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Chrysotile as a Cause of Mesothelioma: An Assessment Based on Epidemiology

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There has been a longstanding debate about the potential contribution of chrysotile asbestos fibers to mesothelioma risk. The failure to resolve this debate has hampered decisive risk communication in the aftermath of the collapse of the World Trade Center towers and has influenced judgments about bans on asbestos use. A firm understanding of any health risks associated with natural chrysotile fibers is crucial for regulatory policy and future risk assessments of synthesized nanomaterials. Although epidemiological studies have confirmed amphibole asbestos fibers as a cause of mesothelioma, the link with chrysotile remains unsettled. An extensive review of the epidemiological cohort studies was undertaken to evaluate the extent of the evidence related to free chrysotile fibers, with particular attention to confounding by other fiber types, job exposure concentrations, and consistency of findings. The review of 71 asbestos cohorts exposed to free asbestos fibers does not support the hypothesis that chrysotile, uncontaminated by amphibolic substances, causes mesothelioma. Today, decisions about risk of chrysotile for mesothelioma in most regulatory contexts reflect public policies, not the application of the scientific method as applied to epidemiological cohort studies.

Keywords Asbestos, Chrysotile, Cohort Studies, Epidemiology, Mesothelioma, Policy, Risk Assessment, Scientific Method, Tissue Burden

I. INTRODUCTION

Mesothelioma is a cancer arising from the peritoneal and parietal pleural epithelium or subepithelium. Three main histological patterns are now recognized: epithelial, desmoplastic (a variant is sarcomatoid), and biphasic (mixed). Although there have been case reports with pathological descriptions consistent with the diagnosis since 1870, mesothelioma was not generally considered a distinct cancer entity until the 1960s (Jones, 2001). Special staining of tissue samples in use since 1985 has helped the clinical assessment of patients substantially by distinguishing most of the differential diagnoses of malignant mesothelioma, including "pseudomesothelioma" (Attanoos and Gibbs, 2003; Sporn and Roggli, 2004; Bueno et al., 2005). Mesotheliomas may develop spontaneously with no apparent link to any exposure—the same applies for most cancers, such as colon and breast malignancies (Doll and Peto, 1981; Spirtas et el., 1994; Meldrum, 1996; Hubbard, 1997; Roggli et al., 1997; Speizer, 2001; Roggli and Sharma, 2004; Patel et al., 2004; Price and Ware, 2004).

There are some known and suspected causes of mesothelioma (Peterson et al., 1984; Pelnar, 1988; Ilgren and Wagner, 1991; Hillerdal, 1999; Sato et al., 2000; Sporn and Roggli, 2004; Sterman, 2004; Lange, 2004). For example, epidemiological evidence indicates that some geologic minerals (e.g., the fibrous silicates erionite–zeolite) and other fibrous minerals such as "Libby amphibole" are associated with an elevated risk of mesothelioma. In the aftermath of the World Trade Center collapse on September 11, 2001, where widespread exposures to mainly chrysotile asbestos are reported, the long-running debate on the potency of chrysotile fibers of whatever physical dimensions to cause mesothelioma (and other health outcomes, which are beyond the scope of this review) hampers unambiguous risk communications (Landrigan et al., 2004; Lange, 2004; Greenberg, 2005; Nolan et al., 2005).

Asbestos is a commercial term used to describe minerals that share certain physical properties and is categorized into two families: serpentine (chrysotile) and amphiboles. Each asbestos type has a distinct chemical formula. Asbestos occurs both as asbestiform (fibrous) and nonasbestiform (massive) structures in nature, and each type retains its chemical composition in either form. Chrysotile is a sheet silicate that rolls into nano-sized tubular structures possessing a hollow core, whereas amphiboles are chain silicates.

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Chrysotile is distinct not only in its chemistry, shape, and size distribution compared to the amphibole asbestos fibers, but also in its biopersistence in the lungs once inhaled. Based on multiple linear regression analyses of asbestos fiber content in human lung tissues, fibers (i.e., aspect ratio >3:1) of chrysotile longer than 10 μm have a half-life of 7.9 years, compared to 150.0 years for tremolite (Finkelstein and Dufresne, 1999); however, all fibers accumulate if lengths are over 18 μm in length for chronic exposures of workers (Case et al., 2000). For fibers longer than 20 μm in animal studies, chrysotile asbestos from Calidria and Canadian mines cleared the lungs with a half-life of 7 hours and 11.5 days, respectively. By 2 days, all long Calidria fibers had dissolved/disintegrated into shorter pieces, and no long Canadian fibers were present after 1 year in the lung (Bernstein et al., 2005a, 2005b).

Of the multiple clearance mechanisms, an important factor for comparing biopersistence of fibers is dissolution rates. For in vitro studies under conditions analogous to biological systems, the measured dissolution rate for crocidolite is 40 times slower than for chrysotile. Dissolution of chrysotile fibers could be accelerated because chrysotile undergoes rapid, longitudinal splitting in the lung while amphiboles do not. Reportedly a chrysotile fiber with a diameter of 1 μm will dissolve in about 1 year, while a crocidolite fiber of the same diameter will take 60 years to dissolve. The distribution of the various asbestos fibers seen in lung tissue after a long period of time is the result of the dissolution and clearances of chrysotile asbestos fibers, compared to the amphiboles, and the amount and size distribution of the original aerosols such that the number of chrysotile fibers over 5 μm in length in the lung tends to be very small (Britton, 2002; Berman and Crump, 2003; Fattman et al., 2004; Bernstein et al., 2003, 2005a). The final draft of the human risk assessment method for the U.S. Environmental Protection Agency (EPA), prepared by Berman and Crump and peer-reviewed by a panel of experts, assigns zero risk to fibers thinner than 0.4 μm and less than 10 μm in length for its optimized exposure index for mesothelioma (Berman and Crump, 2003, p. 7.49).

For purposes of research into its unique properties, the channels of chrysotile asbestos fibers have been filled under pressure by molten Hg, Sn, Bi, In, Pd, Se, and Te. These ultrathin, parallel filaments are similar to quantum wires in many ways and open the door to new microelectronic developments. Availability of synthetic chrysotile nanotubes with constant morphology and structure is crucial for nanotechnology because natural chrysotile has contamination with other minerals (Fe, Al, Ca, Ni, Mn, Na), contains different proportions of polytypes (*ortho-para*-clino-chrysotile), and is interspersed by its polymorphs lizardite and antigorite, whereas synthetic chrysotile does not possess these characteristics (Kumzerov et al., 2003; Falini, 2004). In view of these developments, elucidation of the true mesotheliogenic potency of natural chrysotile fibers absent of amphiboles has added importance in the rapidly emerging nanoparticle field in terms of occupational, consumer, environmental and medicinal exposures.

II. EPIDEMIOLOGY FOR TESTING HYPOTHESES ABOUT TOXIC EXPOSURES

Science can be defined as a methodical approach to the acquisition of knowledge. The scientific method involves problem identification, hypothesis generation, and a study designed to test the initial hypothesis. Confirmation occurs when the results supporting or refuting the hypothesis are seen in repeated observations (Cohen, 1950; Irani, 1971; Feyerabend, 1981). An example of the application of scientific method is the investigation of a causal association between amphibole asbestos and mesothelioma. Wagner et al. (1960) wrote a preliminary publication describing 33 cases of diffuse pleural mesothelioma. Early in the investigation, the authors suspected that asbestos might be implicated, but this hypothesis was not supported at once from the original histories from the patients. After obtaining detailed occupational and residential histories, it was found that all but one case had a probable exposure to crocidolite asbestos called Cape blue. This landmark report opened a large area for epidemiological studies to test the initial hypothesis and replicate the finding (Newhouse, 1969; Wagner, 1991; McDonald and McDonald, 1998; Miller, 2004).

Epidemiology is the field of public health that studies the incidence, distribution, and etiologies of disease in human populations. It focuses on evaluating associations between exposures and disease in human populations. Well-performed epidemiological studies are the best way to determine potential risks and the effects of substances on humans. A U.S. Surgeon General's report describes the approach as a "direct measurement of association" (Bayne-Jones et al., 1964). The staff of the Office of Scientific Advisor writes, "EPA prefers high-quality human studies over animal studies because they provide the most relevant kind of information for human health identification" (U.S. EPA, 2004). Epidemiology requires a comparison group as opposed to case reports or case series. Case series such as the one by Wagner et al. (1960) are descriptions of selected patients and as such are not analytical studies.

The aim of a body of epidemiological literature is to infer whether an association is causal and to derive an estimate of the magnitude of the excess risk, if one exists. An association is defined as a statistical dependence between two or more events, characteristics, or other variables. Association between two variables does not imply that one event causes the second. All associations reported in epidemiology studies can reflect varying degrees of bias (i.e., systematic errors), chance, and the reality of the situation under study. Errors may arise from biased selection of study participants, misinformation concerning the study or control groups, and confounding factors (Fraser, 1987; Rothman and Greenland, 2001; Savitz, 2003; U.S. Preventive Services Task Force, 2003). Confounding occurs whenever the effect of an exposure is distorted because of the association of the exposure with other factor(s) that influence the disease. Confounding can attenuate or exaggerate a relationship (Last, 2001) and pose obstacles to the interpretation of any epidemiological study (Savitz, 2003). Amphibole asbestos becomes a confounder

when it is present in the air and/or tissues of study subjects when the intention is to test the hypothesis that chrysotile exposure causes a cancer risk.

Scientists use animal studies to study various toxicological aspects of substances to help assess human health risks. Although animal studies involve controlled exposures to well-characterized agents, many uncertainties are introduced when extrapolating the results of animal data to humans (Brent, 2004). With regard to modeling asbestos risk specifically, attempts to use animal data for human dose-response factors are not recommended (Berman and Crump, 2003). "In the end, if a choice has to be made between animal and human evidence as a basis for assessing human risk, adequate human data must be given a priority" (Hodgson and Darnton, 2000). The question of whether humans develop mesothelioma as a result of exposure to chrysotile asbestos fibers must be answered based on human experience rather than on animal experimentation (Elmes, 1994).

In a speech at the Royal Society of Medicine to occupational medicine physicians over 40 years ago, Sir Austin Bradford Hill, Professor Emeritus of Medical Statistics at the University of London, proposed a list of "nine different viewpoints" when interpreting observational and related studies as evidence of causation. Researchers and policymakers are still using the approach widely today. His decisive question was whether the frequency of undesirable event B will be influenced by a change in the environmental feature A. No formal tests of significance can determine cause and effect (Hill, 1965). Using the list as a "causation model" (see Lemen, 2004) without first establishing an association was not the original intent of Professor Hill. Discussed also in the section of the report called "Establishment of Association" for the U.S. Surgeon General by Bayne-Jones et al. (1964, pp. 179–182), this point was clearly reiterated by Hill when he introduced the list in his speech:

> Disregarding then any such problem in semantics we have this situation. Our observations reveal *an association between two variables, perfectly clear-cut* and beyond what we would care to attribute to chance. What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation? [italics added] (Hill, 1965)

> *If it be shown that an association exists*, then the question is asked, 'Does the association have a causal significance?' ... To judge or evaluate the causal significance of the association between the attribute or agent and the disease, or effect on health, a number of criteria must be utilized. [italics added] (Bayne-Jones, 1964)

Because the list of considerations was meant for studying positive associations "before we cry causation" according to Hill, the need to consider the credibility of an observed *absence* of association is not addressed (Savitz, 2003). Consideration of the Hill aspects should not be initiated at the current time because of the lack of a well-documented, "clear-cut" association with mesothelioma in the chrysotile epidemiological studies (as discussed later).

III. BASIS FOR THIS REVIEW

The extensive epidemiological literature on this topic was reviewed by following searches in the MEDLINE database and bibliographies and citations in articles. Seventy-one peer-reviewed cohort studies matched the inclusion criteria: cohort design in settings of mainly occupational exposures to free (raw) asbestos fibers; enumeration of mesothelioma cases; specific information on asbestos fiber types; and latest published reports for cohorts. Cohort epidemiological studies can provide fiber type information, which typically only exists within cohort data sets rather than case control studies. Detailed exposure information is usually obtained for industrial cohort studies. Listed in Tables 1, 2, and 3 are cohort studies found to have sufficient information on the asbestos fiber types. Classification for the studies was based on this reported information unless there was reasonable evidence to indicate that members of the cohort were exposed to mixed fibers. Due to insufficient reports for rates of mesothelioma in cohorts, a formal meta-analysis could not be undertaken.

As seen in the tables, exposure data was provided by two major risk assessment efforts of this decade and other published papers, such as the number of subjects and cases, estimated average exposure levels in short-term samples (fibers/milliliter, milligrams/cubic meter of air, etc.), or cumulative exposures (fibers/milliliter times years of exposure [f/ml-yr]), industries, processes, and fiber types. The time frame for exposures in the tables refers to the ascertained start date of operation of the plant or study period until the end of follow-up of the cohort.

IV. RESULTS

A. Epidemiological Cohort Studies on Amphiboles Causing Mesothelioma (Table 1)

1. Crocidolite

Many studies support the conclusion that there is a causal association of exposures to crocidolite, a form of riebeckite, with mesothelioma. The relationship between crocidolite asbestos exposures and mesothelioma was demonstrated by applying the scientific method to epidemiology studies designed to formally examine the findings that Wagner and his colleagues published in 1960 (Wagner et al., 1960). A cohort study of a cigarette filter factory in Massachusetts consisted of 33 men exposed during the manufacturing process using crocidolite; 5 died of mesothelioma (Talcott et al., 1989). Two hundred thirty-one mesotheliomas were diagnosed among a group of 6908 persons (6493 men and 415 women) who had worked at a former crocidolite mine and mill in Wittenoom, Australia, at some time between 1943 and 1966. Nine percent of the known deaths in this group were attributed to mesothelioma (Berry et al., 2004). Among 3430 crocidolite miners in South Africa contributing about 49,000 person-years of follow-up, mesotheliomas were discovered in 20 men (Sluis-Cremer et al., 1992). These cohorts had average cumulative exposures of 17–120 f/ml-yr for crocidolite fibers (see Hodgson and Darnton, 2000). Gas mask

TABLE 1
Characteristics of cohort studies for amphibole asbestos

Authors, year	Study	Fiber type	Number of # cases	Approx. number of subjects	Estimated exposure level	Process	Time frame
Acheson et al., 1982	Leyland	o	5	852	—	G	1939–1980
Berry et al., 2004	Wittenoom	o	231	6908	23 f/ml-yr	M	1943–2000
Browne and Smither, 1983	Cape Factory D	a	0	1500 approx.	—	I	1954–1980
Finkelstein, 1989a	Ontario	a	2	133	640 f/ml; up to 134 mppcf in 1958	I	1956–1986
Gaensler et al., 1988	Mass. Plant A	o	12	136	<5 mppft in 1953	G,O	1943–1988
Hilt et al., 1981	Saltpeter	o	2	21	—	O	1943–1980
Jones 1976, 1996	Nottingham	o	67	1172	—	G	1940–1995
Levin et al., 1998	Tyler TX	a	6	1130	16–91 f/ml	I	1954–1986
Luo et al., 2003	Da-yao I	o	3	5603	—	O	1977–1983
Luo et al., 2003	Da-yao II (III)	o	7 (5)	4598 (1610)	—	O	1987–1995
McDonald et al., 1978	S Dakota	c	1	1321	—	M	1905–1973
McDonald et al., 2004; also see Amandus et al., 1987	Libby	l	12	406	162 f/ml-yr; 18 f/ml	M	1963–1999
Meurman et al., 1994	Finnish mines	n	4	903	—	M	1918–1991
Seidman et al., 1986	Paterson	a	17	820	65 f/ml-yr	I	1941–1982
Sluis-Cremer et al., 1992	SA crocidolite	o	20	3430	17 f/ml-yr	M	1946–1980
Sluis-Cremer et al., 1992	SA amosite	a	4	3212	24 f/ml-yr	M	1946–1980
Sluis-Cremer et al., 1992	SA mixed	oa	6	675	—	M	1946–1980
Talcott et al., 1989	Massachusetts	o	5	33	120 f/ml-yr	O	1951–1988
18 cohorts			404	Approx. 32,853			

Note. See Table 5 for explanations of symbols.

production using crocidolite from Western Australia in plants was associated with 67 mesothelioma cases among 1172 workers in a plant in Nottingham, UK (Jones et al., 1976, 1996). Twenty-one men were heavily exposed to crocidolite during the construction of a saltpeter plant from 1928 to 1929, and two mesothelioma cases were reported by 1980 in the group with 0.21 cases expected (Hilt et al., 1981). In a cohort of 136 filter paper makers using crocidolite for gas masks and cigarettes working from 1943 to 1972 in Massachusetts (Plant A), 12 mesotheliomas were found, including another case in the wife of a worker (Gaensler and Goff, 1988). A study of 435 workers making gas masks in Leyland, UK, using primarily crocidolite, found 5 mesothelioma cases in the records; 3 pleural mesothelioma cases at Blackburn had amphiboles found in their lung tissue (Acheson et al., 1982).

