of exhaust ventilation to machines not included in the Asbestos Regulations; and (4) 1970–1979: following the introduction of the 2 f/ml threshold limit value (TLV) (Berry and Newhouse, 1983). In general, fiber concentrations in period 1 exceeded 20 f/ml. In period 2, most operations had exposures of under 5 f/ml with the exceptions of grinding (5–10 f/ml) and fiber preparation (10–20 f/ml). In period 3 all operations were below 5 f/ml, and in period 4 all exposures were generally in compliance with the TLV. The simulation studies employed the basic materials and original equipment operated in the appropriate work setting for the given time periods. Personal samples were collected in the workers' breathing zones for periods of 4 to 5 hours in order to calculate 8-h TWAs, and static area samplers were mounted nearby at head height to provide information on general atmospheric concentrations of asbestos fibers.

A case-control study nested within this cohort evaluated the association between asbestos exposure and lung cancer mortality (Berry and Newhouse, 1983). This study was restricted to men who entered the workforce between 1941 and 1960 and who had survived for at least 10 years after starting work at this factory. Although follow-up on this population continued until 1986 (Newhouse and Sullivan, 1989), risk estimates stratified by cumulative exposure were only available for a follow-up to 1979 (Berry and Newhouse, 1983). The mean year of initiation of employment for the lung cancer cases was mid-1949, and the mean year of death due to lung cancer among the cases was the end of 1970. Three controls were selected for each case, matched on (1) the year they started working in factory, (2) year of birth, and (3) survival up to the time of death of the case. The study population was divided into 4 exposure categories: 0–9, 10–49, 50–99, and 100–356 f/cc-yr. The authors observed no increased risk of lung cancer in any of the cumulative exposure groups with the exposure level-specific odds ratios of 1.0, 0.79, 0.86, and 0.88. Individual confidence intervals for the risk estimates were not presented by the authors. The NOAEL for lung cancer observed in this cohort was therefore taken to be 100–356 f/cc-yr.

Ten deaths due to mesothelioma were observed. The authors did not estimate the cumulative exposures for these cases, nor did they calculate a risk estimate for mesothelioma, and therefore a mesothelioma NOAEL could not be identified for this study group. It is worth noting that in a subsequent internal case-control study (Berry and Newhouse, 1983), the authors reported that 80% of the mesothelioma deaths occurred in people who worked on the crocidolite contract, compared with only 8% of the controls.

Connecticut

McDonald and colleagues (1984) studied a Connecticut friction products and packing manufacturing facility as part of their investigation into the effects of fiber type on asbestos-related disease. Until 1957, chrysotile, mainly from Canada, was the

only mineral type used in the plant; some anthophyllite was subsequently added in making paper discs and bands. In addition, between 1964 and 1972 approximately 400 lb crocidolite was handled experimentally in the company laboratory. Based on the data provided in McDonald et al. (1984), it was estimated that only 0.5% (range 0–2) of total asbestos used in this factory was amphiboles (see Table 7–16).

McDonald et al. (1984) analyzed the mortality of men who had worked for one calendar month or more before January 1, 1959 and who had a Social Security number and name matching the data in the U.S. Social Security Administration (SSA) records. Of the 3513 men who were traced until the end of the study period (December 31, 1977), 1267 (36%) had died, and death certificates were obtained for 1228 (96.9%). Cohort-specific information such as mean employment duration and age was not provided.

Information on exposure was available from surveys conducted by Metropolitan Life Insurance Company in 1930, 1935, 1936, and 1939. There was little additional information on exposure conditions until the 1970s. Estimates of exposure by process and period were made by an industrial hygienist who reviewed information related to process and jobs in the plant, as well as records on environmental conditions and dust control measures. Before 1970, measurements were made using the impinger method; in later years membrane filters were used. Individual work history records were obtained; these indicated the department in which the employee worked, but seldom specified a job description or the processes involved. Due to varying dust levels generated by tasks within a single department, all processes were taken into account when estimating airborne asbestos concentrations. The authors indicated that this strategy could lead to overestimation of exposure for many of the employees in these departments, and underestimation for a few. A conversion factor was not provided by the authors to convert mppcf-yr to f/cc-yr. For cement products manufacturing a factor of 1.4 (f/cc:mppcf) has been recommended (Hammad et al., 1979), and the U.S. EPA used a factor of 1.5 for asbestos products manufacturing (Nicholson, 1986); a conversion factor for friction products manufacturing was not found. For the purposes of our analysis, and for the sake of conservatism, we have used a factor of 1.4 (f/cc:mppcf) to convert dust measurements into fiber levels.

The authors classified male deaths 20 years after first employment into 5 cumulative exposure groups, the lowest being <10 mppcf-yr, and the highest being ≥ 80 mppcf-yr. The authors observed a significant increase in respiratory cancer in the lowest exposure group (SMR = 1.67) in comparison to age-, sex-, race-, and year-specific death rates in Connecticut (CI 1.26–2.19;* not reported by authors). However, no statistically significant increase was observed in the four higher exposure categories. Likewise, there was an inverse relationship between duration of service and the calculated SMRs for respiratory cancer for ex-

posures <10 mppcf-yr. The authors suggested that the lack of an apparent dose-response relationship could be explained by the selective employment of men in relatively poor health or with unhealthy habits, such as heavy smoking, in low-exposure jobs where they often remained for a fairly short time. They also considered the likelihood that the short-term employees had worked in other hazardous industries prior to or after their employment at the friction products plant. Following a further review of the occupational histories of low-exposure employees, the authors indicated that the increase in respiratory cancer was most likely the result of some form of selection bias. Due to the lack of increased risk in the four higher exposure groups, we have assumed that the highest exposure group represents the NOAEL for this cohort. No deaths due to mesothelioma were reported in any of the exposure groups in this study. Using the previously stated conversion factor of 1.4 (f/cc:mppcf), the NOAEL for this group was taken to be ≥ 112 f/cc-yr for respiratory cancer and mesothelioma.

Asbestos Textile Manufacturing

Pennsylvania

A cohort mortality and subsequent case-referent study were conducted among workers at a Pennsylvania plant producing a variety of textiles and friction products (McDonald et al., 1983a). Chrysotile obtained primarily from Canada and Rhodesia was the predominant type of asbestos used at this facility, with between 3000 and 6000 tons processed annually. From 1924 on, both crocidolite and amosite were incorporated into insulation blankets for turbines, as well as equipment for chemical factories and paper mills. Based on the data provided in McDonald et al. (1983), it was estimated that the percentage of amphiboles used in this facility was 8% (see Table 7–16).

The cohort consisted of men ($n = 4137$) and women ($n = 998$) employed in the factory before January 1, 1959, for at least 1 month with a verified Social Security number. Survival status was determined through local inquiries and from information provided by the SSA as of December 31, 1977. Tracing was completed for 97% and 94% of the men and women, respectively, and of those traced, 35% of the men and 18% of the women had died. Death certificates were obtained for 97% ($n = 1354$) of the men who had died and 97% ($n = 165$) of the women. The authors chose to exclude females from further analysis, and noted that relevant information would be reported separately. The final study group consisted of 1392 male deaths. The process for determining the cause of death ($n = 38$) in those without death certificates was not disclosed. The average age at the start of employment was 28.92 and the average duration of service was 9.18 years. Roughly 31% of the study population was employed for less than 1 year, and slightly more than 25% of the population remained at the factory for 20 years or more. The authors indicated that of the men born between 1910 and 1919 included in this cohort, 75% smoked or had smoked cigarettes in their lifetime.

*The SMR in McDonald 1984 was reported as a percentage (167.4). For consistency with the other studies, we have converted it to a proportion.

Air samples were taken in the factory by the Metropolitan Life Insurance Company from 1930 to 1939, by the U.S. Public Health Service in 1967 and 1970, and collected routinely by the company from 1956 onward. Until 1967, measurements were made by the midget impinger method. An industrial hygienist (A. J. Woolley) estimated dust levels for each department over time. The process used for estimating individual cumulative exposure was not discussed.

