MESOTHELIOMA

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DEFINITION

The primary malignant neoplasm of the pleura —diffuse pleural mesothelioma—has been recognized and accepted as a nosologic entity only during the last 20 years (77), although as early as 1767 Joseph Lieutand (cited by Robertson) reported two cases of probable mesothelioma among 3,000 autopsies, and E. Wagner described the pathology in 1870 (53)(72).

It is not known with certainty when the term "mesothelioma" was first used; one of the early reports indicating a primary and malignant tumor of the pleura and using the term mesothelioma was that by DuBray and Rosson (14).

In 1931, Klemperer and Rabin published a comprehensive description of the distinctive features of diffuse pleural neoplasms and recommended these tumors "should be designated mesothelioma," since they arise from the surface lining cells of the pleura, the mesothelium (27). The malignant, diffuse pleural mesothelioma arises from the multipotential coelomic mesothelial cell of the pleura. Similarly, malignant tumors originating in the mesothelial cells of the peritoneum are peritoneal mesothelioma.

The definition of pleural mesothelioma thus includes:

- the origin of the tumor in the mesothelial cells of pleura
- the diffuse character of the tumoral growth, often involving a large surface or even the entire pleura of one lung, at the time of diagnosis
- the characteristic rapid growth and extension over the surface of the pleural serosa (closely related to the diffuse character)
- the high degree of malignancy, expressed in rapid growth, local invasiveness (soft tissue and bone structures of chest wall, underlying lung, adjacent pericardium. regional lymph nodes), and frequent metastases to a variety of organs, including brain, liver, kidney, adrenals, etc. These characteristics of pleural mesothelioma have an integrative expression in the mean survival time after diagnosis, which does not exceed 12 months in most reported series, with or without therapeutic attempts.

The association between malignant "endothelioma of the pleura" (mesothelioma) and asbestos exposure was first reported by Wyers (80). Wagner et al., published a report on 33 cases of diffuse pleural mesothelioma from the North West Cape Province of South Africa; most of these cases had occurred over a four year period, and in all but one, exposure to asbestos (crocidolite) could be established (77). Mesothelioma was not necessarily preceded by asbestosis (interstitial pulmonary fibrosis); the exposure was occupational in some cases, but in others, only environmental (residential) exposure had occurred. The long latency period—a mean of 40 years—between initial asbestos exposure and the development of malignant pleural mesothelioma was another striking characteristic of these cases. The carcinogenic hazard of relatively low levels of asbestos exposure; the possibility that pleural mesothelioma associated with asbestos exposure may develop in the absence of preceding pulmonary interstitial fibrosis; and the long latency period between onset of exposure and development of the malignant mesothelioma, were thus outlined.

LIST OF CAUSATIVE AGENTS

Asbestos fiber is widely accepted as the causative agent in the vast majority of mesothelioma cases. So far, asbestos is the only fibrous mineral

where epidemiologic data have shown an association between exposure and pleural and peritoneal mesothelioma in man.

Asbestiform minerals are grouped in two major categories: chrysotile, which is a serpentine, and the amphiboles, which include crocidolite, amosite, anthophyllite, and tremolite.

The first large group of malignant pleural mesothelioma cases due to asbestos exposure was related to crocidolite in South Africa (77). This fact, and subsequent reports on mesothelioma cases from Great Britain where crocidolite had been extensively used, contributed to the empirical and one-sided view that crocidolite was the main or even the only type of asbestos with a specific carcinogenic potential resulting in the eventual development of mesothelioma.

The major increase in mesothelioma incidence in the United States—where chrysotile has been and still is the main type of asbestos used—supports a causal association between chrysotile exposure and development of mesothelioma (4)(31)(59)(63)(64). Epidemiologic evidence for worker cohorts has shown chrysotile to be equally as potent as other fiber types insofar as lung cancer is concerned (13)(49)(80). While the number of mesothelioma cases from populations exposed only to chrysotile has been small, an association with chrysotile exposure has been definitively established. Amosite has also been shown to have a similar carcinogenic effect; a significant number of mesothelioma cases have occurred in a cohort of 933 amosite factory workers(62). Experimental studies on rats using inhalation of five types of asbestos fiber resulted in the development of mesothelioma with chrysotile (Canadian), crocidolite, amosite, and anthophyllite (74). Previous experiments using intrapleural administration of amosite, chrysotile, and crocidolite had given similar results, with chrysotile giving the largest number of mesotheliomas, followed by crocidolite and amosite (73). Shabad et al. also reported on the experimental production of pleural mesothelioma in rats, with intrapleural administration of chrysotile (65). Thus, both epidemiologic evidence and experimental confirmation indicate that chrysotile, amosite, and crocidolite asbestos are causative agents for mesothelioma.