Many cases of mesothelioma and other asbestos diseases for two cohorts and one subcohort are reported as associated with environmental and occupational exposures to crocidolite in a rural county in southwestern China. Not only were there exposures from ambient air and during the common application of crocidolite-containing clay as stucco, but also asbestos stoves and stove pipes were made in family-style production for selling locally and beyond the Da-yao area until this practice was officially banned in 1984. The annual mortality rate is 85–365 per million in that region of China. In comparison, the current rates in North America are about 15–20 cases per million in men and much lower in women (Sporn and Roggli, 2004). Also, the more highly exposed peasants in this Chinese study had a fivefold increased risk of mesothelioma relative to the counterparts with lower exposure (Luo et al., 2003).

2. Amosite (Insulation)

Exposure to another commercial amphibole, fibrous grunerite (commonly called "amosite" from the acronym AMOS, representing Asbestos Mines of South Africa), has resulted in an excess risk of mesothelioma. It is unclear in some occupational studies that the exposures are to asbestiform mineral. Among 3212 amosite miners in South Africa (51,000 person-years with cumulative exposure of 24 f/ml-yr), 4 mesotheliomas were found (Sluis-Cremer et al., 1992; Hodgson and Darnton, 2000). Mesothelioma was diagnosed in 17 men among 820 workers exposed to amosite in a factory located in Paterson, NJ. The

incidence among those with short-term work exposures showed a strong relationship with advancing time (Seidman et al., 1986). The worker cohort in New Jersey had cumulative amosite exposure of 65 f/ml-yr (Hodgson and Darnton, 2000). A study of a cohort involved in amosite insulation manufacturing at Tyler, TX, reported 6 mesotheliomas among 130 workers (Levin et al., 1998). Two mesothelioma cases were found among 12 exposed workers at an Ontario factory manufacturing amosite asbestos insulation materials under poorly controlled environmental conditions (up to 640 f/ml in 1973) (Finkelstein, 1989a). Another cohort with exposure to cummingtonite-grunerite, a mineral that is closely related to amosite, had one case of mesothelioma diagnosed by needle biopsy (McDonald and McDonald, 1978). Workers at one factory of Cape Industries Ltd. (Factory D) producing insulation boards containing amosite had no reported mesotheliomas among approximately 1500 workers (Browne and Smither, 1983).

3. Tremolite and Libby Amphibole

Fibers of the tremolite-actinolite series are a widespread mineral that has little commercial value. Marked inflammatory and fibrotic responses are seen after tremolite deposition in the lungs of animals, in contrast to the lack of histopathology after Calidria chrysotile exposures (Bernstein et al., 2005b). Since 1978, the human health effects of vermiculite contaminated with this asbestiform mineral have been studied (Amandus et al., 1987; ASTDR, 2003). The U.S. EPA now calls the complex tremolite-containing mineral "Libby asbestiform amphibole." A recent epidemiological study was published of 406 vermiculite mineworkers in Libby, MT, who were employed before 1963 and followed until 1999 and had average exposure for 9 years of 18 f/ml-yr. Twelve deaths (4.2% of all deaths) were attributed to mesothelioma. The overall proportional mortality is similar to that of crocidolite miners in South Africa and in Australia (McDonald et al., 2004). Locally widespread use of tremolite-containing whitewash is reported to be the cause of the "Metsovo mesothelioma epidemic" (Constantopoulos et al., 1987; Langer et al., 1987; Sakellariou et al., 1996) and is strongly associated with mesothelioma risk in New Caledonia (Luce et al., 1994, 2000) and Anatolia (Baris et al., 1988; Metintas et al., 1999).

4. Anthophyllite

Tossavainen et al. (1994), from Finland, where anthophyllite was mined and used, reports the permanent persistence of longer (>5 to 17 μm), thicker anthophyllite fibers in the lung and the predominance of these fibers in some lung cancer and mesothelioma cases. Hillerdal (2004) writes that anthophyllite's potential to cause mesothelioma seems to be low. On the other hand, there is a mesothelioma case report that the authors link to neighborhood environmental (i.e., low) exposure to anthophyllite asbestos, while relating this case to reports of asbestos-associated disorders among workers exposed to anthophyllite (Rom et al., 2001). A cohort of 736 men and 167 women work-ing in two Finnish mines was followed from 1953 until 1991. There were 4 cases of mesothelioma among this group versus 0.1 expected, all in men with "heavy" exposure to this form of asbestos for 13 to 31 years (Meurman et al., 1994).

B. In Workers Exposed to Both Chrysotile and Amphibole, There Are Fewer mesothelioma Cases Than in Studies of Amphiboles (Table 2)

1. South Carolina

One of the largest studies of asbestos exposures involved a plant in Charleston, SC, using primarily chrysotile asbestos received from Quebec and (then-called) Rhodesia. This facility began producing asbestos packing materials for steam engines and pumps in 1896, then switched to textile manufacturing in 1909. Reportedly less than 2000 lb of crocidolite was used annually for about 20 years to make tape or braided yarn. Amosite exposures are believed to have occurred at the plant mostly before 1950 based on lung fiber results of workers; amosite was also acquired in the late 1950s for experimental purposes (McDonald, 1998; Berman and Crump, 2003, p. 6-4, footnote 2). Studied by two separate investigative teams using slightly different inclusion criteria (McDonald et al., 1983a; Dement et al., 1994), the latter cohort had a total of 3022 subjects with estimated cumulative exposures to asbestos of 26–28 f/ml-yr based on particle counts. No mesothelioma cases were found for the 1229 women of this cohort group who were at risk of exposure for 52,000 person-years. Among the white male workers of the plant, two mesothelioma cases based on death certificates were observed in the study cohort of Dement et al. (1994). They were employed at the plant for 25 and 32 years, primarily in the spinning operations. An additional case (not included in the cohort) that occurred after the study closure was observed in a white male employed mostly in nontextile operations. McDonald et al. (1983b) found only one of these cases using different criteria for subjects being studied resulting from different follow-up times. The notion that the Carolina cohort was exposed almost exclusively to chrysotile asbestos fibers is very questionable (Berman and Crump, 2003). The lungs of deceased workers of this Carolina plant cohort contained substantial amounts of amosite, crocidolite, anthophyllite, tremolite, mullite, and other fibers (Case, 1994; Green et al., 1997). Green et al. (1997) reported mineralogical findings for lung samples taken from necropsies of employees during 1940 to 1965 at the Charleston plant who were in the Dement cohort and matched cases from the same hospitals. They compared the results of 38 textile production workers to 31 controls who did not have personnel file records at the Charleston plant. They found that the geometric mean of the number of crocidolite and amosite fibers was increased compared to controls ($p < 0.05$) and that 28% of asbestos workers and 13% of the controls had values of crocidolite or amosite exceeding 1×10^6 fibers per gram of dry lung, a cutoff level indicating a "substantially increased" number of fibers at the authors' laboratory. The results suggest that at least some workers at the Carolina textile plant were significantly

TABLE 2

Characteristics of cohort studies of workers exposed to mixed asbestos fibers

Authors, year	Study	Fiber types	Number of # cases	Approx. number of subjects	Estimated exposure level	Process	Time frame
Acheson et al., 1984; also see Browne and Smither, 1983	London (Cape Factory C)	ay	5	4820	<30 f/ml until 1964	I	1947–1980
Albin et al., 1990a	Sweden	yao	13	1929	13 f/ml-yr; 0.3–6.3 f/ml	C	1907–1986
Alies-Patin et al., 1985	Paray-Le-Monial	yo	4	1506	—	C	1940–1982
Battista et al., 1999	Italy railcars	yo	7	734	—	L	1945–1997
Browne and Smither, 1983; Newhouse et al., 1985	Cape Factory A	oay	120 est.	10,000 approx.	—	F,L	1913–1980
Browne and Smither, 1983	Cape Factory B	oay	13	2000 approx.	—	T,I	1939–1980
Camus et al., 2002	Quebec towns	yt	11	11,000 women est.	0.1–3 f/ml before 1970	O	1970–1989
Dement et al., 1994; also see McDonald et al., 1983a ; Green et al., 1997	Carolina	ytaon	2	3022	26–28 f/ml-yr	T,I	1896–1990
Elmes and Simpson, 1977	Belfast	mixed	13	162	—	L	1940–1975
Enterline et al., 1987	Johns Manville retirees	yao	8	1074	750 f/ml-yr	I	1941–1980
Finkelstein, 1984	Ontario	yo	21	535	60 f/ml-yr; 7% > 150 f/ml-yr	C	1948–1977
Germani et al., 1999	Italy (textile)	yo	6	276 women	Asbestosis	T	1979–1997
Germani et al., 1999	Italy (cement)	oy	18	278 women	Asbestosis	C	1979–1997
Hughes et al., 1987	New Orleans (Plant 1)	yao	2	2565	79 f/ml-yr; 7.8 mppft	C	1942–1982
Hughes et al., 1987	New Orleans (Plant 2)	yo	7	1231	47 f/ml-yr; 7.8 mppft	C	1937–1982
Jarvholm and Sanden, 1998	Swedish insulators	yao	7	248	—	L	1958–1994
Kolonel et al., 1980, 1985	Pearl Harbor	ya	8	7971	40 mppft (max.)	S	1950–1982
Lacquet et al., 1980	Belgium	yoa	1	1973	3200 f/ml-yr (max.)	C	1963–1977
Liddell et al., 1997; McDonald et al., 1997	Quebec	ytao	38	10918	600 f/ml-yr	M,F	1904–1992
McDonald and McDonald, 1978	Canada	oyt	9	199	—	G	1939–1975
McDonald et al., 1983b	Pennsylvania	yao	14	5135	60 f/ml-yr	T,F	1938–1977
Mancuso, 1988; Ohlson, 1989	U.S. rail machinists	yoa	14	181	—	L	1920–1986
Neuberger, 1990	Vocklabruck	yo	4	2816	25 f/ml-yr	C	1950–1987
Nokso-Koivisto and Pukkala, 1994	Finnish locomotives	ny	8	8391	10–20 f/ml-yr	L	1953–1991
Peto et al., 1985	Rochdale	yo	10	3211	138 f/ml-yr	T	1933–1983
Pira et al., 2005	Grugliasco	yoa	37	1966	"experimental" levels	T,F	1946–1996
Newhouse et al., 1989; Berry et al., 1983	Ferodo Manchester	yo	13	13450	35 f/ml-yr; <5 f/ml since 1950	F	1941–1986
Raffn et al., 1989	Denmark	yao	13	8580	50–800 f/ml until 1948	C	1928–1984
Robinson et al., 1979	NIOSH/OSHA	yao	17	3276	—	T,F	1940–1975
Rossiter and Coles, 1980	Devonport	mixed	31	6292	—	S	1947–1978
Sanden and Jarvholm, 1987	Swedish shipyard	yoa	4	3787	—	L	1930–1983
Seidman and Selikoff, 1990	U.S./Canada insulators	yao	458	17800	500 f/ml-yr	L	1967–1986
Selikoff et al., 1979	U.S. shipyard	ya	8	440	4–12 f/ml	L	1967–1977
Silvestri et al., 2001	Balangero	yb	5	1058	300 f/ml-yr; 1064 f/ml-yr max.	M	1946–1987
Smailyte et al., 2004; Tossavainen et al., 2000	Lithuania	ytn	1	1887	1.9–4 mg/m^3 in 1975–1989	C	1956–2000
Szeszenia-Dabrowska et al., 1997	Poland	yoa	5	3563 men	8 f/ml max. in 1990	C	1924–1991
Thomas et al., 1982	Wales	yo	2	1970	0.1–20+ f/ml until 1968	C	1936–1977
Ulvestad et al., 2002	Norway	yoa	18	541	50–1000 f/ml until 1950	C	1942–1999
Tulchinsky et al., 1999	Israel	yo	21	3057	0.3–40.0 f/ml	C	1953–1992
39 cohorts			Approx. 994	Approx. 147,384			

Note. See Table 5 for explanations of symbols.

exposed to amphiboles. Both mesothelioma cases reported by Dement et al. (1994) worked in the spinning area of the plant and possibly were exposed to amphiboles (Sebastien et al., 1989). Although no corresponding published information was found for the South Carolina facility, inhalable crocidolite fibers from bushings in spinning machines were linked to a case of mesothelioma in a worker at a nonasbestos textile factory in Korea. The standard (B-style) bushings were used to protect against gear abrasion in the spinning machines (Yu et al., 2002).

2. Quebec

A large cohort of nearly 11,000 chrysotile miners, millers, and factory workers who worked in Asbestos and Thetford, Quebec, has been intensively studied. Thirty-six mesotheliomas were found for those first employed at the Asbestos mine/mill (8 cases), Asbestos factory (5 cases), and two Thetford Mines companies (23 cases), and there were two more cases that did not meet inclusion criteria (Liddell et al., 1997; also see Nicholson et al., 1979; McDonald et al., 1997). Exposures to fibers of amosite, crocidolite, tremolite, and chrysotile in the Canadian asbestos districts are well documented (Case and Sebastien, 1987; Churg, 1998; Berman and Crump, 2003, section 3), even though tremolite was not detected in a chrysotile mixed sample from eight mines (Frank et al., 1998). Airborne exposures are indicated by lung tissue results of mesothelioma cases in Canada (McDonald et al., 1989; Sebastien et al., 1989; Churg et al., 1993; McDonald et al., 1997). Eleven mesotheliomas were observed in a population-based study of women (over 220,000 person-years) residing in Asbestos (1 peritoneal mesothelioma) and Thetford Mines (6 definite or probable and 4 possible pleural mesotheloma). Of the pleural cases, the mean cumulative exposure to asbestos was 226.1 f/ml-yr, and 5 of them worked in the asbestos industry. Ambient asbestos fibers were chrysotile contaminated with tremolite ranging from 0.1 to 3 f/ml before 1970. The mesothelioma incidence rates were 67.5 per million person-years in the Thetford area and 13.7 per million person-years in the Asbestos area. The authors explained that the greater risk in the Thetford district could have been due to the higher level of contamination of the chrysotile with tremolite in some of Thetford's mines (Camus et al., 2002; Case et al., 2002a).

3. Asbestos Cement

Mixed exposures to chrysotile and amphiboles are reported in asbestos cement manufacturing, and some mesothelioma cases are found among the workers. In Lithuania, a study was done of cancer incidence and cause-specific deaths among workers in two asbestos cement factories. Accessing cancer registry records, 1 case of pleural mesothelioma was observed with 0.3 expected, which was "noninformative concerning asbestos exposure and mesothelioma risk," according to the researchers. One factory started operations in 1956 and the other in 1963, and both factories have only used almost 600,000 tons of raw

chrysotile asbestos that was imported from the Sverdlovsk region of Russia (Smailyte et al., 2004). A lung tissue study of workers after occupational and environmental exposure to asbestos in the Russian chrysotile industry rebuts the assumption that asbestos from Russia is only chrysotile, showing that about 5% of all mineral fibers were amphiboles (Tossavainen et al., 2000). A small group of Italian women who worked in the asbestos-cement industry, mainly exposed to crocidolite, and subsequently compensated for asbestosis, had 18 deaths reportedly due to mesothelioma (Germani et al., 1999).