The authors classified male deaths 20 years after first employment into 5 cumulative exposure groups, the lowest being <10 mppcf-yr, and the highest being ≥ 80 mppcf-yr. The authors observed a significant increase in respiratory cancer in only the highest exposure group (SMR = 4.16) in comparison to death rates in Pennsylvania prevalent at that time.* The authors did not provide a factor to convert particle counts to fiber counts; however, the ratios recommended for textile manufacturing have ranged from 1 mppcf = 3 f/cc to 1 mppcf = 6 f/cc (Ayer et al., 1965; Dement et al., 1982). In this analysis the conversion factor derived in the South Carolina textiles studies (1 mppcf-yr = 3 f/cc-yr) was applied to the results of McDonald et al. (1983). This factor was selected because (1) it is in the middle of the range of recommended factors in the published literature, and (2) there were some similarities in operations at the two plants. The respiratory cancer NOAEL for this cohort was therefore between 40 and 80 mppcf-yr (120–240 f/cc-yr).

Ten deaths due to pleural mesothelioma were identified from death certificates. Although specific exposure-response information was not provided for these cases (and hence, a mesothelioma NOAEL could not be identified), the authors indicated that they observed “the special risk of mesothelioma associated with exposure to even quite small proportions of amphibole,” in this case predominantly amosite (McDonald et al., 1983a, p. 373).

Rochdale

Employees of a Rochdale asbestos textile factory were traced until June 30, 1983 (Peto et al., 1985). Chrysotile had always been the predominant fiber type used in the factory, although from 1932 to 1968 roughly 10322 tons of crocidolite was purchased, which accounted for approximately 2.6% of the total amount of asbestos purchased over that time period, and for roughly 5% of the amount used in the manufacture of textiles. Berman and Crump (2003) estimated that 5% (range 2–15%) of the asbestos processed was amphibole (see Table 7–16).

The cohort consisted of the following two subcohorts: (1) men first employed in 1933 or later, who had completed 5 years of total employment by the end of 1974, and who had ever worked in scheduled areas or in maintenance, and (2) a 1 in 10 sample of all male employees first employed between January 1, 1933, and December 31, 1974, irrespective of where or how long they had worked. Workers with Asian surnames (due to difficulty

in tracing) and those with known previous occupational exposures were excluded, resulting in a principal cohort of 3211 men. Cohort demographics and ranges of occupational tenure were not specified. The company was aware of most suspected mesothelioma cases; however, a few additional cases were identified from the national mesothelioma register and from a review of death certificates. All obtainable diagnostic information was also reviewed by Sir Richard Doll, and each case was labeled as “established” on the basis of postmortem evidence with or without histological confirmation, “presumptive” on the basis of death certificate information alone, “uncertain” due to conflicting medical evidence, or “incorrect.” Lung cancer deaths were obtained from company records. The mortality experience of the principal cohort was compared to the national mortality rates for selected causes in the United Kingdom, as well as those observed in Rochdale County Borough from 1969 to 1973.

Area dust measurements in particles per milliliter were taken in 23 locations with a thermal precipitator between 1951 and 1961 and later with static membrane filters. These exposure estimates were reevaluated and adjusted by industrial hygienists to account for advances in technology and knowledge regarding the conversion from particles/ml to fibers/cc; the authors suggested that 35 p/ml was equivalent to 1 f/cc. Dust levels prior to 1951 were assumed to be equivalent to those measured from 1951 to 1955 for departments in which no major changes had been made. For areas that underwent significant industrial hygiene improvements, higher values were assigned for the pre-1951 period. Cumulative exposure estimates were calculated for each of the subjects, allowing for a 5-year lag time between exposure to asbestos and any observed increase in mortality. Jobs were assigned average dust measurements for each 5-year period from 1951 onward. Although details are not provided, it appears that individual exposures were calculated based on the duration of time spent performing each job.

The authors classified men with 20 or more years since their first employment into 6 cumulative exposure groups that ranged from <1000 p/ml-yr (<28.6 f/cc-yr) to ≥ 5000 p/ml-yr (≥ 142.9 f/cc-yr). The cohort was further segregated by year of first exposure (1933 and 1951). No increase in lung cancer risk was reported at exposures up to 3000–3999 p/ml-yr in either subcohort (risks were elevated at higher exposures for both subcohorts). Accordingly, for the purposes of this analysis, the NOAEL for lung cancer risk is 3000–3999 p/ml-yr (85.7–114.3 f/cc-yr).

Fourteen men in the principal (post-1933) cohort died of mesothelioma. The authors did not develop exposure-related estimates of mesothelioma risk, and therefore a mesothelioma NOAEL could not be identified from this study.

South Carolina

A retrospective cohort mortality study was conducted among workers at a South Carolina textiles plant (Brown, et al., 1994; Dement and Brown, 1994, 1998; Dement et al., 1982, 1983a,

*The SMR in McDonald 1983 was reported as a percentage (416.1). For consistency with the other studies, we have converted it to a proportion.

1983b, 1994; McDonald et al., 1983b). According to company personnel, 6 to 8 million pounds of chrysotile was processed annually. Small amounts of crocidolite yarn (less than 2000 pounds) were woven into tape or made into braided packing beginning in the 1950s until approximately 1975. The authors indicated that crocidolite processing was done using wet methods, resulting in very low exposures (Dement et al., 1983a). Berman and Crump (2003) provided a best estimate percentage of amphiboles as 0.5% (range 0–2), based on data reported in Sebastien et al. (1989) (see Table 7–16).

The cohort consisted of workers employed for at least 1 month between January 1, 1940, and December 31, 1965. In several analyses the cohort was limited to white male employees (Dement et al., 1982, 1983a, 1983b; Dement and Brown, 1998); however, parallel studies expanded the population to include white male ($n = 1247$) and female ($n = 1229$), as well as black male workers ($n = 549$) (Brown, et al., 1994; Dement et al., 1994). A nested case-control analysis was also undertaken on the expanded cohort to eliminate possible confounding effects due to mineral oil exposure in the authors' assessment of lung cancer risk (Dement et al., 1994).

Participants were initially followed until December 31, 1975, and subsequent tracing extended through December 31, 1990. Mortality information was based on SSA files for deaths occurring from 1976 to 1978, and records kept by the National Death Index (NDI) from 1979 to 1990. If a worker was known to be alive in 1975, he/she was assumed to be alive as of 1990 if his/her information could not be located in either the SSA or NDI files. The average number of years of observation was 35 for white females and black males, and 43 for white males. By December 31, 1990, 41.7% of the expanded cohort was known to be deceased; this was true for 48.7%, 29.5%, and 53.0% of white male, white female, and black male participants, respectively. For the overall cohort mortality study, age-, race-, sex-, and calendar-time specific death rates for the U.S. population were used to calculate expected deaths and SMRs.

The demographic variables for the entire cohort were not available; however, this information was provided for participants in the nested case-control analysis. Since age at death was the incidence density matching variable, cases and controls were nearly identical for this parameter. In addition, the authors reported that the mean year of birth (range cases: 1913–1917; controls: 1909–1911), mean employment initiation dates (range cases: 1941–1944; controls: 1941–1942), and mean time since first employed (range cases: 34.1–38.7; controls: 3 1.1–35.1) were similar for cases and controls (Dement et al., 1994, see Table 7). The mean and median exposure levels experienced by the cases and controls varied according to race and sex, and were thought to reflect the difference in job assignment patterns. Among lung cancer cases, the reported mean exposure level among black males was the highest (12.0 f/cc), followed by white males (5.5 f/cc) and white females (4.9 f/cc). A similar trend was observed for the controls. Mean cumulative exposures for black males, white males, and white females were

38400, 24500, and 13200 f/cc-day, respectively. Cases also experienced higher mean cumulative asbestos exposures than controls; mean cumulative exposures for black male, white male, and white female cases were 16400, 14600, and 11900 f/cc-day, respectively.