Recently another type of fibrous mineral—naturally occurring zeolites (aluminum silicates) of the fibrous variety (erionite, mordenite)—has come under close scrutiny as a potential causative agent for malignant mesothelioma. The evidence for this association is based on the findings in a rural area of endemic mesothelioma in Turkey, where mineralogic investigations have not found any asbestos minerals, but have identified fibrous zeolites. Although this is still being actively researched and conclusive evidence is not yet resolved, fibrous zeolites are considered highly suspicious at the present time.

Reports on endemic mesothelioma in other parts of the world—such as in a rural area in India—have not yet identified the etiologic agent; the possibility that zeolites may be the causative agent cannot be excluded, since zeolites are known to be present in that area.

Experimental studies using intrapleural application suggest that other fibrous materials, such as fibrous glass, may also induce malignant mesothelioma (68). Epidemiologic evidence for fibrous glass as a causative agent for mesothelioma has not been reported, but fibrous glass has to be included as a suspected causative agent.

LIST OF OCCUPATIONS AND INDUSTRIES INVOLVED

Occupations and industries at risk to mesothelioma include all of those listed for asbestosis.

All available information indicates that mesothelioma may be the result of low levels and/or relatively short (of the order of several weeks to several months) asbestos exposure. The dose-response relationship for mesothelioma is therefore different than that for asbestosis (which develops with higher exposure levels over longer time periods) or bronchial carcinoma associated with asbestos exposure (which increases in incidence even after short periods of high asbestos exposure levels, but shows a marked increase in incidence with duration of exposure)(58). Since low asbestos exposure levels carry a significant risk of mesothelioma, occupations and industries characterized by relatively low asbestos levels (auto mechanics and brake repair, tapers in dry wall construction, handling of finished asbestos products including asbestos cement), while at relatively low risk for the development of parenchymal interstitial fibrosis (asbestosis), are nevertheless at high risk for mesothelioma.

Equally important is the fact that numerous workers in the various trades which do not simply direct asbestos exposure, such as electricians, painters, welders, carpenters, etc., in shipbuilding or ship repair, in construction, in maintenance

work at chemical plants, and even automobile salesmen supervising repair work, are frequently exposed to asbestos due to their mere presence in work areas where asbestos is being handled. This "bystander" exposure has been repeatedly documented to be responsible for numerous cases of mesothelioma (20)(51). It is therefore important to establish the principle that such indirect exposure carries a significant risk of mesothelioma.

Whitwell et al. found that 83% of mesothelioma cases reviewed contained over 100,000 asbestos fibers per gram of dried lung tissue; in cases of asbestosis the number of asbestos fibers was much higher, exceeding 3,000,000 per gram of dried lung tissue (79).

In shipyard workers, more and more mesothelioma cases have been reported; most of these have occurred in trades other than insulation workers, indicating that the risk is widespread (20)(61). The distribution of trades in private shipyards in the United States in 1943 is presented in Table VIII-24. A list of occupational titles in an Eastern U.S. shipyard in 1975 is given in Table VIII-25.

It is difficult to construct a complete list of all occupations in which asbestos exposure may occur at one time or another. Since short-term asbestos exposure (several weeks to several months) is often responsible for mesothelioma occurring 25, 30, 40, or 50 years later, the occupation/industry involved at the time of the diagnosis of a malignant tumor may differ from the occupation/industry where the exposure actually occurred. Therefore, at any point in time, much higher numbers of individuals are at risk for the development of mesothelioma than those working in industries and occupations known to be associated with asbestos exposure. Recollection of remote past exposures and of specific jobs in which they occurred is a formidable task, but crucial when assessing whether one particular case of mesothelioma is related to past asbestos exposure.