In Ontario, mortality was investigated among 535 asbestos-exposed and 205 nonexposed employees of a factory manufacturing asbestos cement pipe, asbestos cement board, and rock-wool insulation materials in separate sheds. Raw materials for the pipe included cement, silica, and chrysotile and crocidolite asbestos; in the board manufacturing operation only chrysotile was used. Personal air sampling for production workers was done after 1969, and the cohort exposure average was 60 f/ml-yr. There were 21 deaths from mesothelioma in the cohort (19 confirmed pathologically), with 17 in production workers. The expected number of mesothelioma deaths for the cohort was 4. All of the men dying of mesothelioma were exposed to both crocidolite and chrysotile asbestos in the pipe plant (Finkelstein, 1984). A Swedish cohort of manufacturing workers was studied for exposures to chrysotile primarily (>95%), but also smaller amounts of amphiboles. Thirteen pleural mesothelioma cases were observed among 2898 workers (22,000 person-years) having a cumulative exposure of 13 f/ml-yr when followed for an average of 62 years (Albin et al., 1990a). A cohort of workers employed during 1950 to 1981 in Vocklabruck, Austria, the oldest asbestos cement factory in the world, was exposed primarily to chrysotile. Crocidolite was used in the pipe factory from 1920 to 1977. Five of 540 deaths were due to mesothelioma among 2816 workers (51,000 person-years) with 25 f/ml-yr cumulative exposure, but all were associated with the use of crocidolite in pipe production (Neuberger and Kundi, 1990). At a factory in Belgium, a cohort study having over 29,000 person-years of follow-up found one mesothelioma. Exposures were up to 3,200 f/ml-yrs during the timeframe of the study, but the authors state that their estimates might be inaccurate by 10-fold. Although 90% of the asbestos by weight used at this facility was chrysotile, the remainder was crocidolite and amosite (Lacquet et al., 1980).

Asbestos cement manufacturing plants in New Orleans that predominately used chrysotile asbestos have been studied, and asbestos content in most products ranged from 15% to 28%. Plant 1 added amosite (1% of product) and infrequently used crocidolite in the manufacture of corrugated bulkhead, and facilities in Plant 2 used crocidolite steadily, which constituted 3% of the pipe material (Weill et al., 1979). Among 6931 workers exposed to mixed fibers, 9 mesotheliomas in Plants 1 and 2 were found (Hughes et al., 1987; Hodgson and Darnton, 2001). In a study of asbestos cement factory in Wales, two mesotheliomas were reported, but both were exposed to crocidolite (Thomas

et al., 1982). Eighteen mesothelioma cases were found among 541 workers in the asbestos cement industry in Norway, where 8% amphiboles were added to the chrysotile used (Ulvestad et al., 2002). For Danish workers in the asbestos cement industry between 1928 and 1984, 13 cases of mesothelioma were observed. For pleural cancer among the male workers, the observed/expected rate was statistically elevated at 5.46, but amphiboles were used starting in 1946 (Raffn et al., 1989). From Poland there is a report of 5 mesotheliomas among 3563 male workers (Szeszenia-Dabrowska et al., 1997), and 21 mesotheliomas were found among Israeli workers using 90% chrysotile and 10% crocidolite mixture to produce asbestos cement products (Tulchinsky et al., 1999). The mortality study of 1506 workers of a French asbestos cement factory at Paray-Le-Monial who were employed at least 5 years (providing nearly 34,000 person-years) observed 4 mesotheliomas, 1 of which was a peritoneal case with a latency period of 13.5 years. The 3 deaths from pleural mesothelioma had an average latency of less than 25 years, resulting in a mean of 22.4 years. Founded in 1940, this factory used not only chrysotile but also crocidolite (Alies-Patin and Valleron, 1985).

4. Insulators (Laggers)

Workers who applied asbestos insulation (called lagging) typically had heavy exposures to loose fibers of chrysotile, amosite, and crocidolite. Among 17,800 American and Canadian insulators, 458 mesothelioma deaths (285 peritoneal) were determined by "best evidence" method for the 1967–1986 time period. This cohort had 301,000 person-years of average exposure at a cumulative level of 500 f/ml-yr (Seidman and Selikoff, 1990; Hodgson and Darnton, 2000, Table 2). The cancer morbidity study of 3787 workers of a shipyard that was abandoned in 1972 found 4 cases of mesothelioma (Sanden and Jarvholm, 1987). Seven cases of peritoneal mesothelioma, none pleural, were observed among 248 insulation workers (Jarvholm and Sanden, 1998). Dr. Selikoff and colleagues reported 8 mesothelioma deaths among 440 U.S. shipyard insulation workers, and all had over 20 years since onset of employment to diagnosis. Chrysotile and amosite (starting just before World War II) were the fiber types for exposures noted in the article (Selikoff et al., 1979). A retrospective study of cancer among 7971 shipyard workers with 5191 of them exposed to asbestos based on job title, including those in the pipecoverer/insulator trade, is included in Table 2, although asbestos measurements are not documented. The authors thought amosite and chrysotile were the major types of asbestos used at the Pearl Harbor Naval Shipyard in terms of this study. Of 9 observed mesothelioma cases, 1 was in the major job category of insulator (Kolonel et al., 1980, 1985). Mortality of 41 insulation workers was also studied for a shipyard in Genoa, Italy, but the authors did not provide the asbestos fiber types (Puntoni et al., 1979), and therefore the study is not in a table of this review. No mesotheliomas were reported for these Genoan insulators.

5. Insulation Manufacture

Almost 5000 men who manufactured insulation board in London used a mixture of chrysotile and amosite, but not crocidolite. In some areas, 30 f/ml of asbestos in air were found in the plant during the late 1960s, but higher levels were probably encountered prior to 1964. Five mesothelioma and nine asbestosis deaths were certified (Cape Factory C in Browne and Smither, 1983; Acheson et al., 1984). In another Cape Industries factory (Cape Factory B), 13 mesotheliomas were observed among approximately 2000 workers (Browne and Smither, 1983). Mortality studies of 162 Belfast insulation workers and 6292 dockyard workers are included in Table 2 because the types of asbestos fibers are reported as mixed, although the composition and exposure levels are unknown (Elmes and Simpson, 1977; Rossiter and Cole, 1980; see Smith and Wright, 1996).

6. Factories

The mortality experience is published of 1074 Johns Manville retirees. Eight deaths from mesothelioma were observed among workers in the textile, maintenance, cement shingle and sheets, insulation, and cement pipe departments experiencing direct and indirect exposures to mixed types of asbestos fibers (Henderson and Enterline, 1979; Enterline et al., 1987). The members of this cohort are estimated to have 750 f/ml-yr cumulative exposure, the highest average level reported in the literature (Hodgson and Darnton, 2000). At a textile plant in Pennsylvania, chrysotile with some amosite and crocidolite were used. Exposure for each man was estimated. Fourteen deaths were recorded of 5135 subjects, though undercounting of mesothelioma cases was a possibility. The risk of mesothelioma was higher for those exposed to processes when even small quantities of amphiboles were used (McDonald et al., 1983b). In addition to the asbestos cement plant workers reported in the same article, a small group of Italian women who worked in the textile industry, mainly exposed to chrysotile, and compensated for asbestosis had six deaths due to mesothelioma (Germani et al., 1999). Chrysotile asbestos was the primary form used in a factory in Rochdale, UK, between 1932 and 1968, though some crocidolite was used (total 2.6%). Exposure data were largely derived from static particle counts, not fiber determinations, but the risk of mesothelioma appeared to be increased from the observation of 10 cases (Peto et al., 1985). A mortality study of workers employed at a factory producing friction products was completed from 1941 to 1986. Other than two short periods before 1944 when crocidolite was used on one particular contract, only chrysotile had been used. Asbestos exposures were high (>20 f/ml) especially before the 1931 Asbestos Regulations, but since 1970, levels had been less than 1 f/ml. Thirteen deaths due to mesothelioma were found, 11 in those with known contact to crocidolite. For the other two cases, the diagnosis was uncertain in 1 person, and the occupational history is unclear in the other cases (Berry and Newhouse, 1983; Newhouse and Sullivan, 1989). Of approximately 10,000 subjects of Factory A covering over 6 decades,

an estimated 120 mesothelioma cases were found (Browne and Smither, 1983; Newhouse et al., 1985). In a mortality study for 1940–1975 among 3276 workers of a plant using chrysotile and amphiboles, 17 cases of mesothelioma were observed (Robinson et al., 1979). A cohort of 889 men and 1077 women employed at a factory in Grugliasco, Italy, worked with various types of asbestos, including crocidolite, and "exposure in this factory almost approached experimental conditions." Thirty-seven pleural and peritoneal mesothelioma cases and many deaths from asbestosis are reported (Pira et al., 2005).

7. Italian Mine

Operating from 1917 until 1990, the Balangero strip mine was Italy's only chrysotile mine. Silvestri et al. (2001) updated the mortality experience for the cohort that had been earlier investigated by Piolatto et al. (1990) rather than using a similar cohort of Rubino et al. (1979). Piolatto et al. (1990) had observed an excess of mortality of all causes, asbestosis and several cancers. Two observed cases of mesothelioma were reported and 0.3 cases expected based on the death rates in Italy, resulting in a standardized mortality rate (SMR) of 667. Silvestri et al. give the 95th percentile confidence interval (CI) as 81–241, but the upper bound is obviously a typographical error, and the correct value should be 2410 (calculated by Stata version 7.0, Stata Corp.). Nevertheless, this increase of the SMR was not statistically significant for the 1990 study. For the two deaths attributed to "pleural cancer" (mesothelioma), the diagnosis was based on clinical, radiographic, and pleural fluid findings in one case, and by a surgical tissue biopsy for the other one. In the 2001 update, 3 additional pleural mesotheliomas were identified in workers having asbestos fiber exposures of 319, 340, and 1064 f/ml-yr and 8 community cases were observed. The authors made some assumptions to determine that 5 deaths from pleural mesothelioma among the cohort's members should be compared to 0.45 expected cases, but no SMR is reported. A fibrous contaminant with morphology and fiber dimensions similar to amphiboles, called balangeroite, accounts for 0.2–0.5% of the total mass of commercialized chrysotile samples from the mine. Piolatto et al. (1990) state that they could not rule out its contribution to inducing the two cases of mesothelioma in their study. Recent laboratory studies indicate that balangeroite fibers act toxicologically like amphibole asbestos fibers (Groppo et al., 2005; Turci et al., 2005; Grazzano et al., 2005). Likely balangeroite would confound epidemiological associations for chrysotile asbestos. In addition, some crocidolite was processed at Balangero (Browne, 2001).

8. Other Cohort Studies

A cohort of 199 workers at 3 plants who were exposed predominately to crocidolite (especially at the Ottawa plant) and chrysotile during the manufacture of gas masks for the Canadian army between 1939 and 1942 indicated that 9 of the deaths were probably due to mesothelioma. Two additional pleural mesothelioma cases in men who had worked for decades at one of the plants were found in a national survey, but they are not included in the study's tables because their names were not on the roster from the plant foreman who had been responsible for production of gas mask filters (McDonald and McDonald, 1978). An epidemiological study of mesothelioma was published of 181 railroad machinists involved with steam engines hired between 1920 and 1929 followed through 1986 whose exposure was "almost exclusively, if not solely" to chrysotile. Of 41 cancer deaths, 14 mesotheliomas were identified (Mancuso, 1988, 1989a, 1989b). It appears that amphibole exposures were likely involved in this cohort (Ohlson, 1989). In a cohort study (734 subjects) of cancer risk associated with asbestos exposure in railway carriage construction and repair in Italy, 7 mesotheliomas were observed. Starting in the 1950s, crocidolite–chrysotile mixtures were sprayed on the entire internal surface of the carriage by workers in the facility (Battista et al., 1999). In a study of locomotive engineers who undertook a 2-year training program where exposures to anthophyllite asbestos with chrysotile were documented, 8 of 8391 subjects were subsequently diagnosed as having mesothelioma (Nokso-Koivista and Pukkala, 1994).

C. Cases of Mesothelioma in Cohorts Where No Amphibole Exposure Was Identified Do Not Demonstrate Chrysotile Is The Cause (Table 3)

The number of mesothelioma cases is very low or zero in all cohorts exposed to chrysotile asbestos that is not known to be contaminated by amphibole fibers. There are 14 identified cohort studies describing exposures solely to chrysotile asbestos. Of approximately 32,000 subjects, only 7 mesothelioma cases are reported, and each case probably had exposure to amphiboles, inaccurate diagnosis, and/or insufficient latency periods (Table 4). The levels of exposures in the studies do not differ substantially from those listed in Tables 1 and 2, given the limitations and heterogeneity of this data.

1. Asbestos Cement Materials

Asbestos cement workers have been exposed to chrysotile during the manufacturing process. One case of mesothelioma was found among 2363 chrysotile-only workers having 20 or more years of latency at a particular building (within Plant 2) in the New Orleans area. From 1927 until 1970, this man was continuously assigned to work in the shingle production area (chrysotile) only, according to his job record. However, the pipe production building was in the same plant where 7 cases of mesothelioma were diagnosed among 1231 subjects using crocidolite additionally (Hughes et al., 1987) and the locale was contaminated with plant asbestos waste (U.S. EPA Region 6 news release, 6/25/1998). At the Tamworth plant in England having 2167 workers in the cohort, 1 mesothelioma was reported, but the authors indicated that it was unlikely to be related to chrysotile because of the short latency in this case (Gardner et al., 1986) From Sweden, a cohort of 1176 workers having 27,000 person-years of follow-up did not have any mesothelioma cases.

TABLE 3

Characteristics of Cohort Studies Where No Amphibole Exposure Was Identified[a]

Authors, year	Study	Number of mesotheliomas	Number of subjects	Person-yrs (k)	Estimated Exposure Level	Process	Timeframe
Acheson et al., 1982	Blackburn	1	628	>14	—	G	1939–1980
Browne and Smither, 1983	Cape Factory E	0	15,000 approx.	—	—	T,F	1902–1980
Cheng et al., 1992	Tianjin	0	1172	17.6	12–167 mg/m^3 in 1964	F,C,T	1949–1985
Finkelstein, 1989b	Ontario	1	324	—	—	F	1929–1974
Gaensler et al., 1988	Mass. Plant B	0	67	—	<2 f/ml after 1971	O	1961–1988
Gardner et al., 1986	Tamworth	1	2167	—	<1f/ml after 1970	C	1931–1984
Hughes et al., 1987	New Orleans	1	2363	—	22 f/ml-yr; 7.5 mppft	O	1927–1982
Kogan et al., 1993	USSR	0	299	—	18.3 mg/m^3 dust max.	F	1949–1988
McDonald et al., 1984	Connecticut	0	3641	—	46 f/ml-yr; up to 13.4 mppft	F	1905–1977
Ohlson et al., 1985	Swedish ACM	0	1176	27	15 f/ml-yr (subcohort 18 f/ml-yr); 2 f/ml	C	1943–1982
Szeszenia-Dabrowska et al., 1988a; Wilczynska et al., 1996	Lodz, Poland	0	2175 men	19.3	8 f/ml ave. max. in 1990	F,C,T	1945–1985
Szeszenia-Dabrowska et al., 1988b	Lodz, Poland	1	1190 women	10.5	8 f/ml ave. max. in 1990	F,C,T	1945–1985
Weiss, 1977	Weiss	0	264	7	<2 f/ml after 1972	O	1896–1974
Yano et al., 2001[a]	Chongqin	2	515	11.5	5-58 f/ml in 1999	T,C,F	1939–1996
14 cohorts		7	Approx. 32,039				

Note. See Table 5 for explanations of symbols.

[a] Amphibole contamination possible for this cohort.