Linear statistical models were used for reconstructing historic exposure levels, taking into account textile processes, dust control measures, and job assignments, based on data from 5952 environmental samples that were collected from 1930 to 1975. Prior to 1965, all samples were taken using the impinger method, from 1965 to 1971 both impinger and membrane filter samples were collected, and from 1971 on, only the membrane filter method was used. Based on 120 side-by-side particle and fiber counts, a f/cc to mppcf ratio of 2.9 (95% CI 2.4–3.5) for all jobs except fiber preparation was derived (Dement, 1980). For fiber preparation, a conversion factor of 7.8 was calculated (95% CI 4.7–9.1). Unit conversions were previously made using a factor of 3 for all operations except fiber preparation, for which a factor of 8 was employed* (Dement et al., 1983a). Cumulative exposure estimates were made for each worker based on these estimated exposure levels in conjunction with detailed work histories. Notably, the cumulative exposures reported in this cohort were on the order of 10 to 10000 times lower than in any of the previously described studies.

The authors classified members of the cohort into exposure groups ranging from <500 to >100000 f/cc-day. With regards to the total cohort, lung cancer mortality, incorporating a 15 year latency period but not controlling for smoking, was significantly increased in the 1000–2500 f/cc-day (2.7–6.8 f/cc-yr) exposure group (SMR = 1.95, $p < .01$) and all higher exposure groups (Dement and Brown, 1994; Dement et al., 1994). There was no increase observed at exposures of 500–1000 f/cc-day (1.4–2.7 f/cc-yr) and lower. When examining the relationship between cumulative exposure and lung cancer mortality by race and sex, it is apparent that the white male and female populations were mostly responsible for the overall increased cohort risk estimates. White males showed a statistically significant increase in lung cancer at 1000–2500 f/cc-day (2.7–6.8 f/cc-yr)[†] and white females had increased deaths due to lung cancer in the lowest exposure group (<1000 f/cc-day; <2.7 f/cc-yr).[‡] This increase was not observed for white females in the second

*It is important to note that in analyzing the same exposure data McDonald et al. (1983) reported a particle to fiber ratio that ranged from 1.3 to 10, with an average of roughly 6 f/cc per mppcf.

†A statistically significant increase in lung cancer is observed for white males in the 1000–2500 f/cc-day exposure group in Dement et al. (1994), Brown et al. (1994) and Dement and Brown (1998). However, the SMRs reported for lung cancer in this exposure group are inconsistent and are reported as 2.59 ($p < 0.01$) in Dement et al. (1994) and 2.42 ($p < .01$) in Brown et al. (1994) and Dement and Brown (1998), although the cohort composition and follow up periods are identical.

‡This increase for white females in the lowest exposure group was not reported in Brown et al. 1994, although the cohort and the duration of follow up appear to be identical.

lowest exposure group (1000–2500 f/cc-day, 2.7–6.8 f/cc-yr), but was present in all of the exposure groups at and above 2500–10000 f/cc-day (6.8–27.4 f/cc-yr). The authors indicated that the inconsistent exposure-response relationship among the females may be the result of the unequal distribution of those lost to follow up (Dement et al., 1994, p. 440). Further, among the 280 females lost to follow-up, 36% worked less than 3 months, 18% worked 3 to 6 months, and 17% worked 6 months to 1 year. The authors also reported that if it was assumed that all females lost to follow-up were alive at the end of the study, the dose-response would be altered for the white females, lowering the risks in the lowest exposure group, and resulting in a statistically significant increased risk due to lung cancer in only those groups with exposures above 2500 f/cc-day. Lastly, black males showed a statistically significant increase in lung cancer in only the highest cumulative exposure group (>40000 f/cc-day, >109.5 f/cc-yr). For the purposes of this analysis, the NOAEL for lung cancer for the expanded cohort is 500–1000 f/cc-day (1.4–2.7 f/cc-yr) (Brown et al., 1994).

Two deaths were attributed to mesothelioma, both of which had a latency of >30 years. Information on cumulative exposure was not provided; thus a NOAEL for mesothelioma could not be identified for this cohort.

Asbestos Mining and Milling

Balangero

A cohort mortality study was conducted on miners in Balangero (northern Italy) (Piolatto et al., 1990; Rubino et al., 1979). Examination of the chrysotile from the mine did not detect measurable concentrations of amphiboles. However, a fibrous silicate (balangeroite) accounted for 0.2–0.5% of the total mass of the samples. A series of recent publications has indicated that based on its chemical composition, form, and durability, balangeroite is most similar to crocidolite (Gazzano et al., 2005; Groppo et al., 2005; Turci et al., 2005). A best estimate of the fraction of asbestos that consisted of amphiboles was 0.3% (range 0.1–0.5) (Berman and Crump, 2003; see Table 7–16).

The cohort consisted of males who had worked for at least 1 year at the factory between 1946 and 1975, and was later expanded to include employment through 1987 ($n = 1058$). Follow-up began on January 1, 1946, and ended on December 31, 1975, in the initial study, and was subsequently extended through December 31, 1987. Cohort-specific demographics were not provided. Vital statuses following termination of employment were ascertained through population registers, and death certificates were obtained from municipal registration offices.

Cumulative exposures were estimated from environmental measurements carried out from 1969 onward, and from simulated working conditions for earlier periods. The factory archives were examined for information on daily production, the equipment used, the nature of the job, and the historical numbers of hours worked per day. Additionally, four workers with continuous employment since 1935 helped to reconstruct the ap-

propriate conditions, after which fiber counts were carried out by membrane filter collection and phase-contrast microscopy (Rubino et al., 1979).

Mortality from lung cancer and mesothelioma was reported for the following cumulative exposure groups: <100, 100–400, and >400 f/cc-yr. Lung cancer mortality was compared to age- and calendar-year-specific rates for Italian men. Statistically nonsignificant SMRs of 0.8, 1.3, and 1.1 were reported for lung cancer mortality for the three groups, respectively; confidence intervals were not provided.

No mesothelioma deaths were observed in the lowest exposure category, and one was noted in each of the higher categories. The expected number of deaths due to mesothelioma in the 100–400 and >400 f/cc-yr exposure groups was 0.1, yielding nonsignificant SMRs of 10.0 for both groups (95% CI 0.25–55.7). Both mesothelioma deaths occurred in individuals for whom at least 20 years had elapsed since their first asbestos exposure. For the purposes of this analysis the NOAEL was assumed to be >400 f/cc-yr for lung cancer and mesothelioma.

Quebec

Multiple analyses have been conducted on a cohort of Quebec chrysotile miners and millers (Liddell and Armstrong, 2002; McDonald et al., 1993; Liddell et al., 1977, 1997, 1998; McDonald et al., 1971, 1973, 1997, 1980). Males born between 1891 and 1920 who were employed in the Quebec chrysotile-producing industry for at least 1 month comprised the study population. Follow-up began for each individual after 20 years from first employment; 9780 men were traced to 1992 (Liddell et al., 1997). Death certificates were obtained for 98% of the cohort, and according to the authors, “adequate information was collected on most of the rest” (p. 16). For mesothelioma deaths, a “best diagnosis” was made after all available clinical, biopsy, and necropsy records were analyzed.

Members of the study population were described according to the location at which they were first employed; additional cohort specific information was not provided (e.g., mean start date and mean duration of employment). Although nine locations were identified, companies 5–9 were excluded from the analysis, leaving 9244 men in the cohort. Company 1 ($n = 4195$) was the mine and mill in the town of Asbestos. Company 2 ($n = 758$) was a factory in the town of Asbestos that in addition to processing chrysotile had also processed some crocidolite and amosite. The amount of amphiboles used at this facility was not included in any of the studies on this cohort. However, it appears that crocidolite was only used for a short duration in the 1940s (McDonald et al., 1973). The authors mention that some employees moved between the Asbestos mine and mill (company 1) and the Asbestos factory (company 2). Company 3 ($n = 4032$) was a large mining and milling complex (13 mines) near Thetford Mines, and company 4 ($n = 259$) consisted of a number of smaller mines and mills in the vicinity of Thetford. Based upon an extrapolation from the air data in Sebastien et al.