Table VIII-24

PERCENTAGE DISTRIBUTION OF TRADES IN PRIVATE SHIPYARDS IN THE UNITED STATES, JUNE 1943

Trade	*Percentage*
Welders	15.3
Shipfitters	11.0
Machinists	8.1
Pipefitters	7.2
Electricians	6.6
Carpenters	6.1
Laborers	5.5
Burners	3.8
Painters	3.1
Sheetmetal workers	3.0
Riggers	2.8
Chippers and caulkers	2.8
Boilermakers	2.3
Crane operators	1.3
Pipe coverers	0.2
All other	21.1

Source: Bureau of Labor Statistics, Bulletin 824, "Wartime Employment, Production, and Conditions of Work in Shipyards," 1945.

EPIDEMIOLOGY

The relationships between asbestos exposure and pleural mesothelioma regarding latency period, dose-response characteristics, populations at risk, and incidence of disease have been presented in the section—List of Occupations and Industries Involved, page 672.

Pleural mesothelioma is a rapidly progressing malignant tumor, the resulting disability is total, and the condition is usually fatal in one to two years. There are no confounding conditions or risk factors which limit the ability to establish cause-effect relationships.

ESTIMATE OF POPULATION AT RISK AND PREVALENCE OF DISEASE

The population at risk for developing mesothelioma includes:

- all occupations with direct contact and handling of asbestos.
- employees with other occupations (electricians, welders, painters, carpenters, etc.) who work or have worked—even for short periods—in areas where asbestos has been handled by others.
- family members (household contacts) of asbestos workers who have been exposed to asbestos fibers brought into the household by the worker. Household contamination has been found to result in asbestos exposure of family members of asbestos workers, sufficient in magnitude to induce mesothelioma (1)(2)(5)(32)(41)(46)(55)(56).
- individuals who have resided in the vi-

Table VIII-25

OCCUPATIONAL TITLES IN AN EASTERN U.S. SHIPYARD, 1975

Guard & Watchman	Heat Treater	Power House Engineer	Shipfitter
Construction Mechanic	Tool Grinder	Molder	Lead Bonder
Laborer	Tool Room Attendant	Foundryman	Welder
Firefighter	Lathe Operator	Foundry Chipper	Burner
Scrap Material Sorter	Miller	Melter	Rigger
Painter	Drill Operator	Coremaker	Sheetmetal Mechanic
Painter Cleaner	Grinder	Pipefitter	Joiner
Maintenance Painter	Machinist	Silver Brazer	Carpenter
Truck Driver	Engraver	Pipecoverer	Industrial Radiography Technician
Fork Lift Operator	Layout	Electrician	Radiological Control Monitor
Warehouseman	Machine Rigger	Electronics Technician	Clerk
Transportation	Make Ready Man	Maintenance Electrician	Data Processor
Locomotive Operator	Crane Operator	Loftsman	Secretary
Toolmaker	Maintenance Machinist	Blacksmith	Timekeeper
	Dock Crew	Furnaceman	
	Inspector		

cinity (one mile) of an asbestos plant, shipyard, or other source of asbestos contamination.

The population at risk at any point in time has to include all persons who have been exposed *in the past*. Given the long latency period between asbestos exposure and development of mesothelioma (on the average 35-40 years), individuals who have been exposed (even for short periods of time) during the last 50 years have to be considered potentially at risk.

Contributing to the population size at risk is (1) the fact that short duration of asbestos exposure (several weeks to several months) is sufficient to induce mesothelioma; (2) the high job mobility, especially during World War II; (3) the marked increase in the total amount of asbestos used per year; and (4) the diversification of its uses. The estimate of the population at risk is, for the same reasons, a complex and difficult task.

Attempts to assess the incidence of mesothelioma in populations at risk are also fraught with difficulties; these have multiple sources.