TABLE 4

Mesothelioma cases in cohort studies where no amphibole exposure was identified

Authors, year	Number of mesotheliomas	Discussion
Acheson et al., 1982	1	Individual had also worked in crocidolite gas mask plant.
Finkelstein, 1989b	1	A beater operator whose death in 1958 was attributed to pleural mesothelioma, but the latency was 13 years and "it was not possible to confirm the diagnosis."
Gardner et al., 1986	1	Worker died within 7 years of hiring date and "death . . . is unlikely to be related to this employment."
Hughes et al., 1987	1	Case was long-term worker (43 yrs) in same plant where crocidolite was used.
Szeszenia-Dabrowska et al., 1988b	1	Peritoneal mesothelioma reported on death certificate is unconfirmed by tissue examination, and no job history, exposure or latency data are provided. Pleural mesotheliomas are lacking in plant's cohorts.
Yano et al., 2001	2	Short latencies (13.8 and 21.8 yrs) noted for these cases, and literature review indicates amphibole contaminants in Chinese chrysotile.

Although they represent less than 1% of all asbestos, 400 tons of crocidolite and 630 tons of amosite were used in 1962 and between 1949 and 1951, respectively. A subcohort of 125 workers had average cumulative exposure of 18 f/ml-yr (Ohlson and Hogstedt, 1985).

2. Factories

A study of several factories of Cape Industries Ltd. was published in 1983. No mesothelioma cases were found among approximately 15,000 subjects of one large factory (Factory E) that started operations in 1902 and used chrysotile solely for producing textiles, insulation and friction materials (Browne and Smither, 1983). A cohort of 3641 men in a Connecticut packings plant is considered as exposed only to chrysotile asbestos. Chrysotile was the only type of asbestos used until 1957, when anthophyllite was added to some product lines, and approximately 400 pounds of crocidolite was used experimentally in the laboratory between 1964 and 1972. The cumulative exposure level for chrysotile was relatively high for this cohort at 46 f/ml-yr. No mesothelioma related to work at this plant was

TABLE 5
Notes and legend for Tables 1–3, which are based in part on Hodgson and Darnton (2000) and Smailyte et al. (2004)

Fiber types
  o: crocidolite
  a: amosite
  y: chrysotile
  l: Libby amphibole
  c: cummingtonite-grunerite
  n: anthophyllite
  b: balangeroite
Exposure metrics and settings
  Person-yrs (K): person-years (in thousands)
  f/ml-yr: fibers per milliliter-years
  mppft: million particles per cubic foot of air
  mg/m^3: milligrams per cubic meter
  M: mining and milling
  I: insulation manufacturing
  T: textile
  C: asbestos cement
  F: factory (various products, or inadequately specified)
  G: gas-mask manufacturing
  L: laggers and other work with insulation
  S: shipyard
  O: other
Notes
  approx.: approximate
  ave.: average
  max.: maximum
  est.: estimate
  SA: South African
  —: not reported

found on the death certificates collected for the study (McDonald et al., 1984; Hodgson and Darnton, 2000). Two mesothelioma cases were nevertheless identified for this cohort by reviewing the state's tumor registry and city directories. Both cases were women who were clerical workers but had confirmed peritoneal and possible pleural mesothelioma, respectively (Teta et al., 1986; McDonald, 1986; Berman and Crump, 2003, pp. 3–13, 3–14). No cases of mesothelioma were reported in a retrospective mortality cohort study of 1172 chrysotile asbestos product workers (17,600 person-years) in Tianjin, China, from 1972 to 1987 (Cheng and Kong, 1992). Researchers followed a cohort of 2175 male workers at an asbestos factory in Lodz, Poland, producing packings, gaskets, needled cloth, yarn, cords, asbestos-rubber cardboards, and friction products, but no cases of mesothelioma were reported in the 1988 update, although one case was subsequently found in a man who had insignificant exposure at the plant. For the cohort of 1190 women who were employed at this Lodz plant, one peritoneal mesothelioma case is reported on a death certificate, but no details on her job history, estimated exposures, or latency period are provided (Szeszenia-Dabrowska et al., 1988a, 1988b; Wilcznska at al., 1996). Raw asbestos was imported by Poland after World War II mainly from the former Soviet Union (chrysotile) and Africa (crocidolite, amosite) (Foltyn, 2000). The maximum average asbestos dust level in Poland in 1990 was reported as 8 f/ml (Dobrovolsky, 1998). Differential diagnosis between this tumor and both serous papillary carcinoma of the peritoneum and ovary can be problematic, and the results of a panel of antibodies (which were unavailable for most of the Polish study's timeframe) should be interpreted to set the diagnosis, especially since peritoneal mesotheliomas have not been convincingly related to chrysotile exposure (National Academy of Sciences, 1984; Doll and Peto, 1985; Smith and Wright, 1996; Roggli et al., 1997; Sporn and Roggli, 2004; Markaki et al., 2005). A 20-year study in a shop in the Ural Mountains (USSR) where chrysotile dust predominated in the making of friction products observed no mesothelioma cases (Kogan et al., 1993), yet regional workers' lung samples revealed amphiboles (Kashansky et al., 2001). A study of a partial cohort of workers of a plant in Cornwall, Ontario, that manufactured fiber conduit from 1929 until 1982 identified one mesothelioma. Exposures to chrysotile asbestos (and coal tar pitch) until 1974 are reported, but no air sampling or dust measurement was ever done at the plant (Finkelstein, 1989b).

3. Chongqin and Other Chinese Plants

A study evaluated lung cancer and mesothelioma in a cohort of workers in an asbestos plant in Chongqin, China. Dust analysis indicated that a "virtually pure form of chrysotile asbestos" (i.e., the concentration of amphiboles was reportedly below the limit of detection at that particular laboratory) was used extensively throughout the plant obtained from two mines in the Sichuan province (Yano et al., 2001; Tossavainen et al., 2001). However, the authors' conclusion that there was no

detectable amphibole contamination rests solely on an unpublished analysis performed by a colleague in Japan in 2000 of four commercial samples from those mines and referenced in the paper as a personal communication. The plant in Chongqin opened in 1939 and expanded operations in 1958. The geometric mean of asbestos fiber exposures was reported in 1999 to be 12.6 f/ml, and the authors presumed that they were higher in the past as handling practices have improved over time. Two cases of pathologically confirmed mesothelioma, 1 pleural and the other peritoneal, were diagnosed among this cohort. The latencies were 13.8 and 21.8 years, respectively, which would be unusually short time periods for the induction of mesothelioma (Weill et al., 2004). Amphibole contamination of chrysotile particularly with tremolite and anthophyllite is known to exist throughout China, including in Sichuan province, which is where the plant studied by Yano et al. (2001) exclusively obtained chrysotile asbestos. Reviews of studies on asbestos in China point out the diagnostic problems as well as the presence of amphiboles in that country (Tossavainen et al., 2001; Cai et al., 2001; Berman and Crump, 2003, p. 3–3). A mortality study for a plant in Qingdao of 530 workers using Chinese and Canadian chrysotile (and thus tremolite contamination presumably) does not report any mesotheliomas without specifically stating an absence of cases (Pang et al., 1997). Conclusions of the studies from China are difficult to draw not only due to the low number of cases (some with short latency), probable amphibole contamination of asbestos exposures, lack of complete occupational histories for the cases, incomplete or unconfirmed outcomes data, and lack of lung fiber analyses, but also due to written language barriers such as lack of translations from Chinese to English, mismatching and misnumbering of references, lack of peer-review publication, and limited data in summary tables (Cai et al., 2001; Li et al., 2004).

4. Italy

In the Piedmont region of Italy, a historical cohort in Grugliasco (just outside of Turin) comprised of 1653 workers of an asbestos textile plant operating from 1900 until 1986 was reportedly exposed heavily "to pure chrysotile asbestos alone, with negligible amphibole contamination." Statistically significant excesses in overall mortality, asbestosis, cardiovascular diseases, and multiple cancers including mesothelioma in men and women are reported in a preconference abstract without giving the actual number of cases (Mamo and Costa, 2004), but PubMed had not cited the publication of this work at press time.

5. Other Cohorts

Among 306 workers in a chrysotile paper manufacturing plant that participated in a study, no cases of mesothelioma, asbestosis, or lung cancer were found among the 67 workers who were followed for 15 to 27 years after asbestos was

first used in the plant (Gaensler and Goff, 1988). A 30-year historical cohort mortality study was made of 264 men hired during 1935–1945 providing 7000 person-years of follow-up. They worked in a chrysotile asbestos products factory. Two men died of asbestosis, but no case of mesothelioma was reported (Weiss, 1977). Mesothelioma has not been found in South African chrysotile miners and millers despite decades of producing about 100,000 tons of the mineral per year. The contention of the study's authors was that South African chrysotile is not heavily contaminated by tremolite or other amphiboles (Rees et al., 2001). Of 570 Blackburn workers making chrysotile gas masks, one case of mesothelioma was observed. However, the authors state that this employee worked also at another Blackburn plant that used crocidolite (Acheson et al., 1982).

6. Comments on Cases

Some published reports of mesothelioma cases have discussed potential exposures to chrysotile. In a multicentered case-control study of 123 mesothelioma patients in South Africa, no case with a history of chrysotile mining was identified, and there was no case involving exclusively environmental exposure to chrysotile (Rees et al., 1999). A case series from Zimbabwe describes 3 mesothelioma cases among 51 workers who worked for some time in an asbestos mining or manufacturing facility and certified subsequently for compensation for lung disorders. Twenty-seven claimants had suspected asbestos-related illnesses. Three cases were noted to have mesothelioma based on "best evidence." One died in 1987 having a pleural mass but no tissue to examine; for another, vital status was unknown but the person had a biopsy; and the third was a manager who had a postmortem examination in 1954 but worked in an asbestos plant from 1951 to 1952. Due to the extent of asbestos-related disease, the authors expressed a concern of the hazard of locally mined chrysotile asbestos (Cullen and Baloyi, 1991). Excluded from consideration was that standard chrysotile from Zimbabwe contains 2% fibrous anthophyllite, a regulated amphibole, as an impurity (Kohyama et al., 1996). Six cases of asbestos-related disease, including two mesothelioma cases, were reported in railway men in Rhodesia (now Zimbabwe), a chrysotile mining region that coincidentally supplied the South Carolina textile plant. However, a careful review indicates that they were exposed also to nonlocally mined amphibole (Mostert and Meintjes, 1979). A case series report comes from the former East Germany in which the authors state that 67 cases of 812 mesothelioma patients (8.25%) were due to exposure only to Russian chrysotile (Sturm et al., 1994). Countering the notion that asbestos from Russia was only chrysotile as suggested by airborne dust analyses (Kashansky et al., 2001), a lung tissue study of workers in the Russian chrysotile industry located in the area of the world's largest asbestos mine, at Asbest in the Ural Mountains, was published 6 years later. This pathology study showed that about 5% of all mineral fibers were amphiboles, ranging from 2% in chrysotile millers and users, to 9%

in miners. No mesothelioma cases had been observed in Russia (Dobrovolsky, 1998). The pattern of lung chrysotile fibers in workers of the mine in Asbest, Russia, was about the same as reported earlier from the Canadian mining and milling industry (Tossavainen et al., 2000). Their results are similar to those for Brazilian chrysotile workers (Case et al., 2002b).

V. DISCUSSION

A. Epidemiological Findings of Cohorts

Chrysotile exposures without identified amphibole fibers do not appear to increase the risk of being diagnosed with mesothelioma based on the results of epidemiological cohort studies of over 220,000 individuals. The 7 cases of mesothelioma reported in the 71 cohort studies (i.e., from baseline, well-defined populations) where no amphibole exposures were identified are summarized in Table 4. However, careful review of these few cases illustrate that their exposures were likely mixed, the diagnosis questionable, and/or the latency period inadequate or unstated. This analysis has not identified a case of mesothelioma from the cohort studies that is definitely documented as solely exposed to raw chrysotile fibers uncontaminated by amphiboles. Morphological and recent toxicological evidence implicates balangeroite as an amphibole-acting contaminant; therefore the five cases reported from the Balangero asbestos mine are in Table 2.

Simply for illustrative purposes, among approximately 32,853 subjects exposed to amphiboles, 404 cases of mesothelioma (1.23%) were reported (Table 1), whereas only 7 cases (at most) were observed for 32,039 subjects exposed to chrysotile, or 0.04% (Table 3). Mixed fiber exposures resulted in an intermediate percentage of 0.67% for cases (994/147,384) (see Table 2). Clearly the trend is greatly slanted towards amphiboles, as found by other reviewers (Hodgson and Darnton, 2000; Berman and Crump, 2003). These latter two sets of cohort studies do not differ greatly when compared to those summarized in Table 1 in terms of time of follow-up, exposures levels, time frames of exposures, and diagnostic methods, so these factors cannot account for the paucity of mesothelioma cases in asbestos cohort studies where amphibole exposures were not identified.

As described earlier, a confounder is a factor or exposure associated with the disease and the exposure of interest. In order for confounding to substantially affect estimates of risk, the association of the potential confounder with disease must be stronger than the observed association between the exposure of interest and the disease. The relative potency of amphiboles in causing mesothelioma is very great relative to chrysotile, assuming chrysotile has any mesotheliogenic potency (ATSDR, 2003, pp. 94–95). From the data in Tables 1 and 2 herein, one can arrive at the same conclusion: The risk of mesothelioma is primarily if not solely from exposure to amphiboles.

Replication by well-designed, relevant studies for confirmation of hypotheses is absolutely necessary to establish an association. Consistency of results in different studies testing the same hypothesis was a guiding principle of the U.S. Surgeon General's report on smoking and health (Bayne-Jones, 1964). Replication is one of the bulwarks of the scientific method that helps distinguish true from false claims. Under its "criteria for causality" the World Health Organization (WHO) states that associations that are replicated are more likely to imply causality. To quote a criterion used by the WHO and International Agency for Cancer Research (IARC) for basing their opinions, "When several epidemiological studies show little or no indication between an exposure and cancer, the judgment may be made that, in the aggregate, they show evidence of lack of carcinogenicity" (IARC, 2000).

B. Tissue Fiber Studies as Indicators of Exposure

The analysis of human tissue for asbestos fibers is another area of continuing investigation, although there are many uncertainties associated with this approach of measuring bodily indicators of exposure (Pooley, 1976; Rogers, 1984; Gibbs et al., 1990; Srebro et al., 1995; De Vuyst et al., 1998; Roggli and Sharma, 2004). Quantification of exposure based on the retained fiber number is a relative index of (a) the fibers' ability to penetrate the alveoli of the lungs, and (b) the extent to which they are retained (Howard, 1984; Langer and Nolan, 1998). The analysis of tissues for asbestos focuses on the residual fiber population because the long, durable fibers are preferentially retained and chrysotile in the tissues has much less biopersistence. The long latency period for mesothelioma and new growth means that chrysotile fibers visible in pathological tissue specimens cannot be relevant to the induction of the malignancy. The range of tissue masses examined, the lack of information in terms of anatomical site, the possibility of contamination of specimens during necropsy and preparation, the lack of valid reference laboratory values for population groups rather than convenience case material (autopsies and lung cancer surgical samples), the lack of interlaboratory standardization for comparability purposes, and problems related to the number of fibers counted (e.g., short-fiber elimination bias and analytical sensitivity) are formidable laboratory challenges (Morgan and Holmes, 1983; Lee et al., 1995; De Vuyst et al., 1998). In general, asbestos fiber biomarkers in tissues can be used to confirm exposure to amphiboles (persistent fibers in the body) and chrysotile (probably more recent exposures for shorter fibers particularly).