(1986), Berman and Crump (2003) reported a "best estimate" fraction of amphiboles of 1% (range 0–4) for companies 1, 3, and 4; an estimate was not provided for company 2 (see Table 7–16).

Estimates of dust concentrations at companies 1, 2, 3, and 4 have been made by year for each of the more than 5000 job classifications up to November 1966 by Gibbs and Lachance (1972) (McDonald et al., 1993). These estimates were based on roughly 4500 midjet impinger dust counts from annual surveys conducted from 1948 to 1966. Estimates of the past and present dust conditions were made after interviews with employees of long service in collaboration with superintendents or others with special knowledge of past conditions. These estimates were later adjusted by Liddell et al. (1997, 1998) to account for new information on hours worked per week. The authors assumed that the dust level for 1967 was equal to that of 1966, and for each subsequent year calculated the annual dust concentration as proportion of that level in accordance with the average trend of fiber concentration for each worker's specific mine or mill. An average conversion factor of 3.14 (f/cc:mppcf) was calculated from side-by-side midjet impinger and optical microscopy measurements (McDonald and McDonald, 1980). A subject's exposure for a particular year was calculated as the product of (the fraction of the year worked in a specific job) multiplied by (the dust level for the year for that job) times (an adjustment for the length of the working week).

Exposure accumulated to the age of 55 was determined for the entire cohort (companies 1, 2, 3, and 4), and each subject was subsequently grouped into one of the 10 following categories: <3, 3–<10, 10–<30, 30–<60, 60–<100, 100–<200, 200–<300, 300–<400, 400–<1000, and ≥ 1000 mppcf-yr. A statistically significant increase in deaths (after age 55) due to cancer of the trachea, bronchus, and lung was observed in the second to highest exposure group, compared to age-specific mortality rates for Quebec males (SMR = 1.84, 95%CI 1.48–2.27). The authors noted that at exposures over 300 mppcf-yr, the excess of lung cancer was 80.4 deaths, one-fifth of which was probably attributable to smoking. Consequently, Liddell and Armstrong (2002) analyzed the effects of smoking on lung cancer risks in this population. Of the initial 9780 men included in Liddell et al. (1997), 7279 met the follow-up study criteria. The SMRs for lung cancer for both nonsmokers and ex-smokers were not elevated even in the highest exposure group (≥ 600 mppcf-yr). Therefore, the lung cancer NOAEL for the entire cohort, when controlling for smoking, was ≥ 1884 f/cc-yr. The mean cumulative exposure for the entire ≥ 600 -mppcf-yr exposure group, including nonsmokers, ex-smokers, and current smokers, was 1220.4 mppcf-yr (3832 f/cc-yr).

In a previous study with follow-up until 1988 (McDonald et al., 1993), standard mortality ratios were stratified by cumulative exposure (accumulated to age 55) for company 1, company 2, and companies 3 and 4 combined. There was no increase in lung cancer in the employees of the Asbestos Mine and Mill (company 1) even at the highest exposure category (≥ 300 mppcf-yr), while employees of the Thetford Mines (com-

panies 3 and 4 combined) and the Asbestos Factory (company 2) demonstrated an elevated risk for lung cancer at this cumulative exposure level with SMRs of 1.89 and 7.00, respectively. The increased risk reported for these two subcohorts was likely the result of amphibole exposures (McDonald et al., 1997). Company 2 does not meet our selection criteria due to the failure to characterize amphibole contamination, and thus it is not considered further in this analysis. Cumulative NOAELs for lung cancer at the Asbestos Mine and Mill (company 1) and Thetford Mines (companies 3 and 4 combined), were ≥ 942 f/cc-yr and 314–942 f/cc-yr, respectively. Due to the difficulty in weighting one study more heavily than the other, values from both Liddell and Armstrong (2002) and McDonald et al. (1993) are included in Table 1.

Thirty-eight deaths due to mesothelioma (all companies combined) were classified into exposure groups and no clear exposure-response relationship was observed (Liddell et al., 1997). However, the authors did not provide the expected number of mesothelioma deaths, and therefore a mesothelioma NOAEL could not be derived from this study.

Summary of Reported Chrysotile No-Effect Levels

Fourteen lung cancer NOAELs were taken from 12 published studies. The majority of the studies did not observe increased risk even at the highest chrysotile exposures; NOAELs in these studies ranged from >25 f/cc-yr (Neuberger and Kundi, 1990) to 1600–3200 f/cc-yr (Lacquet et al., 1980). NOAELs in those studies where increased lung cancer risks were reported ranged from 1.4–2.7 f/cc-yr (Brown et al., 1994) to 314–942 f/cc-yr (McDonald et al., 1993).

Four cohorts were identified in which pleural mesothelioma risk was stratified according to cumulative chrysotile exposure, two of which did not observe an increased risk at the highest cumulative exposures. NOAELs from these cohorts were >400 and ≥ 112 f/cc-yr for Piolatto et al. (1990) and McDonald et al. (1984), respectively. The mesothelioma NOAELs taken from Lacquet et al. (1980) and Albin et al. (1990) were 800–1599 f/cc-yr and <15 f/cc-yr, respectively.

DISCUSSION

Identifying and cataloging the cumulative exposures at which no increased lung cancer or mesothelioma risk was reported in the studies considered here was a fairly straightforward exercise. Nonetheless, we are unaware of any other published paper that has attempted to summarize these data, even though the potential insight to be gained could be substantial. We recognize that none of the studies examined in this analysis were conducted for the strict purposes of identifying a NOAEL cumulative asbestos exposure. It is also understood that the studies cover a very broad range of industries and occupational practices, in addition to having large differences in air sampling methods and exposure estimation techniques. There are also known differences in latencies, cohort size, and percent amphibole exposure. As discussed next, where possible, we identify the limitations,

uncertainties and potential biases, and their influences on the reported NOAELs.

Variability in Study Quality

We did not attempt to differentially weight the studies in this analysis; however, as would be expected, there is some degree of variability in the quality of the data collection and interpretation methods, particularly with respect to air sampling techniques, latency, use of an appropriate control population, cohort size, adjustment for smoking, length of follow-up, and loss during follow-up. Goodman et al. (2004) recently conducted a meta-analysis of 11 epidemiological studies concerning lung cancer and mesothelioma risk in vehicle mechanics. In that analysis, a scoring approach was used to classify the studies into three tiers based upon characteristics similar to those mentioned here. We did not employ a scoring system when evaluating the quality of the studies which met our inclusion criteria; however, it is apparent that some studies are indeed more informative than others. Perhaps, in a subsequent analysis, the technique used by Goodman et al. (2004) may be utilized to perform a similar analysis of the cohorts discussed in this study.

Consistency of Findings

With respect to characterizing the exposure-response relationship for lung cancer or mesothelioma, some general observations can be made which apply to all the cohorts considered in this analysis: 1) all of the studies reported a NOAEL (i.e., none of the studies reported increased risk at all exposures), 2) the studies did not report an increased risk at an exposure below its respective NOAEL, and 3) all of the studies that reported a LOAEL (lowest exposure at which effects occurred) also observed significant risks at all exposures above the LOAEL. There are two exceptions to these general observations. McDonald et al. (1984) observed a significant increase in respiratory cancer in the lowest exposure group of <14 f/cc-yr (SMR = 1.67, 95% CI 1.26–2.18). This “effect level” of <14 f/cc-yr conflicts with the lung cancer NOAELs observed in the other studies (which range from >25 to 1600–3200 f/cc-yr) and, more importantly, no statistically significant increase in respiratory cancer was observed in the 4 higher exposure categories (up to ≥ 112 f/cc-yr, which we took to be the NOAEL from this study) in McDonald et al. (1984). The authors suggested that this incongruity might be explained by the selective employment of men of relatively poor health or health habits (e.g., heavy smokers) into low-exposure jobs where they often remained for a fairly short time.

Similarly, Brown et al. (1994) observed significant increases in lung cancer risk at a cumulative exposure range of 2.7 to 6.8 f/cc-yr, but found no increase at a higher cumulative exposure range of 6.8 to 27.4 f/cc-yr (nonetheless, we took the NOAEL from this study to be 1.4–2.7 f/cc-yr). Therefore, like the McDonald et al. (1984) cohort, the low-exposure increased risk reported in Brown et al. (1994) (2.7–6.8 f/cc-yr) is internally inconsistent, and is also inconsistent with the lung cancer NOAELs reported in the other cohorts. It is not possible to determine from

the information reported in Brown et al. (1994) whether the selective employment issues noted by McDonald et al. (1984) might also be applicable to or explain the incongruous low exposure effects that they reported. However, it is noteworthy that the methods used to estimate expected mortalities in this particular study have been previously criticized by other investigators. Expected mortalities in Brown et al. (1994) were developed from yearly mortality rates in the United States. Yet it was known at the time that the local, age-adjusted county rates were 75% higher than those reported for the United States as a whole (Mason and McKay, 1974). As noted by the U.S. EPA (Nicholson, 1986) and McDonald et al. (1983b), the increase in local rates was possibly the result of nearby shipyard employment (and perhaps by the study plant). It is unclear whether use of local lung cancer rates would yield a significant change in the findings of Brown et al. (1994). In short, the internal inconsistencies noted in McDonald et al. (1984) and Brown et al. (1994) are likely a result of study design issues, but a definitive conclusion cannot be reached from the available data.

The LOAEL for mesothelioma reported by Albin et al. (1990) (15–39 f/cc-yr) was not consistent with the findings of the other studies, which reported mesothelioma NOAELs ranging from >400 to 800–1599 f/cc-yr. This inconsistency may simply be a result of the inherent variability in the design and interpretation of the various cohort studies, but it may also be the result of significant amphibole exposure. Specifically, in Albin et al. (1990), the exposure-response relationship for pleural mesothelioma was evaluated in a nested case-referent study. For each of the cases ($n = 14$), 5 controls were selected based on the following factors: same nationality, alive at the time of the diagnosis of the case, and within 4 years of year of birth and first employment. The authors reported a significant relationship between cumulative exposure 40 years or more before diagnosis, and calculated a multiplicative risk of 1.9 for each f/cc-yr. Following an examination of lung tissue from seven of the mesothelioma cases, the authors found “much higher crocidolite and also higher total asbestos and tremolite counts when compared with matched nonexposure cases from the cohort” (p. 609). The authors suggested that exposure to amosite and crocidolite may have occurred in all of the mesothelioma cases. In short, it is difficult to determine whether the mesothelioma NOAEL of Albin et al. (1990) conflicts with (is lower than) the mesothelioma NOAELs from other studies due to methodological issues or uncertainties, or whether this simply reflects the inherent variability in these cohort studies.

The respiratory cancer NOAEL from Lacquet et al. (1980) also deserves mention. The authors reported no increased risk at estimated cumulative asbestos exposures of 1600–3200 f/cc-yr. Aside from the Brown et al. (1994) results discussed earlier, this is well beyond the cumulative exposures reported to be associated with the NOAELs reported in McDonald et al. (1983a) (120–240 f/cc-yr), Peto et al. (1985) (85.7–114.3 f/cc-yr), and McDonald et al. (1993) (314–942 f/cc-yr). This could very well be a result of an insufficient observation period (up to 15 years) accounting for the long latency for disease.

It is admittedly difficult to determine any degree of "consistency" when a majority of the studies reported no increased risk at any cumulative exposure. Further, most of the studies did not develop an estimate of a mean cumulative exposure that can be considered representative of the NOAEL [exceptions are Hughes et al. (1987), Albin et al. (1990), Liddell and Armstrong (2002); see Table 1]. Therefore, for example, the observation that the >25 f/cc-yr NOAEL from Neuberger and Kundi (1990) is "consistent with" the ≥ 140 f/cc-yr NOAEL from Hughes et al. (1987) is constrained by the fact that there is no information regarding the SMRs in the 25–140 f/cc-yr and ≥ 140 f/cc-yr exposure ranges from Neuberger and Kundi (1990). This also makes it difficult to identify a discrete exposure range from these studies that can be considered a NOAEL for chrysotile-related lung cancer or mesothelioma. At best, one can observe that in chrysotile-exposed cohorts where amphibole exposure was thought to be relatively low, the preponderance of the cumulative exposure NOAELs for lung cancer and mesothelioma fall in a range of approximately 25–1000 f/cc-yr and 15–500 f/cc-yr, respectively.

Limitations, Uncertainties, and Potential Biases

General Limitations and Uncertainties

One of the greatest sources of uncertainty in the chrysotile studies is the potential misclassification in the cumulative exposure estimates. None of the studies provided exposure information specific to the individuals in the cohort, such as job classification, airborne asbestos concentration, duration, or cumulative exposure estimate. Therefore, it was not possible to evaluate the accuracy of the exposure estimates.

Also, in many cases the asbestos levels were derived from total dust measurements, not asbestos fiber counts (see Table 1). This uncertainty is minimized somewhat by the fact that in most studies the measured dust levels were compared to fiber levels based on side-by-side samples, which were then used to derive a plant- or operation-specific conversion factor. However, as noted by Berman and Crump (2003), the "correlation between fiber counts and total dust is sometimes poor within a plant and generally poor between plants" (p. 5.2). To date, no universal conversion has been established to compare earlier dust measurements and current fiber counts, although as described previously, several "manufacturing-specific" conversion factors have been reported in the literature. McDonald et al. (1983a, 1984) collected dust data without developing a specific conversion factor, so for these analyses we applied the conversion factor derived in the South Carolina textiles studies ($1 \text{ mppcf-yr} = 3 \text{ f/cc-yr}$) to the estimated cumulative exposures. If the lowest conversion factor reported in the literature (1.4 f/cc/mppcf) were used instead, the calculated no-effect exposure range would be reduced by a factor of 2 (60–120 f/cc-yr); if the highest conversion factor reported in the literature (6 f/cc/mppcf) were used, the calculated no-effect exposure range would increase by a factor of 2 (240–480 f/cc-yr).

We also recognize that the measured concentrations in some of these studies may not correlate well with specific work prac-

tices or even temporally with the cohort's tenure in the facility. In many cases, the air concentrations were measured years after the exposures began (Berry and Newhouse, 1983; Hughes et al., 1987; Lacquet et al., 1980; Neuberger and Kundi, 1990). In general, this measurement would likely result in an underestimation of exposure if the asbestos concentrations declined over time (e.g., due to changes in processes and/or hygiene controls and greater awareness of the asbestos hazard). In a majority of the studies, the investigators did, in fact, attempt to "correct" for possibly higher concentrations in previous years, although the accuracy of these corrections is difficult to determine. Also, many of the samples were "area" samples that may not represent exposures for specific occupations that might experience higher or lower exposures. Individual worker exposures were generally calculated using job descriptions described in factory records in conjunction with the duration of time spent in each job category. Within a company, specific jobs and processes were assigned expected asbestos concentrations over time, an approach that does not take into account variability in the ways that tasks were performed by different workers in different factories or locations within a single factory. Cumulative exposure estimates are therefore also dependent upon the accuracy of the work histories documented in the factory records.

Fiber length information was not reported in any of the studies evaluated in this paper, yet it is known that inhaled fiber size is directly related to respiratory disease potential (risk of disease generally increases with increasing fiber length). It is likely that the mining cohorts, and perhaps many of the manufacturing cohorts, were exposed to unprocessed fibers with average fiber lengths greater than those associated with handling finished end products that were made primarily from "short" ($<5 \mu\text{m}$) fiber chrysotile (e.g., most joint compound and friction products). Lack of fiber size information may therefore introduce a degree of uncertainty in the reported NOAELs, particularly if they are used to characterize exposure and risk associated with shorter fibers.