In view of the many uncertainties, tissue fiber studies cannot be used in isolation to reach conclusions regarding causation. For example, asbestos fiber counts determined in the lung tissue and samples of tumor tissue and pleural plaques for mesothelioma cases at one institution suggested to the authors that chrysotile has a major causal role in mesothelioma, even if the fibers were short and very thin (Suzuki and Yuen, 2002; Suzuki et al., 2005). These short fibers are actually fine dust with no pathogenic effect, and their presence in malignant tissue is unexplained. Along with the lack of a comparison group for the case series, use of a nonstandard technique without controls, and possible asbestos fiber contamination of laboratory substances contacting

the samples, their contention that very short asbestos fibers (particles) cause mesothelioma is not supported by comprehensive analyses, such as that performed as part of the proposed methodology for a quantitative human risk assessment based on epidemiological studies by Berman and Crump (2003) and by an expert panel for the Agency for Toxic Substances and Disease Registry (ATSDR, 2003). In a video-thoracoscopic study of the "black spots" of the pleura, normal appearing pleura and lung tissue of 14 patients with various pulmonary diagnoses, including 3 patients with mesothelioma and 6 without a history of asbestos exposures, amphiboles outnumbered chrysotile fibers in all samples. These results contradict those of Suzuki and Yuen (Boutin et al., 1996). Based on a series of 1445 cases having analyses of lung asbestos fibers, other investigators concluded that commercial amphiboles are responsible for most of the mesothelioma in the United States (Roggli et al., 2002).

Estimating a risk of mesothelioma based on tissue fiber analyses has been attempted (McDonald et al., 1989; Rogers et al., 1991, 1994; McDonald, 1994; Dufresne et al., 1996; Rodelsperger et al., 1999). A study examined lung tissues from 78 Canadian men and women who died of mesothelioma, as well as 78 lung tissues from age-, sex-, and hospital-matched controls. The lung samples were from the pathologists' stock without information on what parts of the lung the samples were collected. Relative risks for developing mesothelioma are reported for different fiber types and lengths. The study found that the risk of mesothelioma was significantly related to concentrations of amphibole fibers longer than 8 μm and that fibers shorter than 8 μm accounted for none of the cancer risk (McDonald et al. 1989). Rogers et al. (1991) indicated that fibers less than 10 μm in length increased risk, but with reanalysis the authors corrected that earlier conclusion (Rogers et al., 1994).

The lung tissue was studied in Sweden for 76 deceased asbestos cement workers (7 with mesothelioma) who were exposed to chrysotile and small amounts of amphiboles and of 96 control subjects. While chrysotile was the main fiber found, the difference between the groups was most pronounced for amphiboles, and strong correlations were found between duration of exposure and with the content of amphiboles in the lungs. The percentage of chrysotile fibers was similar for cases, exposed control subjects, and nonexposed subjects (Albin et al., 1990b). As noted earlier, these researchers published an analytic epidemiology study to test the hypothesis about mesothelioma and asbestos exposures, which showed an increased risk of exposures of mixed asbestos fibers among the workers (Albin et al., 1990a).

C. Review Articles on Chrysotile as a Cause of Mesothelioma

Although the association of amphibole asbestos and mesothelioma is clear, the risk from chrysotile exposure has been studied and debated for many years (Browne, 1983; Howard, 1984; Huncharek, 1987; Mancuso, 1989a, 1989b; Churg and Green, 1990; Stayner et al., 1996; Smith and Wright, 1996;

Cullen, 1998; Landrigan, 1998; Camus and Siemiatycki, 1998; Osinubi et al., 2000; ATSDR, 2001; Hodgson and Darnton, 2001; Liddell, 2001, Berman and Crump, 2001, 2003; Britton, 2002; Marchevsky et al., 2003; Egilman et al., 2003; Sporn et al., 2004). Several pertinent reviews are discussed here.

In the final draft to the U.S. EPA of the proposed new method for risk analysis of airborne asbestos fibers, chrysotile is predicted to be 0.13% as potent as amphibole in causing mesothelioma (after adjusting for fiber size). The calculated potency factors are consistent with chrysotile not being associated with mesothelioma. Invited peer reviewers agreed unanimously that the epidemiology literature provides compelling evidence that amphibole fibers have far greater mesothelioma potency than do chrysotile fibers and that short fibers have little or no potency. The authors write on pages 7.49 and 7.50 of the report, "The data are consistent with the hypothesis that chrysotile has zero potency toward the induction of mesothelioma. . . . Moreover, the hypothesis that chrysotile and amphibole are equally potent in causing mesothelioma, the assumption inherent in the U.S. EPA (1986) asbestos document, is clearly rejected ($p = 0.0007$)" (Berman and Crump, 2003). Recent trend estimates for mesothelioma reinforce the concept that amphiboles pose for a greater risk of mesothelioma compared to chrysotile, if chrysotile has any risk (Weill et al., 2004).

Nicholson relied upon the U.S. EPA 1986 risk assessment to conclude that chrysotile is a potent cause of mesothelioma, having a risk that is similar to amosite on a per fiber basis, and that crocidolite has 4 to 10 times higher potency than the other two types (Nicholson, 2001). The final draft of the risk assessment done for the U.S. EPA by Berman and Crump (described earlier) derives more refined and updated results compared to the 1986 U.S. EPA model, one that had its most recent study being published in 1984. Berman and Crump calculated risk coefficients for chrysotile using five cohort studies with exposure quantification that Nicholson did not have in his paper. For chrysotile, Nicholson used the Rochdale cohort studied by Peto et al. (1985) for comparison, but Berman and Crump considered this study to be a mixed fiber cohort. The risk coefficient of Rochdale is approximately 100 times more than the risk coefficients calculated for chrysotile cohorts (see Tables 7–9 of Berman and Crump, 2003). Therefore Nicholson's direct calculation of mesothelioma risk is highly skewed toward that of amphiboles. In another quantified risk assessment, Hodgson and Darnton included 17 studies for mesothelioma exposure-specific risk estimates as opposed to 5 of Nicholson (Hodgson and Darnton, 2000). The new risk assessment model indicates that amphiboles have an optimized dose-response coefficient that is 750-fold higher compared to chrysotile (see Tables 7–18 and page 7.60 of Berman and Crump, 2003). In an effort to arrive at the potency of asbestos fiber types, Hodgson and Darnton (2000) performed a risk assessment focused on cohort studies having adequately quantified exposure data. They determined that the potency rankings for asbestos linked to mesothelioma

were in order of magnitude as follows: crocidolite > amosite > contaminated chrysotile.

Smith and Wright (1996) argued that calculations derived from asbestos cohort studies show that the carcinogenic potency of chrysotile is not less than that of crocidolite. They ranked 25 cohort studies having mesotheliomas by the number of pleural mesothelioma cases per 1000 deaths from any cause observed in each cohort. Proportions may generate hypotheses but are not a direct measure of association (Bayne-Jones, 1964). The low numbers of cases and deaths in most of the listed cohort studies result in much uncertainty of the values. For instance, if the foreman had recalled the two other workers' names of many years earlier who were also diagnosed with mesothelioma as having worked on the gas mask line of the plant, then the crude rate would substantially increase (3 cases becomes 5 of 56 members), and the cohort of McDonald and McDonald (1978) would have been ranked first rather than seventh. More important is using up-to-date results from cohort studies. Jones et al. (1996) updated the Nottingham cohort study of crocidolite gas mask workers in the paper of Smith and Wright 14 years later, the same year as their publication. There were 67 rather than 17 mesothelioma cases reported in the update. Of approximately 500 deaths noted in the updated report, 53 pleural mesotheliomas were observed resulting in 106.0 per 1,000 deaths, so this cohort would be at the top of their list. Similarly, use of figures of Berry et al. (2004) rather than Armstrong et al. (1988) results in top ranking for crocidolite miners and millers. Also, a cohort of workers making gas mask filters is not included (i.e., Gaensler and Goff, 1988). It is not clear why all deaths rather than cancer deaths are used for the calculations. Smith and Wright (1996) did not consider any quantification of exposures but concluded that chrysotile is similar in potency to amphiboles. Their approach is seriously flawed because a conclusion about relative risk of mesothelioma cannot be drawn from a simple ranking unless exposures have been measured, and they ignored small quantities of contaminating fiber types in some cohorts according to Hodgson and Darnton (2000).

Amphibole exposures occurred in America earlier than some authors surmise, which is important is judging potencies of asbestos fiber types. Nicholson analyzed the time course of mesothelioma risk using the 1986 U.S. EPA equation. His hypothesis that pure chrysotile exposure causes mesothelioma is based in part on presumptions about the amount of chrysotile asbestos consumed by the United States from the 1890s to 1930s. In analyses of U.S. insulators who were exposed to asbestos before 1935, several investigators reported that amosite was not used before that year. More specifically, some authors state that U.S. insulation workers were exposed to mixtures of chrysotile and amosite after 1940, but prior to 1937 their exposures was only to chrysotile, and until 1940, only occasionally to amosite (Nicholson and Landrigan, 1996; Stayner et al., 1996; Nicholson, 2001). Nicholson and Landrigan estimate the exposures to U.S. insulators have been 60% chrysotile and 40% amosite based on published product compositions. However,

the supposition that crocidolite exposure did not occur earlier for U.S. workers, especially among insulators, has been rejected based on fiber studies of lung tissue (Langer and Nolan, 1998).

Approval dates of the U.S. Navy do not mark the earliest onset of commercial amphibole exposures to any American workers. Asbestos insulation products date from 1866 and had been used and perfected for 8 decades by the close of World War II. The development of amosite felt started in 1934, and the U.S. Navy approved the type made by a specific manufacturer in September 1934 for turbine insulation only. Amosite was the Navy's predominant asbestos fiber. The Navy approved amosite pipe covering from 1937 until about 1971 (Fleischer et al., 1946; Rushworth, 2005). Actually, crocidolite and amosite were used in the United States through the 1920s, according to monthly issues of a trade journal during that time period (see Hodgson and Darnton, 2000). Both crocidolite and amosite were imported for manufacture of thermal insulation products from 1924 or earlier. After 1930, (at least) some of the 81 workers were exposed to crocidolite and all were exposed to amosite based on lung tissue results (Langer and Nolan, 1998), and similar results were seen in a cohort of chrysotile workers (Case et al., 2000).

D. Regulatory Decisions Concerning Chrysotile and Mesothelioma

Regulatory agencies look to research data to formulate rules, procedures, and regulations to support policy decisions. It is not always the case, however, that decisions by various organizations reflect the best or the latest assessment of the data or are based on the scientific method. The regulation of toxic and other substances is customarily divided into two discrete aspects: risk assessment and risk management. Risk assessment is a scientific activity, whereas risk management is always a sociopolitical one, and they are not necessarily separate. The process of risk assessment has been accepted as a necessary base on which to build rational policy decision making, and at the same time it provides an opportunity for improved dialogue for scientists to have an important role in shaping public policy that is scientifically defensible (Hughes and Weill, 1986; Mossman et al., 1990; Camus, 2001a; Savitz, 2003; U.S. EPA, 2004). In a special treatise for the Geological Society of America, calling for asbestos regulations based more on science, the authors state:

> The scientific and medical information available does not justify the claim that exposure to any amount of any fiber presents an unacceptable health risk. (Ross and Nolan, 2003)

In any regulatory context, the integration of administrative policies with risk assessment is a key concept used now by decision makers for the purpose of protecting health. Modern standard setting serves to minimize the exposure of workers, but also addresses technical and societal choices and decisions (Corn, 1992). The U.S. Occupational Safety and Health Administration (OSHA) must make a determination if a "significant" health risk exists and that a new standard will reduce or eliminate that risk (*Fed. Reg.* 51:22646, June 20, 1986). For its latest

standard setting, OSHA made no distinction for "asbestos" among the asbestos types and defined a "fiber" as one that possesses an aspect ratio of equal to or greater than 3:1. The basis for the OSHA permissible exposure limit (PEL) included epidemiological studies involving mixed-type asbestos exposures. Future uses of asbestos were thought likely to be mixed, so there was no practical need at that time to distinquish fiber types. OSHA requires fiber counts to be made using a phase-contrast microscope. Although the method is quick, easy, inexpensive, and detects low concentrations, it does not enable identification of fiber type. According to OSHA, assigning a higher PEL to chrysotile would present OSHA and employers with analytical difficulties in separately monitoring exposures to different fiber types (OSHA, 1994). Thus the presumption that all exposures would be to mixed fiber types and the use of phase-contrast microscopy to detect exposures prevented important distinctions to be made in the assessment of potential risk of different fiber types.

Referring to the U.S. Supreme Court's ruling in *Industrial Union Department, AFL-CIO v. American Petroleum Institute*, the following explanation of precautionary health regulations was provided in the OSHA asbestos standard. The U.S. Supreme Court indicated that a significant risk determination for federal health regulations is "not a mathematical straitjacket," and that "OSHA is not required to support its finding that a significant risk exists with anything approaching scientific certainty." The Court ruled that "a reviewing court [is] to give OSHA some leeway where its findings must be made on the frontiers of scientific knowledge [and that] . . . the Agency is free to use conservative assumptions in interpreting the data with respect to carcinogens, risking error on the side of over protection rather than under protection." The Court also stated that "while the Agency must support its finding that a certain level of risk exists with substantial evidence, we recognize that its determination that a particular level of risk is 'significant' will be based largely on policy considerations" (*Fed. Reg.* 51:22615, June 20, 1986).

Precaution provides a means of guiding decisions under conditions of uncertainty: "The precautionary principle encourages policy makers and public health officials to consider, in their approach to public health, how to account for growing complexicity and uncertainty" (WHO, 2004). Called conservatism in a recent staff paper of the U.S. EPA Office of the Science Advisor, the agency "seeks to adequately protect public and environmental health by *ensuring that risk is not likely to be underestimated*" [italics as in document] (U.S. EPA, 2004). The effect of the approach on the science of asbestos risk assessment is illustrated by an example from the U.S. EPA in 1986 when the risk assessors' choices tended to overestimate the final exposure risk gradient (Camus, 2001b). Precautionary-based measures should be maintained "as long as scientific data are inadequate, or inclusive, and as long as the risk is considered too high to be imposed on society" (Jordan and O'Riordan, 2004). According to Siemiatycki et al. (2004), lists of identified carcinogens have been limited by "unclear criteria" and "by inconsistent and

incomplete information" and provide no basis for strength of the effect. Determination of carcinogenic status can change as new data emerge. This review suggests that the application of the precautionary principle is no longer supported by the cohort epidemiological data for chrysotile absent amphiboles and mesothelioma (see Tables 3 and 4).

VI. CONCLUSIONS

The extensive scientific literature related to asbestos fiber types relevant to industry and mesothelioma was reviewed. Human exposures to various amphibole fiber types have been linked to mesothelioma, but this article concerns the hypothesis of the existence of a causal association of mesothelioma with exposure to chrysotile fibers without contamination with amphiboles. The following points are addressed:

1. The use of scientific method requires the development and testing of hypotheses.
2. Epidemiology tests hypotheses about exposures potentially toxic to humans. The results of these tests to date indicate:
   a. Epidemiological studies show amphiboles cause mesothelioma in humans.
   b. In workers exposed to both chrysotile and amphibole, there are fewer mesothelioma cases than in studies of amphiboles alone.
   c. Cases of mesothelioma in cohorts where no amphibole exposure was identified do not demonstrate chrysotile is the cause of mesothelioma.
3. Epidemiological review of cohorts does not support the hypothesis that exposures to chrysotile fibers, uncontaminated by amphiboles, cause mesothelioma.
4. As indicators of exposure to asbestos, fiber burden studies of mesothelioma cases can generate hypotheses. They cannot replace analytical epidemiology, which is required to assess better exposure–outcome associations and infer causation.
5. Patient reports, case series, and ecological surveys do not provide independent scientific evidence for chrysotile causing mesothelioma.
6. Regulatory decisions about chrysotile reflect policy and are based not only on scientific results and conclusions concerning mesothelioma.