A majority of the studies utilized national or state age-adjusted mortality rates as reference values. While these rates are easily accessible and a more appropriate comparison may not be feasible, it is understood that such standard populations contain both unhealthy and healthy individuals, while working populations are generally comprised of those healthy enough to work. As a result, the calculated SMRs for total mortality are sometimes lower than expected (the so-called "healthy worker effect"). Although most of the studies considered here did use state or national mortality rates as a comparison group, in many cases a healthy worker effect was explicitly evaluated and determined to have no influence on the results (Brown et al., 1994; Lacquet et al., 1980; Liddell and Armstrong, 2002; McDonald et al., 1984; Neuberger and Kundi, 1990; Piolatto et al., 1990). Peto et al. (1985) is the only study to have concluded the likely presence of such an effect; the others did not evaluate the influence of a healthy worker effect (Berry and Newhouse, 1983; Hughes et al., 1987; McDonald et al., 1983a). Conversely, use

of national or state mortality rates for reference values can lead to an overestimate of worker risk if regional asbestos exposures contribute significantly to disease, vis-à-vis the aforementioned critique of Brown et al. (1994), Mason and McKay (1974), and Nicholson (1986).

Frequently, the diagnosis of lung cancer and/or mesothelioma in asbestos cohort studies is based primarily on death certificates. Information on the causes of death is then commonly supplemented with additional material from hospital records, pathology reports and autopsy data. Due to the regular discordance between death certificate diagnoses and diagnoses made after reviewing all relevant clinical and histopathological data, if the same diagnostic procedure is not adhered to for both the study and the reference populations (i.e., if the diagnoses were based solely on death certificate data for the control population), differential misclassification could result (Selikoff and Seidman, 1992). As described by Enterline (1976), "Supplementing death certificates with other information and, in effect, changing causes of death in the study populations (but not in the control populations) invalidates comparisons and the calculated relative risks" (p. 152). Differential classification likely did not have a large effect on the estimates reported in these cohorts because the investigators retrieved and relied upon death certificates for both the cases and noncases. An exception to this may have occurred in Albin et al. (1990) due to the rate of necropsies performed on the mesothelioma cases compared to those performed on referents. The percentage of necropsies in the referents was not reported due to the fact that they were found in regional and national cancer registry databases; however, it is very likely that necropsies were not performed for this group. Similarly, asbestos-related diseases may have been preferentially diagnosed in asbestos-exposed workers due to increased rates of necropsies as a result of worker's compensation packages.

Loss due to follow-up can also play a critical role in the uncertainty of epidemiology studies. When addressing this matter, the U.S. EPA has noted that "Generally, 10 percent to 30 percent of an observation cohort will be deceased (sometimes even less). If 10 percent of the group is untraced and most are deceased, very large errors in the determination of mortality could result, even if no person-years are attributed to the loss-to-follow-up group" (Nicholson, 1986, p. 46). The loss-to-follow-up was minimal in the studies included in this analysis. With few exceptions, the tracing was complete for upwards of 95% of the populations in each study.

Insufficient latency was a general limitation of many of the studies evaluated. The latency between first exposure and the development of disease is believed to be at least 30 years for mesothelioma, and at least 20 years for lung cancer (ATSDR, 2001; Lanphear and Buncher, 1992). Six of the 11 lung cancer cohorts evaluated in this analysis allowed for at least 20 years of latency (Table 1), while the others ranged from 10 to 15 years.*

Three of the four mesothelioma cohorts had a minimum of a 20-year latency period (McDonald et al., 1984; Albin et al., 1990; Piolatto et al., 1990), while the other's was not specified (Lacquet et al., 1980). As with any epidemiology study involving a chronic disease with a long latency, it is possible that an asbestos-related disease was diagnosed in one or more individuals; however, their death occurred after the study was completed. Since the risk estimates were based on deaths within the cohort during a given follow up period, this may have resulted in an overestimation of the NOAEL. However, depending on the distribution of cases throughout the study period, insufficient latency may have underestimated the NOAEL. As seen in Tables 1 and 2, there was no clear relation between minimum disease latency and the risk for lung cancer or mesothelioma (i.e., the risk estimates reported do not increase with increasing minimum latency).

Lastly, as noted earlier, in many studies increased risks were not observed for any of the cumulative exposure groups, and thus the no effect level for these studies was defined as the highest cumulative exposure group in the study. For certain studies the highest exposure group was reported by the authors as greater than (" $>$ "), greater than or equal to (" $\geq$ "), or less than (" $<$ ") a certain cumulative exposure. In these instances, if reported by the authors, the mean or median of the NOAEL was included in Tables 1 and 2. This limits the ability to accurately quantify a NOAEL, as it could be slightly or substantially higher than the highest cumulative exposure group reported.

Potential Factors That Could Underestimate the Reported NOELs

There are several potential or known biases that could result in underestimation of a cumulative chrysotile NOAEL reported in these studies. For example, smoking is by far the leading cause of lung cancer in the world, yet smoking-adjusted risk estimates were only reported for 2 of the 11 lung cancer cohorts included in this analysis (the Austrian cement workers and the Quebec miners and millers). This lack of reporting is particularly important because the percentages of blue-collar workers and tradesmen who smoke exceed the national averages (Bang and Kim, 2001; Blair et al., 1985; Hall and Rosenman, 1991). Limited evidence suggests that smoking may in fact have contributed to elevated lung cancer rates in these studies. Specifically, Neuberger and Kundi (1990) calculated smoker-adjusted and nonadjusted SMRs for lung cancer, stratified by cumulative exposure for the Austrian cement worker cohort. The nonadjusted SMRs for lung cancer for both cumulative exposure groups (≤ 25 and > 25 f/cc-yr) were significantly elevated; however, after adjusting for smoking, the SMRs for both groups were close to the null value (see Table 2, p. 617). In addition, when controlling for smoking, Liddell and Armstrong (2002) found no increased lung cancer risk at any dose in the Quebec millers and miners. When McDonald et al. (1993) examined subgroups of this cohort, they did not control for smoking and reported increased risk at exposures lower than the NOAEL reported in the Liddell and Armstrong (2002) study (> 1884 f/cc-yr).

*Three of the cohorts had unspecified latencies (Lacquet et al. 1980; Neuberger and Kundi 1990; Piolatto et al. 1990). See Table 1 for more details.

Exposure to amphiboles (amosite and crocidolite) is likely to have occurred to some degree in all cohorts. On average the cohorts experienced exposure to chrysotile asbestos that contained over 3% amphiboles (Berman and Crump, 2003). As noted earlier, amphiboles have been estimated to be 100–500 times as potent as chrysotile for producing mesothelioma (Hodgson and Darnton, 2000). Thus, in some cases amphibole exposures alone might have been sufficient to induce lung disease, particularly mesothelioma. Furthermore, because the previous exposure histories of the individuals are unknown, it is not possible to determine whether significant amphibole exposure may have occurred in workers prior to their employment at the facility studied (e.g., in shipyards).

The presence of other known or suspected respiratory carcinogens, such as crystalline silica, which was often used in cement production, and mineral oil, which was frequently used to suppress airborne asbestos during manufacturing processes, could also have biased the no-effect levels for lung cancer towards lower values. There is no clear consensus regarding the risks of lung cancer with respect to silica exposure in cement production workers (Jakobsson et al., 1993; McDowall, 1984; Smailyte et al., 2004; Vestbo et al., 1991), and none of the studies in our analysis examined this issue. It has been suggested that exposures to mineral oil are responsible for the elevated lung cancer risk seen in textile workers (but not in other similar chrysotile-exposed cohorts) (McDonald, 1998). However, a nested case-control study evaluating the potential effect of mineral oil exposure on lung cancer risk in the South Carolina textile workers concluded that “mineral oil exposure does not appear to be a significant confounder in the risk estimates associated with cumulative asbestos exposure (Dement et al., 1994, p. 442). Based on the results of this analysis, it appears that exposure to other carcinogens (besides possible amphibole exposure) did not contribute to the increased lung cancer risk observed in this cohort.