Conclusions regarding causation of mesothelioma from chrysotile uncontaminated by identified amphiboles must be based on the application of the scientific method. Observations, hypothesis generation, hypothesis testing, and replication of results (i.e., the scientific method) are the accepted process steps for deriving conclusions about a theory. The basis for determining whether chrysotile asbestos causes mesothelioma should rest primarily on the results of analytic epidemiological studies. Most cohort studies that have been published have the potential for concomitant amphibole fiber exposures. Epidemiological studies investigating mesothelioma risk from exposures of cohort members to chrysotile asbestos fibers not known to be

contaminated with amphiboles do not justify a conclusion of causality at this time. Whenever mesothelioma cases have been observed in cohort studies, the presence of amphiboles has not been ruled out. Although the causal hypothesis has been studied intensively for cohorts primarily exposed to chrysotile, the number of mesotheliomas observed has been far fewer than those where amphibole exposures occurred, and the possibility of unidentified amphibole exposures remains in these few individual cases where only exposure to chrysotile asbestos was identified for the entire cohort. Hopefully, risk communications and public policy can be improved by thorough medical review of the literature of human studies spanning most of the last century.

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REFERENCES

Acheson, E.D., Gardner, M.J., Pippard, E.C., and Grime, L.P. (1982). Mortality of two groups of women who manufactured gas masks from chrysotile and crocidolite asbestos: A 40-year follow-up. *Br. J. Ind. Med.* **39:**344–348.

Acheson, E.D., Gardner, M.J., Winter, P.D., and Bennett, C. (1984). Cancer in a factory using amosite asbestos. *Int. J. Epidemiol.* **13:**3–10.

Agency for Toxic Substances and Disease Registry. (2001). Toxicological profile for asbestos. Atlanta, GA: U.S. Department of Health and Human Services.

Agency for Toxic Substances and Disease Registry. (2003). Report on the expert panel on health effects of asbestos and synthetic vitreous fibers: the influence of fiber length. Atlanta, GA: Agency for Toxic Substances and Disease Registry, Division of Health Assessment and Consultation.

Albin, M., Jakobsson, K., Attewell, R., Johansson, L., and Welinder, H. (1990a). Mortality and cancer morbidity in cohorts of asbestos cement workers and referents. *Br. J. Ind. Med.* **47:**602–610.

Albin, M., Johansson, L., Pooley, F.D., Jakobsson, K., Attewell, R., and Mitha, R. (1990b). Mineral fibres, fibrosis, and asbestos bodies in lung tissue from deceased asbestos cement workers. *Br. J. Ind. Med.* **47:**767–774.

Alies-Patin, A.M., and Valleron, A.J. (1985). Mortality of workers in a French asbestos cement factory 1940–82. *Br. J. Ind. Med.* **42:**219–225.

Amandus, H.E., and Wheeler, R. (1987). The morbidity and mortality of vermiculite miners and millers exposed to tremolite-actinolite: Part II. Mortality. *Am. J. Ind. Med.* **11:**15–26.

Armstrong, B.K., De Klerk, N.H., Musk, A.W., and Hobbs, M.S.T. (1988). Mortality in miners and millers of crocidolite in Western Australia. *Br. J. Ind. Med.* **45:**5–13.

Attanoos, R.L., and Gibbs, A.R. (2003). "Pseudomesotheliomatous" carcinomas of the pleura: A 10-year analysis of cases from the Environmental Lung Disease Research Group, Cardiff. *Histopathology* **43:**444–452.

Baris, Y.I., Bilir, N., Artvinli, M., Sahin, A.A., Kalyoncu, F., and Sebastien, P. (1988). An epidemiologic study in an Anatolian village environmentally exposed to tremolite asbestos. *Br. J. Ind. Med.* **45:**838–840.

Battista, G., Belli, S., Comba, P., Fiumalbi, C., Grignoli, M., Loi, F., et al. (1999). Mortality due to asbestos-related causes among railway carriage construction and repair workers. *Occup. Med. (Lond.)* **49:**536–539.

Bayne-Jones, S. (1964). The Surgeon General's Advisory Committee on Smoking and Health. Washington, DC: U.S. Department of Health, Education, and Welfare. Report No.: No. 1103.

Berman, D.W., and Crump, K.S. (2001). Assessing asbestos-related risk: New thinking/new protocol. 2001 Asbestos Health Effects Conference, Oakland, CA.

Berman, D.W., and Crump, K.S. (2003). Final draft: Technical support document for a protocol to assess asbestos-related risk. Washington, DC: Prepared for Office of Solid Waste and Emergency Response, U.S. Environmental Protection Agency.

Bernstein, D.M., Chevalier, J., and Smith, P. (2003). Comparison of Calidria chrysotile asbestos to pure tremolite: Inhalation biopersistence and histopathology following short-term exposure. *Inhal. Toxicol.* **15:**1387–1419.

Bernstein, D.M., Rogers, R., and Smith, P. (2005a). The biopersistence of Canadian asbestos following inhalation: Final results through 1 year after cessation of exposure. *Inhal. Toxicol.* **17:**1–14.

Bernstein, D.M., Chevalier, J., and Smith, P. (2005b). Comparison of Calidria chrysotile asbestos to pure tremolite: Final results of the inhalation biopersistence and histopathology examination following short-term exposure. *Inhal. Toxicol.* **17:**427–449.

Berry, G., and Newhouse, M.L. (1983). Mortality of workers manufacturing friction materials using asbestos. *Br. J. Ind. Med.* **40:**1–7.

Berry, G., de Klerk, N.H., Reid, A., Ambrosini, G.L., Fritschi, L., Olsen, N.J., et al. (2004). Malignant pleural and peritoneal mesotheliomas in former miners and millers of crocidolite at Wittenoom, Western Australia. *Occup. Environ. Med.* **61:**e14.

Boutin, C., Dumortier, P., Rey, F., Viallat, J.R., and De Vuyst, P. (1996). Black spots concentrate oncogenic asbestos fibers in the parietal pleura. Thoracoscopic and mineralogic study. *Am. J. Respir. Crit. Care Med.* **153:**444–449.

Brent, R.L. (2004). Utilization of animal studies to determine the effects and human risks of environmental toxicants (drugs, chemicals, and physical agents). *Pediatrics* **113:**984–995.

Britton, M. (2002). The epidemiology of mesothelioma. *Semin. Oncol.* **29:**18–25.

Browne, K. (1983). The epidemiology of mesothelioma. *J. Soc. Occup. Med.* **33:**190–194.

Browne, K. (2001). The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. *Ann. Occup. Hyg.* **45:**327–329.

Browne, K., and Smither, W.J. (1983). Asbestos-related mesothelioma: Factors discriminating between pleural and peritoneal sites. *Br. J. Ind. Med.* **40:**145–152.

Bueno, R., Reblando, J., Glickman, J., Jaklitsch, M.T., Lukanich, J.M., and Sugarbaker, D.J. (2005). Pleural biopsy: A reliable method for determining the diagnosis but not subtype in mesothelioma. *Ann. Thorac. Surg.* **78:**1774–1776.

Cai, S.X., Zhang, C.H., Zhang, X., and Morinaga, K. (2001). Epidemiology of occupational asbestos-related diseases in China. *Ind. Health* **39:**75–83.

Camus, M. (2001a). A ban on asbestos must be based on a comparative risk assessment. *Can. Med. Asso. J.* **164:**491–494.

Camus, M. (2001b). Do risk assessments justify banning chrysotile or not? *Can. Mineral Spec. Publ.* **5:**227–238.

Camus, M., and Siemiatycki, J. (1998). Correspondence. *N. Engl. J. Med.* **339:**999–1002.

Camus, M., Siemiatycki, J., Case, B.W., and Desy, M. (2002). Risk of mesothelioma among women living near chrysotile mines versus US EPA asbestos risk model: Prelimanry findings. *Ann. Occup. Hyg.* **46:**95–98.

Case, B.W. (1994). Biological indicators of chrysotile exposure. *Ann. Occup. Hyg.* **38:**503–518, abstract 410–411.

Case, B.W., and Sebastien, P. (1987). Environmental and occupational exposures to chrysotile asbestos: A comparative microanalytic study. *Arch. Environ. Health* **42:**185–191.

Case, B.W., Dufresne, A., McDonald, A.D., McDonald, J.C., and Sebastien, P. (2000). Asbestos fiber type and length in lungs of chrysotile textile and production workers: Fibers longer than 18 microns. *Inhal. Toxicol.* **12:**411–418.

Case, B.W., Camus, M., Richardson, L., Parent, M.E., Desy, M., and Siemiatycki, J. (2002a). Preliminary findings for pleural mesothelioma among women in the Quebec chrysotile mining regions. *Ann. Occup. Hyg.* **46:**128–131.

Case, B.W., Dufresne, A., Bagatin, E., and Capelozzi, V.L. (2002b). Lung-retained fibre content in Brazilian chrysotile workers. *Ann. Occup. Hyg.* **46:**144–149.

Cheng, W.N., and Kong, J. (1992). A retrospective mortality cohort study of chrysotile asbestos products workers in Tianjin 1972–1987. *Environ. Res.* **59:**271–278.

Churg, A. (1998). Nonoccupational exposure to chrysotile asbestos and the risk of lung cancer. *N. Engl. J. Med.* **339:**999; author reply 1001–1002.

Churg, A., and Green, F. (1990). Re: Mesothelioma in railroad machinists. *Am. J. Ind. Med.* **17:**523–530.

Churg, A., Wright, J.L., and Vedal, S. (1993). Fiber burden and patterns of asbestos-related disease in chrysotile miners and millers. *Am. Rev. Respir. Dis.* **148:**25–31.

Cohen, H. (1950). Harvey and the scientific method. *Br. Med. J.* **23:**1405–1410.

Constantopoulos, S.H., Malamou-Mitsi, V.D., Goudevenos, J.A., Papathanasiou, M.P., Pavlidis, N.A., and Papadimitriou, C.S. (1987). High incidence of malignant pleural mesothelioma in neighboring villages of northwestern Greece. *Respiration* **51:**266–271.

Corn, J.K. (1992). *Response to Occupational Health Hazards: A Historical Perspective.* New York: Van Nostrand Reinhold.

Cullen, M.R. (1998). Chrysotile asbestos: Enough is enough. *Lancet* **351:**1377–1378.

Cullen, M.R., and Baloyi, R.S. (1991). Chrysotile asbestos and health in Zimbabwe: I. Analysis of miners and millers compensated for asbestos-related diseases since independence (1980). *Am. J. Ind. Med.* **19:**161–169.

Dement, J.M., Brown, D.P., and Okun, A. (1994). Follow-up study of chrysotile asbestos textile workers: Cohort mortality and case-control analyses. *Am. J. Ind. Med.* **26:**431–447.

De Vuyst, P., Karjalainen, A., Dumortier, P., Pairon, J.C., Monso, E., Brochard, P., et al. (1998). Guidelines for mineral fibre analyses in biological samples: Report of the ERS Working Group. European Respiratory Society. *Eur. Respir. J.* **11:**1416–1426.

Dobrovolsky, L. (1998). Asbestos in the countries of central and eastern Europe. *Indoor Built Environ.* **7:**122–123.

Doll, R., and Peto, J. (1981). *The Causes of Cancer: Quantitative Estimates of Avoidable Risks of Cancer in the United States Today.* Oxford: Oxford University Press.

Doll, R., and Peto, J. (1985). Asbestos: Effects on health of exposure to asbestos. Health & Safety Commission, London.

Dufresne, A., Begin, R., Churg, A., and Masse, S. (1996). Mineral fiber content of lungs in patients with mesothelioma seeking compensation in Quebec. *Am. J. Respir. Crit. Care Med.* **153:**711–718.

Egilman, D., Fehnel, C., and Bohme, S.R. (2003). Exposing the "myth" of ABC, "anything but chrysotile": A critique of the Canadian asbestos mining industry and McGill University chrysotile studies. *Am. J. Ind. Med.* **44:**540–557.

Elmes, P. (1994). Mesotheliomas and chrysotile. *Ann. Occup. Hyg.* **38:**547–553, 415.

Elmes, P.C., and Simpson, M.J.C. (1977). Insulation workers in Belfast. A further study of mortality due to asbestos exposure (1940–75). *Br. J. Ind. Med.* **34:**174–180.

Enterline, P.E., Hartley, J., and Henderson, V. (1987). Asbestos and cancer: A cohort followed up to death. *Br. J. Ind. Med.* **44:**396–401.

Falini, G., Foresti, E., Gazzano, M., et al. (2004). Tubular-shaped stoichiometric chrysotile nanocrystals. *Chem. Eur. J.* **10:**3043–3049.

Fattman, C.L., Chu, C.T., and Oury, T.D. (2004). Experimental models of asbestos-related diseases. In Roggli, V.L., ed., *Pathology of Asbestos-Associated Diseases*, New York: Springer. Chapter 10.

Feyerabend, P.K. (1981). *Realism, Rationalism & Scientific Method* (Philosophical Papers, vol. 1). Cambridge: Cambridge University Press.

Finkelstein, M.M. (1984). Mortality among employees of an Ontario asbestos-cement factory. *Am. Rev. Respir. Dis.* **129:**754–761.

Finkelstein, M.M. (1989a). Mortality among employees of an Ontario factory manufacturing insulation materials from amosite asbestos. *Am. J. Ind. Med.* **15:**477–481.

Finkelstein, M.M. (1989b). Mortality among employees of an Ontario factory that manufactured construction materials using chrysotile asbestos and coal tar pitch. *Am. J. Ind. Med.* **16:**281–287.

Finkelstein, M.M., and Dufresne, A. (1999). Inferences on the kinetics of asbestos deposition and clearance among chrysotile miners and millers. *Am. J. Ind. Med.* **35:**401–412.

Fleischer, W.E., Viles, F.J., Gade, R.L., and Drinker, P. (1946). A health survey of pipe covering operations in constucting naval vessels. *J. Ind. Hyg. Toxciol.* **28:**9–16.

Foltyn, M. (2000). The problem of asbestos in Poland as seen by labour inspectors. ECOHSE 2000 Symposium, Kaunas, Lithuania (4–7 October 2000). Accessed on May 9, 2005, at www.gla.ac.uk/ecohse/2000papers/foltyn.pdf

Frank, A.L., Dodson, R.F., and Williams, M.G. (1998). Carcinogenic implications of the lack of tremolite in UICC reference chrysotile. *Am. J. Ind. Med.* **34:**314–317.

Fraser, D.W. (1987). Epidemiology as a liberal art. *N. Engl. J. Med.* **316:**309–314.

Gaensler, E.A., and Goff, A.M. (1988). Asbestos-related disease in crocidolite and chrysotile filter paper plants. In: *ILO Proceedings of the VIIth International Pneumoconioses Conference, Part I; 1988: NIOSH*, pp. 397–401.

Gardner, M.J., Winter, P.D., Pannett, B., and Powell, C.A. (1986). Follow up study of workers manufacturing chrysotile asbestos cement products. *Br. J. Ind. Med.* **43:**726–732.

Germani, D., Belli, S., Bruno, C., Grignoli, M., Nesti, M., Pirastu, R., and Comba, P. (1999). Cohort mortality study of women compensated for asbestosis in Italy. *Am. J. Ind. Med.* **36:**129–134.

Gibbs, A.R., Griffiths, D.M., Pooley, F.D., and Jones, J.S. (1990). Comparison of fibre types and size distributions in lung tissues of paraoccupational and occupational cases of malignant mesothelioma. *Br. J. Ind. Med.* **47:**621–626.

Grazzano, E., Riganti, C., Tomatis, M., Turci, F., Bosia, A., Fubini, B., and Ghigo D. (2005). Potential toxicity of nonregulated asbestiform minerals: Balangeroite from the Western Alps. Part 3: Depletion of antioxidant defenses. *J. Toxicol. Environ. Health A* **68:**41–49.

Green, F.H., Harley, R., Vallyathan, V., Althouse, R., Fick, G., Dement, J., et al. (1997). Exposure and mineralogical correlates of pulmonary fibrosis in chrysotile asbestos workers. *Occup. Environ. Med.* **54:**549–559.

Greenberg, M. (2005). The art of perpetuating a public health hazard. *J. Occup. Environ. Med.* **47:**137–144.

Groppo, C., Tomatis, M., Turci, F., Gazzano, E., Ghigo, D., Compagnoni, R., and Fubini, B. (2005). Potential toxicity of non-regulated asbestiform minerals: Balangeroite from the Western Alps. Part 1: Identification and characterization. *J. Toxicol. Environ. Health A* **68:**1–19.

Henderson, V.L., and Enterline, P.E. (1979). Asbestos exposure: Factors associated with excess cancer and respiratory disease mortality. *Ann. NY Acad. Sci.* **330:**117–126.

Hill, A.B. (1965). The environment and disease: Association or causation? *Proc. R. Soc. Med.* **58:**295–300.

Hillerdal, G. (1999). Mesothelioma: Cases associated with non-occupational and low dose exposures. *Occup. Environ. Med.* **56:**505–513.

Hillerdal, G. (2004). Mesothelioma. In: *Pleural Disease*, Chapter 28, Bouros, D., ed. Marcel Dekker, New York.

Hilt, B., Rosenberg, J., and Langard, S. (1981). Occurrence of cancer in a small cohort of asbestos-exposed workers. *Scand. J. Work Environ. Health* **7:**185–189.

Hodgson, J.T., and Darnton, A. (2000). The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. *Ann. Occup. Hyg.* **44:**565–601.

Hodgson, J., and Darnton, A. (2001). The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure: Asbestos and cancer. *Ann. Occup. Hyg.* **45:**336–338.

Howard, J.K. (1984). Relative cancer risks from exposure to different asbestos fibre types. *N. Z. Med. J.* **97:**646–649.

Hubbard, R. (1997). The aetiology of mesothelioma: Are risk factors other than asbestos exposure important? *Thorax* **52:**496–497.

Hughes, J.M., and Weill, H. (1986). Asbestos exposure—quantitative assessment of risk. *Am. Rev. Respir. Dis.* **133:**5–13.

Hughes, J.M., Weill, H., and Hammad, Y.Y. (1987). Mortality of workers employed in two asbestos cement manufacturing plants. *Br. J. Ind. Med.* **44:**161–174.

Huncharek, M. (1987). Chrysotile asbestos exposure and mesothelioma. *Br. J. Ind. Med.* **44:**287–288.

Ilgren, E.B., and Wagner, J.C. (1991). Background incidence of mesothelioma: Animal and human evidence. *Regul. Toxicol. Pharmacol.* **13:**133–149.

International Agency for Research on Cancer. (2000). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Ionizing Radiation, Part 1: X- and Gamma(γ)-Radiation, and Neutrons.* Lyon, France.

Irani, K.D. (1971). The evolution of scientific method in medicine. *Mt. Sinai J. Med.* **38:**450–456.

Jarvholm, B., and Sanden, A. (1998). Lung cancer and mesothelioma in the pleural and peritoneum among Swedish insulation workers. *Occup. Environ. Med.* **55:**766–770.

Jones, J.S. (2001). The pleura in health and disease. *Lung* **179:**397–413.

Jones, J.S., Pooley, F.D., and Smith, P.G. (1976). Factory populations exposed to crocidolite asbestos—A continuing survey. *IARC Sci. Publ.* 117–120.

Jones, J.S.P., Gibbs, A.R., McDonald, J.C., and Pooley, F. (1996). Mesothelioma following exposure to crocidolite (blue asbestos). A 50 year follow up study. In: *Proceedings of Second International Congress on Lung Cancer*. Bologna, Italy: Monduzzi Editore SpA, pp. 407–411.

Jordan, A., and O'Riordan, T. (2004). The precautionary principle: Legal and policy history. In: Martuzzi, M., and Tickner, J.A., ed., *The Precautionary Principle: Protecting Public Health, the Environment and the Future of Our Children*, Chapter 3. Copenhagen: World Health Organization Regional Office for Europe.

Kashansky, S.V., Domnin, S.G., Kochelayev, V.A., Monakhov, D.D., and Kogan, F.M. (2001). Retrospective view of airborne dust levels in workplace of a chrysotile mine in Ural, Russia. *Ind. Health* **39:**51–56.

Kogan, P.M., Yatsenko, A.S., Tregubov, E.S., Gurvich, E.B., and Kuzina, L.E. (1993). Evaluation of carcinogenic risk in friction product workers. *Med. Lav.* **84:**290–296.

Kohyama, N., Shinohara, Y., and Suzuki, Y. (1996). Mineral phases and some reexamined characteristics of the International Union Against Cancer standard asbestos samples. *Am. J. Ind. Med.* **30:**515–528.

Kolonel, L.N., Hirohata, T., Chappell, B.V., Viola, F.V., and Harris, D.E. (1980). Cancer mortality in naval shipyard workers in Hawaii: Early findings. *JNCI* **64:**739–743.

Kolonel, L.N., Yoshizawa, C.N., Hirohata, T., and Myers, B.C. (1985). Cancer occurence in shipyard workers exposed to asbestos in Hawaii. *Cancer Res.* **45:**3924–3928.

Kumzerov, Y.A., Parfen'eva, L.S., Smirnov, I.A., Misiorek, H., Mucha, J., and Jezowski, A. (2003). Thermal conductivity of chrystalline chrysotile asbestos. *Phys. Solid State* **45:**56–59.

Lacquet, L.M., van der Linden, L., and LePoutre, J. (1980). Roengenographic lung changes, asbestosis and mortality in a Belgian asbestos-cement factory. In: Wagner, J.C., ed., *Biological Effects of Mineral Fibres*. Lyon, France: International Agency for Research on Cancer (IARC).

Landrigan, P.J. (1998). Asbestos—Still a carcinogen. *N. Engl. J. Med.* **338:**1618–1619.

Landrigan, P.L., Lioy, P.J., Thurston, G., et al. (2004). Health and environmental consequences of the World Trade Center disaster. *Environ. Health Perspect.* **112:**731–739.

Lange, J.H. (2004). Letter to the editor—Re: "Mesothelioma trends in the United States: An update based on surveillance, epidemiology, and end results program data for 1973 through 2003." *Am. J. Epidemiol.* **160:**823.

Langer, A.M., and Nolan, R.P. (1998). Asbestos in the lungs of persons exposed in the USA. *Monaldi Arch. Chest Dis.* **53:**168–180.

Langer, A.M., Nolan, R.P., Constantopoulos, S.H., and Moutsopoulos, H.M. (1987). Association of Metsovo lung and pleural mesothelioma with exposure to tremolite-containing whitewash. *Lancet* 965–967.

Last, J.M. (2001). *A Dictionary of Epidemiology.* New York: Oxford University Press.

Lee, R.J., Florida, R.G., and Stewart, I.M. (1995). Asbestos contamination in paraffin tissue blocks. *Arch. Pathol. Lab. Med.* **119:**528–532.

Lemen, R. (2004). Chrysotile as a cause of mesothelioma: Application of the Hill causation model. *Int. J. Occup. Environ. Health* **10:**233–239.

Levin, J.L., McLarty, J.W., Hurst, G.A., Smith, A.N., and Frank, A.L. (1998). Tyler asbestos workers: Mortality experience in a cohort exposed to amosite. *Occup. Environ. Med.* **55:**155–160.

Li, L., Sun, T.-D., Lai, R.-N., Li, X.-Y., Fan, X.-J., and Morininaga, K. (2004). Cohort studies on cancer mortality among workers exposed only to chrysotile asbestos: A meta-analysis. *Biomed. Environ. Sci.* **17:**459–468.

Liddell, D. (2001). Asbestos and cancer. *Ann. Occup. Hyg.* **45:**329–335; author reply 336–338.

Liddell, F.D., McDonald, A.D., and McDonald, J.C. (1997). The 1891–1920 birth cohort of Quebec chrysotile miners and millers: Development from 1904 and mortality to 1992. *Ann. Occup. Hyg.* **41:**13–36.

Luce, D., Brochard, P., Quenel, P., Goldberg, P., Salomon-Nekiriai, C., Billon-Galland, M.A., et al. (1994). Malignant pleural mesothelioma associated with exposure to tremolite. *Lancet* **344:**1777.

Luce, D., Bugel, I., Goldberg, P., Goldberg, M., Salomon, C., Billon-Galland, M.A., et al. (2000). Environmental exposure to tremolite and respiratory cancer in New Caledonia: A case-control study. *Am. J. Epidemiol.* **151:**259–265.

Luo, S., Liu, X., Mu, S., Tsai, S.P., and Wen, C.P. (2003). Asbestos related diseases from environmental exposure to crocidolite in Dayao, China. I. Review of exposure and epidemiologic data. *Occup. Environ. Med.* **60:**35–41; discussion 41–42.

Mamo, C., and Costa, G. (2004). Mortality experience in a historical cohort of chrysotile asbestos textile workers (abstract). Global Asbestos Congress, Waseda University, Tokyo, Japan. November 20, 2004 (http://park3.wakwak.com/~gac2004/en/abstract/ws_E_Carlo_Mamo_e.html, accessed 9/22/04).

Mancuso, T.F. (1988). Relative risk of mesothelioma among railroad machinists exposed to chrysotile. *Am. J. Ind. Med.* **13:**639–657.

Mancuso, T.F. (1989a). Letter to the editor: Response to Dr. C.-G. Ohlson. *Am. J. Ind. Med.* **15:**353–356.

Mancuso, T.F. (1989b). Letter to the editor: Response to Drs. Churg and Green. *Am. J. Ind. Med.* **17:**525–530.

Marchevsky, A.M., and Wick, M.R. (2003). Current controversies regarding the role of asbestos exposure in the causation of malignant mesothelioma: The need for an evidence-based approach to develop medicolegal guidelines. *Ann. Diagn. Pathol.* **7:**321–332.

Markaki, S., Protopapas, A., Milingos, S., Lazaris, D., Antsaklis, A., and Michalas, S. (2005). Primary malignant mesothelioma of the peritoneum: A clinical and immunohistochemical study. *Gynecol. Oncol.* **96:**860–864.

McDonald, A.D. (1986). Mesothelioma in Connecticut. *J. Occup. Med.* **28:**808–809.

McDonald, A.D., and McDonald, J.C. (1978). Mesothelioma after crocidolite exposure during gas mask manufacture. *Environ. Res.* **17:**340–346.

McDonald, A.D., Fry, J.S., Woolley, A.J., and McDonald, J. (1983a). Dust exposure and mortality in an American chrysotile textile plant. *Br. J. Ind. Med.* **40:**361–367.

McDonald, A.D., Fry, J.S., Woolley, A.J., and McDonald, J.C. (1983b). Dust exposure and mortality in an American factory using chrysotile, amosite, and crocidolite in mainly textile manufacture. *Br. J. Ind. Med.* **40:**368–374.

McDonald, A.D., Fry, J.S., Woolley, A.J., and McDonald, J.C. (1984). Dust exposure and mortality in an American chrysotile asbestos friction products plant. *Br. J. Ind. Med.* **41:**151–157.

McDonald, A.D., Case, B.W., Churg, A., Dufresne, A., Gibbs, G.W., Sebastien, P., and McDonald, J.C. (1997). Mesothelioma in Quebec chrysotile miners and millers: Epidemiology and aetiology. *Ann. Occup. Hyg.* **41:**707–719.

McDonald, J.C. (1994). Epidemiological significance of mineral fiber persistence in human lung tissue. *Environ. Health Perspect.* **102**(Suppl. 5):221–224.

McDonald, J.C. (1998). Unfinished business: The asbestos textiles mystery. *Ann. Occup. Hyg.* **42:**3–5.

McDonald, J.C., and McDonald, A.D. (1998). The epidemiology of mesothelioma in historical context. *Eur. Respir. J.* **9:**1932–1942.

McDonald, J.C., Armstrong, B., Case, B., Doell, D., McCaughey, W.T., McDonald, A.D., et al. (1989). Mesothelioma and asbestos fiber type. Evidence from lung tissue analyses. *Cancer* **63:**1544–1547.

McDonald, J.C., Harris, J., and Armstrong, B. (2004). Mortality in a cohort of vermiculite miners exposed to fibrous amphibole in Libby, Montana. *Occup. Environ. Med.* **61:**363–366.

Meldrum, M. (1996). *Review of Fibre Toxicology.* Health and Safety Executive. Sudbury, UK: HSE Books.

Metinas, M., Nozdemir, G., Hillerdal, G., Ucgun, I., Metinas, S., Baykul, C., et al. (1999). Environmental asbestos exposure and malignant mesothelioma. *Respir. Med.* **93:**349–355.

Meurman, L.O., Pukkala, E., and Hakama, M. (1994). Incidence of cancer among anthophyllite asbestos miners in Finland. *Occup. Environ. Med.* **51:**421–425.

Miller, R.W. (2004). How environmental hazards in childhood have been discovered: Carcinogens, teratogens, neurotoxicants, and others. *Pediatrics* **113:**945–951.

Morgan, A., and Holmes, A. (1983). Distribution and characteristics of amphibole asbestos fibres, measured with the light microscope, in the left lung of an insulation worker. *Br. J. Ind. Med.* **40:**45–50.

Mossman, B.T., Bignon, J., Corn, M., Seaton, A., and Gee, J.B. (1990). Asbestos: Scientific developments and implications for public policy. *Science* **247:**294–301.

Mostert, C., and Meintjes, R. (1979). Asbestosis and mesothelioma on the Rhodesia railways. *Cent. Afr. J. Med.* **25:**72–74.

National Academy of Sciences. (1984). *Asbestiform Fibers: Nonoccupational Health Risks.* National Academy Press, Washington, DC.

Neuberger, M., and Kundi, M. (1990). Individual asbestos exposure: Smoking and mortality—A cohort study in the asbestos cement industry. *Br. J. Ind. Med.* **47:**615–620.

Newhouse, M.L. (1969). A study of the mortality of workers in an asbestos factory. *Br. J. Ind. Med.* **26:**294–301.

Newhouse, M.L., and Sullivan, K.R. (1989). A mortality study of workers manufacturing friction materials: 1941–86. *Br. J. Ind. Med.* **46:**176–179.

Newhouse, M.L., Berry, G., and Wagner, J.C. (1985). Mortality of factory workers in east London 1933–80. *B. J. Ind. Med.* **42:**4–11.

Nicholson, M.J., and Landrigan, P.J. (1996). Asbestos: A status report. *Curr. Issues Public Health* **2:**118–123.

Nicholson, W.J. (2001). The carcinogenicity of chrysotile asbestos—A review. *Ind. Health* **39:**57–64.

Nicholson, W.J., Selikoff, I.J., Seidman, H., Ellis, R., and Formby, P. (1979). Long-term mortality experience of chrysotile miners and millers in Thetford Mines, Quebec. *Ann. NY Acad. Sci.* **330:**11–22.

Nokso-Koivisto, P., and Pukkala, E. (1994). Past exposure to asbestos and combustion products and incidence of cancer among Finnish locomotive drivers. *Occup. Environ. Med.* **51:**330–334.

Nolan, R.P., Ross, M., Nord, G.L., Axten, C.W., Osleeb, J.P., Domnin, S.G., Price, B., and Wilson, R. (2005). Risk assessment for asbestos-related cancer from the 9/11 attack on the World Trade Center. *J. Occup. Environ. Med.* **47:**817–825.

Occupational Safety and Health Administration. (1994). Occupational exposure to asbestos: Final rule amendments. Accessed on 6-2-04 at http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=FEDERAL_REGISTER&p_id=13404

Ohlson, C.G. (1989). Is chrysotile a significant risk factor for mesothelioma? *Am. J. Ind. Med.* **15:**351–356.

Ohlson, C.G., and Hogstedt, C. (1985). Lung cancer among asbestos cement workers. A Swedish cohort study and a review. *Br. J. Ind. Med.* **42:**397–402.

Osinubi, O.Y., Gochfeld, M., and Kipen, H.M. (2000). Health effects of asbestos and nonasbestos fibers. *Environ. Health Perspect.* **108(Suppl. 4):**665–674.

Pang, Z.C., Zhang, Z., Wang, Y., and Zhang, H. (1997). Mortality from a Chinese asbestos plant: Overall cancer mortality. *Am. J. Ind. Med.* **32:**442–444.

Patel, J.D., Bach, P.B., and Kris, M.G. (2004). Lung cancer in US women: A contemporary epidemic. *J. Am. Med. Assoc.* **291:**1763–1768.