As noted earlier, in most cases the original investigators often attempted to account for higher airborne asbestos concentrations that likely existed prior to sampling events. However, in some instances it was not feasible to account for certain activities that were likely to generate very high concentrations. For example, according to McDonald et al. (1983b), high-exposure tasks that were performed at the South Carolina textiles facility were not considered in the exposure estimates. In particular, during the years 1937 through 1953, the facility’s dust filtration system (receiving dust from ventilation inflow in the preparation and carding departments) consisted of burlap bags stretched across wooden frames. The baghouse operators would beat the burlap bags with whips on a daily basis to dislodge the accumulated dust, resulting in extremely high exposures. Tasks such as this were often carried out on weekends or as optional overtime, and were performed by anyone who volunteered. In addition, from 1945 to 1964 the mixing of fibers, which until that time was subject to varying degrees of control, was transferred to an alternate location in the plant (the mezzanine), where asbestos was moved around by men with pitch forks without any form

of dust suppression. As noted by the authors, “these mezzanine and baghouse exposures, which could neither be assessed nor identified in any analysis, have not been included in any analysis” (p. 363). Clearly, failure to incorporate such high exposure tasks into the cumulative exposure estimates can lead to a significant underestimate of the NOAEL.

Potential Factors That Could Overestimate the Reported NOAELs

Overestimation of worker exposure may have biased the NOAELs toward higher values in some cases. For example, such overestimation could occur if samples taken in high dust- or asbestos-producing operations were subsequently used to characterize exposures to workers involved in lower-exposure tasks. In addition, the NOAELs could have been overestimated if the workers with the highest exposure were lost to follow-up.

The primary factor that could bias the reported NOAEL in any given study toward an artificially high value would be lack of statistical power. Indeed, it is entirely possible that in many of these studies a power analysis would indicate that statistically significant risks could exist at (or below) the reported NOAEL, but that the increased risks were simply not measurable due to small cohort size, insufficient number of f/cc-years, or other factors (it is primarily for this reason that we have chosen not to refer to the NOAELs in this article as “thresholds,” since that term often implies a known exposure or dose below which effects do not occur). While it is beyond the scope of this article to conduct a detailed power analysis of all of these studies, a preliminary review suggests that the confidence with which the NOAELs can truly be considered “maximum exposures at which no measurable effect was observed” varies considerably from study to study. For example, the McDonald et al. (1993) lung cancer cohorts (company 1 and companies 3 and 4) appear to be sufficiently powerful to detect an increased risk of disease. Specifically, at 95% confidence, the power is 100% for detecting a minimum SMR of 2.0 for company 1’s 363,000 person-years and companies 3 and 4’s 607,000 person-years at the NOAEL of 100–300 f/cc-years. However, for the Brown et al. 1994 lung cancer cohort, the power to detect a minimum SMR of 2.0 for the 21,901 person-years associated with the <1000 f/cc-day NOAEL is only 29.8%. The minimum SMR detectable for this study at the NOAEL with a power of 80% is 3.5.

Hence, we believe that the NOAELs summarized in this article cannot be taken as true “thresholds” unless and until a thorough statistical analysis supports such a conclusion. Along these lines, it is worth noting that Berman and Crump (2003) recently evaluated exposure-response data from several asbestos-exposed cohorts, including many of those summarized in this article. For both lung cancer and mesothelioma, they found that a nonthreshold, linear model provided an “adequate” description of the cumulative exposure–cancer response results. However, to our knowledge there has been little effort to determine whether one or more “threshold models” might also provide a

reasonable fit to the exposure-response data, and the use of such models warrants future research.

All of the studies considered here were cohort studies wherein relative risks were determined by comparing disease rates in an exposed versus nonexposed (or general) population. This study design is usually appropriate for diseases with fairly high incidence, such as lung cancer. However, a case-control study design is more appropriate for rare diseases such as mesothelioma, particularly if the size of the cohort is fairly small (Wong, 2001). Of the four cohorts in the mesothelioma analysis, three reported two or fewer cases of mesothelioma in total (Lacquet et al., 1980; McDonald et al., 1984; Piolatto et al., 1990) and one reported no cases (and therefore no risk at any dose) (McDonald et al., 1984). It is unknown whether a case-control study or an alternate study design, with a larger cohort, would have yielded a significantly different outcome. While only four of the mesothelioma studies considered in this analysis stratified risk by cumulative exposure, it is important to note that many of the other studies reported cases of mesothelioma in workers (Berry and Newhouse, 1983; Hughes et al., 1987; McDonald et al., 1983a, 1993; Neuberger and Kundi, 1990; Peto et al., 1985; Dement and Brown, 1998; Liddell et al., 1997). In most of these instances, the authors suggested that amphibole exposure was more likely responsible for the mesothelioma cases than chrysotile.

Comparison of Chrysotile NOAELs to Vehicle Mechanic Cumulative Exposures

Finley et al. (2007) recently developed estimates of cumulative chrysotile exposures experienced by vehicle mechanics

working with friction products in the 1970s. Automotive friction products (brakes and manual clutches) in this time frame typically contained chrysotile, and the numerous published industrial hygiene surveys of vehicle repair garages in the 1970s permit a fairly thorough analysis of these historical exposures. Finley et al. (2007) reported that the 95th percentile and 99th percentile cumulative exposures for vehicle mechanics in the 1970s were 2.0 and 5.7 f/cc-yr, respectively. As shown in Figure 1, with the exception of the studies of South Carolina textile workers (Brown et al., 1994), all of the reported cumulative chrysotile NOAELs reported for lung cancer were far above the 95th percentile and 99th percentile cumulative vehicle mechanic exposures. As shown in Figure 2, the cumulative chrysotile NOAELs reported for mesothelioma are all well above the 95th and 99th percentile cumulative asbestos exposure for vehicle mechanics. These results are consistent with the epidemiology literature showing that vehicle mechanics are not at an increased risk of developing asbestos-related diseases (e.g., Goodman et al. 2004).

Recent Research on Chrysotile Exposure and Mesothelioma Risk

The question of whether or not chrysotile exposure is a risk factor for mesothelioma is a matter of ongoing debate, and there are some relatively recent published papers that have reviewed the epidemiological evidence and reached conclusions on this issue. Some researchers support the proposition that chrysotile exposures theoretically might cause mesothelioma, but that the epidemiological weight of evidence is

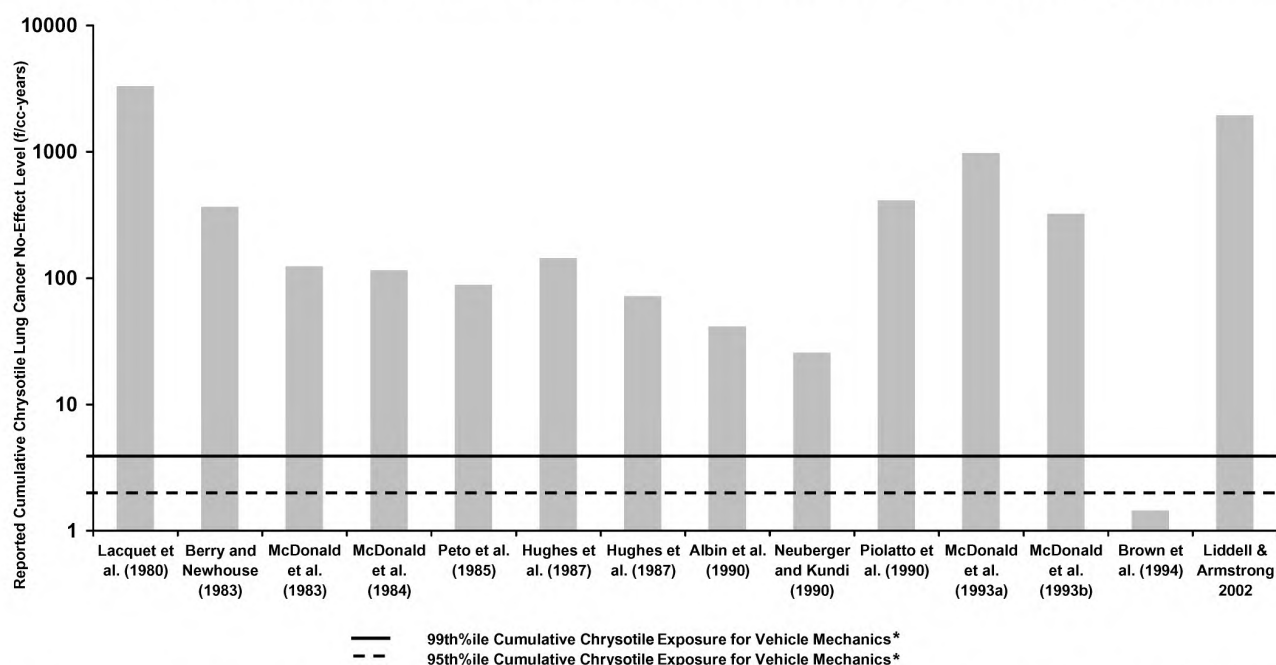


FIG. 1. Comparison of upper bound cumulative chrysotile exposures for vehicle mechanics to reported Lung Cancer No-Effect Levels.¹

*Presented in Finley, 2007

¹see Table 1 for the cumulative NOAEL presented in each study.

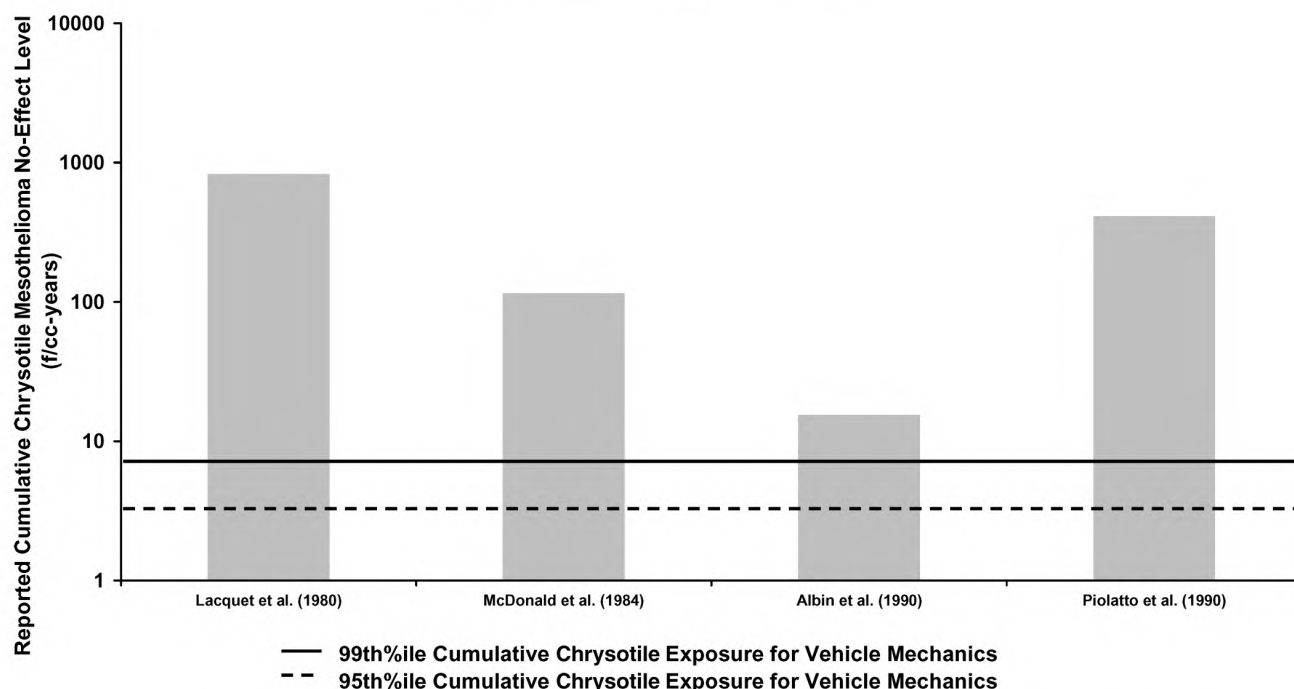


FIG. 2. Comparison of upper bound cumulative chrysotile exposures for vehicle mechanics to reported Mesothelioma No-Effect Levels.¹

¹see Table 2 for the cumulative NOAEL presented in each study.

lacking (Doll, 1989; McDonald and McDonald, 1991), while others believe the evidence clearly demonstrates that only amphiboles, not chrysotile, can induce mesothelioma (Ilgren and Chatfield, 1998; Yarborough, 2006; Dunnigan, 1988). For example, Yarborough (2006) recently analyzed the results of 71 asbestos-exposed cohorts studies, and concluded that “Epidemiological review of cohorts does not support the hypothesis that exposures to chrysotile fibers, uncontaminated by amphiboles, cause mesothelioma” (p. 180). It should be noted that the “chrysotile-only” cohorts considered by Yarborough suffer from the same study design limitations as those considered here (i.e., lack of case-control methodology for a relatively rare disease).

Conversely, others have concluded that the evidence is clear that chrysotile alone can cause mesothelioma. For example, in an analysis conducted by Smith and Wright (1996), 25 asbestos cohort studies were examined, and the authors stated that “Since asbestos is the major cause of mesothelioma, and because chrysotile constitutes 95% of all asbestos used worldwide, it can be concluded that chrysotile asbestos is the main cause of pleural mesothelioma in humans” (p. 252). In a more recent analysis, Li et al. (2004) reviewed the evidence from 26 different cohorts and concluded that chrysotile asbestos exposure alone can cause both mesothelioma and lung cancer. According to the authors, “Only cohort studies on cancer mortality among workers exposed to chrysotile alone were incorporated in to the meta-analysis” (Li et al., 2004, p. 460). However, at least half of the cohorts included in this analysis were known or suspected to have some

degree of amphibole exposure (Dement et al., 1994; Hughes et al., 1987; McDonald et al., 1983b, 1984; Peto et al., 1985; Piolatto et al., 1990; Newhouse and Sullivan, 1989; Liddell et al., 1997; Germani et al., 1999; Raffn et al. 1996; Gardner et al., 1986; Thomas et al., 1982; Ohlson and Hogstedt, 1985).

While the exposure-response summary described in this article cannot directly address the general question “Is chrysotile a risk factor for mesothelioma under any circumstances?” due to the presence of amphiboles in most of the mesothelioma cohorts considered here, it does seem to indicate that low occupational exposures to chrysotile (e.g., exposures historically experienced by vehicle mechanics) are unlikely to cause mesothelioma. Our findings suggest that a thorough understanding of chrysotile exposures that might occur in a given setting (e.g., estimated exposures that might occur during manufacture or use of microelectronics with synthetic chrysotile fibers) will provide assistance in reaching conclusions regarding the relative safety of such activities.

ACKNOWLEDGMENTS

The research supporting this analysis and the time needed to write the article were funded almost entirely by Chrysler Corporation, Ford Motor Company, and General Motors Corporation, which have been and are currently involved in litigation involving brake dust. These three funding sources (and their counsel) did not provide editorial comments or review

the manuscript prior to submission to the journal. Some of the authors have served and may continue to serve as expert witnesses regarding the historical exposures of mechanics to asbestos during brake repair.

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