Pelnar, P.V. (1988). Further evidence of nonasbestos-related mesothelioma. A review of the literature. *Scand. J. Work Environ. Health* **14:**141–144.

Peterson, J.T., Jr., Greenberg, S.D., and Buffler, P.A. (1984). Non-asbestos-related malignant mesothelioma. A review. *Cancer* **54:**951–960.

Peto, J., Doll, R., Hermon, C., Binns, W., Clayton, R., and Goffe, T. (1985). Relationship of mortality to measures of environmental asbestos pollution in an asbestos textile factory. *Ann. Occup. Hyg.* **29:**305–355.

Piolatto, G., Negri, E., La Vecchia, C., Pira, E., Decarli, A., and Peto, J. (1990). An update of cancer mortality among chrysotile asbestos miners in Balangero, northern Italy. *Br. J. Ind. Med.* **47:**810–814.

Pira, E., Pelucchi, C., Buffoni, L., Palmas, A., Turbiglio, M., Negri, E., Piolatto, P.G., and la Vecchia, C. (2005). Cancer mortality in a cohort of asbestos textile workers. *Br. J. Cancer* **92:**580–586.

Pooley, F.D. (1976). An examination of the fibrous mineral content of asbestos lung tissue from the Canadian chrysotile mining industry. *Environ. Res.* **12:**281–298.

Price, B., and Ware, A. (2004). Mesothelioma trends in the United States: An update based on Surveillance, Epidemiology, and End Results Program data for 1973 through 2003. *Am. J. Epidemiol.* **159:**107–112.

Puntoni, R., Vercelli, M., Merlo, F., Valerio, F., and Santi, L. (1979). Mortality among shipyard workers in Genoa, Italy. *Ann. NY Acad. Sci.* **330:**353–377.

Raffn, E., Lynge, E., Juel, K., and Korsgaard, B. (1989). Incidence of cancer and mortality among employees in the asbestos cement industry in Denmark. *Br. J. Ind. Med.* **46:**90–96.

Rees, D., Goodman, K., Fourie, E., Chapman, R., Blignaut, C., Bachmann, M.O., et al. (1999). Asbestos exposure and mesothelioma in South Africa. *S. Afr. Med. J.* **89:**627–634.

Rees, D., Phillips, J.I., Garton, E., and Pooley, F.D. (2001). Asbestos lung fibre concentrations in South African chrysotile mine workers. *Ann. Occup. Hyg.* **45:**473–477.

Robinson, C., Lemen, R., and Wagoner, J.K. (1979). Mortality patterns, 1940–1975 among workers employed in an asbestos textile friction and packing products manufacturing facility. In: Lemen, R., and Dement, J.R., ed., *Dusts and Disease: Proceedings of the Conference on Occupational Exposures to Fibrous and Particulate Dust and Their Extension Into the Environment.* Forest, IL: Pathotox, pp. 131–143.

Rodelsperger, K., Woitowitz, H.J., Bruckel, B., Arhelger, R., Pohlabeln, H., and Jockel, K.H. (1999). Dose-response relationship between amphibole fiber lung burden and mesothelioma. *Cancer Detect. Prev.* **23:**183–193.

Rogers, A.J. (1984). Determination of mineral fibre in human lung tissue by light microscopy and transmission electron microscopy. *Ann. Occup. Hyg.* **28:**1–12.

Rogers, A.J., Leigh, J., Berry, G., Ferguson, D.A., Mulder, H.B., and Ackad, M. (1991). Relationship between lung asbestos fiber type and concentration and relative risk of mesothelioma. A case-control study. *Cancer* **67:**1912–1920.

Rogers, A.J., Leigh, J., Berry, G., Ferguson, D.A., Mulder, H.B., Ackad, M., and Morgan, G.G. (1994). Dose-response relationship between airborne and lung asbestos fiber type, length and concentration, and the relative risk of mesothelioma. *Ann. Occup. Hyg.* **38(supp. 1):**631–638.

Roggli, V.L., Oury, T.D., and Moffatt, E.J. (1997). Malignant mesothelioma in women. *Anat. Pathol.* **2:**147–163.

Roggli, V.L., and Sharma, A. (2004). Analysis of tissue mineral fiber content. In: *Pathology of Asbestos-Associated Diseases*, 2nd ed., Roggli, V.L., Oury, T.D., and Sporn, T.A., eds., Chapter 11. New York: Springer.

Roggli, V.L., Sharma, A., Butnor, K.J., Sporn, T., and Vollmer, R.T. (2002). Malignant mesothelioma and occupational exposure to asbestos: A clinicopathological correlation of 1445 cases. *Ultrastruct. Pathol.* **26:**55–65.

Rom, W.N., Hammar, S.P., Rusch, V., Dodson, R., and Hoffman, S. (2001). Malignant mesothelioma from neighborhood exposure to anthophyllite asbestos. *Am. J. Ind. Med.* **40:**211–214.

Ross, M., and Nolan, R.P. (2003). History of asbestos discovery and use and asbestos-related disease in context with the occurence of asbestos within ophiolite complexes. In: Dilek, Y., and Newcomb, S., eds., *Ophiolite Concept and the Evolution of Geological Thought.* Boulder, CO: Geological Society of America, pp. 447–470.

Rossiter, C.E., and Coles, R.M. (1980). HM Dockyard, Devonport: 1947 Mortality study. In: Wagner, J.C., ed., *Biologic Effects of Mineral Fibers*. Lyon, France: International Agency for Research on Cancer (IARC). pp. 713–721.

Rothman, K.J., and Greenland, S. (2001). *Modern Epidemiology*. Philadelphia: Lippincott-Raven.

Rubino, G.F., Piolatto, G., Newhouse, M.L., Scansetti, G., Arsenini, G.A., and Murray, R. (1979). Mortality of the chrysotile asbestos workers at the Balangero mine, northern Italy. *Br. J. Ind. Med.* **36:**187–194.

Sakellariou, K., Malamou-Mitsi, V.D., Haritou, A., Koumpaniou, C., CStachouli, C., Dimoliatis, I.D., et al. (1996). Malignant pleural mesothelioma from non-occupational asbestos in Metsovo (northwest Greece): Slow end to an epidemic? *Eur. Respir. J.* **9:**1206–1210.

Sanden, A., and Jarvholm, B. (1987). Cancer morbidity in Swedish shipyard workers 1978–1983. *Int. Arch. Occup. Environ. Health* **59:**455–462.

Sato, F., Yamazaki, H., Ataka, K., Mashima, I., Suzuki, K., Takahashi, T., et al. (2000). Malignant peritoneal mesothelioma associated with deep vein thrombosis following radiotherapy for seminoma of the testis. *Intern. Med.* **39:**920–924.

Savitz, D.A. (2003). *Interpreting Epidemiologic Evidence: Strategies for Study Design and Analysis*. New York: Oxford University Press.

Sebastien, P., McDonald, J.C., McDonald, A.D., Case, B., and Harley, R. (1989). Respiratory cancer in chrysotile textile and mining industries: Exposure inferences from lung analysis. *Br. J. Ind. Med.* **46:**180–187.

Seidman, H., Selikoff, I.J., and Gelb, S.K. (1986). Mortality experience of amosite asbestos factory workers: Dose-response relationships 5 to 40 years after onset of short-term work exposure. *Am. J. Ind. Med.* **10:**479–514.

Seidman, H., and Selikoff, I.J. (1990). Decline in death rates among asbestos insulation workers 1967–1986 associated with diminution of work exposure to asbestos. *Ann. NY Acad. Sci.* **609:**300–317; discussion 317–318.

Selikoff, I.J., Lilia, R., and Nicholson, W.J. (1979). Asbestos disease in the United States shipyards. *Ann. NY Acad. Sci.* **330:**295–311.

Siemiatycki, J., Richardson, L., Straif, K., Latreille, B., Lakhani, R., Campbell, S., et al. (2004). Listing occupational carcinogens. *Environ. Health Perspect.* **112:**1447–1459.

Silvestri, S., Magnani, C., Calisti, R., and Bruno, C. (2001). The experience of the Balangero chrysotile asbestos mine in Italy: Health effects among workers mining and milling asbestos and the health experience of persons living nearby. *Can. Mineral Spec. Publ.* **5:**177–186.

Sluis-Cremer, G.K., Liddell, F.D., Logan, W.P., and Bezuidenhout, B.N. (1992). The mortality of amphibole miners in South Africa, 1946–80. *Br. J. Ind. Med.* **49:**566–575.

Smailyte, G., Kurtinaitis, J., and Andersen, A. (2004). Cancer mortality and morbidity among Lithuanian asbestos-cement producing workers. *Scand. J. Work Environ. Health* **30:**64–70.

Smith, A.H., and Wright, C.C. (1996). Chrysotile asbestos is the main cause of pleural mesothelioma. *Am. J. Ind. Med.* **30:**252–266.

Speizer, F.E. (2001). Environmental lung diseases. In: *Harrison's Principles of Internal Medicine*, Braunwald, E., et al., eds. New York: McGraw-Hill, pp. 1469–1470.

Spirtas, R., Heineman, E.F., Bernstein, L., Beebe, G.W., Keehn, R.J., Stark, A., et al. (1994). Malignant mesothelioma: Attributable risk of asbestos exposure. *Occup. Environ. Med.* **51:**804–811.

Sporn, T.A., and Roggli, V.L. (2004). Mesothelioma. In: *Pathology of Asbestos-Associated Diseases,* 2nd ed., Roggli, V.L., Oury, T.D., and Sporn, T.A., eds., chapter 5 New York: Springer.

Srebro, S.H., Roggli, V.L., and Samsa, G.P. (1995). Malignant mesothelioma associated with low pulmonary tissue asbestos burdens: A light and scanning electron microscopic analysis of 18 cases. *Mod. Pathol.* **8:**614–621.

Stayner, L.T., Dankovic, D.A., and Lemen, R.A. (1996). Occupational exposure to chrysotile asbestos and cancer risk: A review of the amphibole hypothesis. *Am. J. Public Health* **86:**179–186.

Sterman, D.H., Litzky, L.A., Kaiser, L.R., and Albelda, S.M. (2004). Epidemiology and pathology of malignant mesothelioma. In: Rose, B.D., ed., *UpToDate*. Wellesley, MA: UpToDate.

Sturm, W., Menze, B., Krause, J., and Thriene, B. (1994). Use of asbestos, health risks and induced occupational diseases in the former East Germany. *Toxicol. Lett.* **72:**317–324.

Suzuki, Y., and Yuen, S.R. (2002). Asbestos fibers contributing to the induction of human malignant mesothelioma. *Ann. NY Acad. Sci.* **982:**160–176.

Suzuki, Y., Yuen, S.R., and Ashley, R. (2005). Short, thin asbestos fibers contribute to the development of human malignant mesothelioma: Pathological evidence. *Int. J. Hyg. Environ. Health* **208:**201–210.

Szeszenia-Dabrowska, N., Wilczynska, U., and Szymczak, W. (1988a). A mortality study among male workers occupationally exposed to asbestos dust in Poland. *Pol. J. Occup. Med.* **1:**77–87.

Szeszenia-Dabrowska, N., Wilczynska, U., and Szymczak, W. (1988b). Mortality among female workers in an asbestos factory in Poland. *Pol. J. Occup. Med.* **1:**203–212.

Szeszenia-Dabrowska, N., Wilczynska, U., and Szymczak, W. (1997). [Cancer risk in asbestos-cement industry workers in Poland]. *Med. Pr.* **48:**473–483.

Talcott, J.A., Thurber, W.A., Kantor, A.F., Gaensler, E.A., Danahy, J.F., Antman, K.H., et al. (1989). Asbestos-associated diseases in a cohort of cigarette-filter workers. *N. Engl. J. Med.* **321:**1220–1223.

Teta, M.J., Lewinsohn, H.C., Meigs, J.W., Vidone, R.A., Mowad, L.Z., and Flannery, J.T. (1986). The authors' reply. *J. Occup. Med.* **28:**808–809.

Thomas, H.F., Benjamin, I.T., Elwood, P.C., and Sweetnam, P.M. (1982). Further follow-up study of workers from an asbestos cement factory. *Br. J. Ind. Med.* **39:**273–276.

Tossavainen, A., Karjalainen, A., and Karhunen, P.J. (1994). Retention of asbestos fibers in the human body. *Environ. Health Perspect.* **102(Suppl. 5):**253–255.

Tossavainen, A., Kotilainen, M., Takahashi, K., Pan, G., and Vanhala, E. (2001). Amphibole fibres in Chinese chrysotile asbestos. *Ann. Occup. Hyg.* **45:**145–152.

Tossavainen, A., Kovalevsky, E., Vanhala, E., and Tuomi, T. (2000). Pulmonary mineral fibers after occupational and environmental exposure to asbestos in the Russian chrysotile industry. *Am. J. Ind. Med.* **37:**327–333.

Tulchinsky, T.H., Ginsberg, G.M., Iscovich, J., Shihab, S., Fischbein, A., and Richter, E.D. (1999). Cancer in ex-asbestos cement workers in Israel, 1953–1992. *Am. J. Ind. Med.* **35:**1–8.

Turci, F., Tomatis, M., Gazzano, E., Riganti, C., Martra, G., Bosia, A., Ghigo, D., and Fubini, B. (2005). Potential toxicity of nonregulated asbestiform minerals: Balangeroite from the Western Alps. Part 2: Oxidant activity of fibers. *J. Toxicol. Environ. Health A* **68:**21–39.

Ulvestad, B., Kjaerheim, K., Martinsen, J.I., Damberg, G., Wannag, A., Mowe, G., et al. (2002). Cancer incidence among workers in the asbestos-cement producing industry in Norway. *Scand. J. Work Environ. Health* **28:**411–417.

U.S. Environmental Protection Agency. (1986). Airborne asbestos health assessment update. Research Triangle Park, NC. Report No. EPA/600/8-84/003F.

U.S. Environmental Protection Agency. (2004). An examination of EPA risk assessment principles and practices. Washington, DC: Office of the Science Advisor. Report No. EPA/100/B-04/001.

U.S. Preventive Services Task Force. (2003). U.S. Preventive Services Task Force Ratings: Strength of recommendations and quality of evidence. In: *Guide to Clinical Preventive Services*, 3rd ed., Periodic Updates, 2000–2003. Rockville, MD: Agency for Healthcare Research and Quality.

Wagner, J.C. (1991). The discovery of the association between blue asbestos and mesotheliomas and the aftermath. *Br. J. Ind. Med.* **48:**399–403.

Wagner, J.C., Sleggs, C.A., and Marchand, P. (1960). Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province. *Br. J. Ind. Med.* **17:**260–271.

Weill, H., Hughes, J.M., and Waggenspack, C. (1979). Influence of dose and fiber type on respiratory malignancy risk in asbestos cement manufacturing. *Amer. Rev. Respir. Dis.* **120:**345–354.

Weill, H., Hughes, J.M., and Churg, A.M. (2004). Changing trends in US mesothelioma incidence. *Occup. Environ. Med.* **61:**438–441.

Weiss, W. (1977). Mortality of a cohort exposed to chrysotile asbestos. *J. Occup. Med.* **19:**737–740.

Wilcznska, U., Szeszenia-Dabrowska, N., and Szymczuk, W. (1996). Mortality due to malignant cancer in men exposed to asbestos dust on the job. *Med. Pr.* **47:**437–443.

World Health Organization. (2004). Executive summary. In: *The Precautionary Principle: Protecting Public Health, the Environment and the Future of Our Children*, Martuzzi, M., and Tickner, J.A., eds. Copenhagen: Regional Office for Europe.

Yano, E., Wang, Z.M., Wang, X.R., Wang, M.Z., and Lan, Y.J. (2001). Cancer mortality among workers exposed to amphibole-free chrysotile asbestos. *Am. J. Epidemiol.* **154:**538–543.

Yu, I.J., Choi, J.K., Kang, S.K., Chang, H.K., Chung, Y.H., Han, J.H., et al. (2002) Potential source of asbestos in non-asbestos textile manufacturing company. *Environ. Int.* **28:**35–39.