1. The complexity of the diagnostic criteria, which require pathologic confirmation; the most rigorous criteria make the diagnosis dependent on a complete autopsy (for the exclusion of another primary site of the tumor, which might have metastasized to the pleural cavity). Only a proportion of all deaths are followed by a postmortem examination. This proportion varies with geographic area, with the time period considered, and with other factors.
2. Even when tissue specimens are examined by experienced pathologists, the diagnosis is not always simple; differences of opinion may persist and result in conclusions on the pathologic characteristics such as "possible mesothelioma" or probable mesothelioma."
3. Evaluation of the incidence of mesothelioma from death certificates has been reported, by all those who have investigated this problem, as incomplete, leading to a marked but quantitatively variable underestimate of the number of cases. This problem is compounded by the fact that the coding of causes of death does not provide a separate code for mesothelioma, but includes it with cancer of the lung or pleura.
4. The most reliable data are those based on the cohort approach: asbestos-exposed employees followed for many years, with a comprehensive assessment of causes of death. The long latency period between

onset of asbestos exposure and mesothelioma has resulted in a limited number of studies with a long enough follow-up period to realistically reflect its incidence. In all these cohort studies, most with several reports published over time, it is a rule without exception that the longer the observation period, the higher the incidence of mesothelioma.

Although the most relevant data on mesothelioma risk in asbestos-exposed populations are derived from long-term cohort studies, other studies following different approaches have also revealed the paramount importance of long-term follow-up and completeness of diagnostic means. The most significant information follows.

By 1965, 160 cases of mesothelioma had been recorded in the United Kingdom, 123 from England and Wales, 36 from Northern Ireland, and only one from Scotland (39). When a systematic review of all necropsy and surgical biopsy reports in all hospitals was undertaken, 80 cases of mesothelioma were found to have occurred in Scotland for the years 1950-1967. Many cases were in employees who had had no direct exposure to asbestos but had been employed in the shipbuilding industry, in a wide variety of trades.

The Mesothelioma Register in Great Britain (Employment Medical Inspector's Advisory Service)—with data sources in death certificates, Cancer Bureau registrations, Pneumoconiosis Medical Panels (claims for benefits under the National Insurance Acts), chest physicians, surgeons, pathologists and coroners—had 413 cases reported for 1967-1968; 75% of the confirmed cases with definite asbestos exposure came from shipbuilding, asbestos factories, and insulation work; the other 25% from a variety of occupations (welders, electricians, gas workers, mechanics, chemical workers, etc.). The highest rate/million per year of mesothelioma (confirmed cases) figures were 8.93 and 8.24, both in shipbuilding areas. The incidence of definite mesothelioma in the United Kingdom for the period 1967-1968 was 120 per year. It was concluded that this figure may considerably understate the true incidence.

McDonald and McDonald reviewed evidence published between 1959 and 1976, including cohort studies of asbestos workers; "population studies" (mesothelioma surveys in Canada and the United States describing "case-series referable to some kind of denominator"); case reports unrelated to any denominator; and mortality statistics, mainly in Canada, the United States, and the United Kingdom (37). Data from the Third U.S. National Cancer Survey (42) was also reviewed. A total of 4,539 cases had been published after 1958. (This figure did not include cases from official mortality statisitics and Third U.S. National Cancer Survey.) The incidence of mesothelioma for the period preceding 1958 had been very low: in 1957 Hachberg mentioned 43 cases in 60,042 autopsies over the 40-year period, 1910-1949, i.e., less than 1 case per year and only 0.07% of the autopsies performed (Philadelphia, Baltimore, Minneapolis, New York, and Toronto in North America and Munich, Prague, and Copenhagen in Europe).

The marked increase in the incidence of mesothelioma over the last 20 years is evident when comparing the total number of reported cases (436) for the period 1955-1959, with that of 1,697 cases of mesothelioma for the period 1965-1969 (an almost fourfold increase). Interestingly, 9% of cases were due to neighborhood or household-family exposure.

In the Third National Cancer Survey (1975), a thorough ascertainment was done using hospital records and pathology material, besides death certificates, in selected areas comprising approximately 10% of the population of the United States (deaths in 1971). The annual rate per million for males 45 and over was 11.20 and for females in the same age range, 3.53.

Reports from other countries, such as Germany, Sweden, the Netherlands and Great Britain, indicate much higher rates than those published for Canada by McDonald (10 per million for males and 4 per million for females, over 45-years-old) for some cities and regions, most with large shipyards: Walcheren had a death rate 23.3 times higher than that expected according to the Canadian rates; Wilhelmshaven (21.5 times higher); Plymouth (14.3 times higher); and Rotterdam, Harlem, Hamburg, Malmo, Nantes, and Trieste (with rates 7-8 times higher) (38)(51)(69). These data indicate that annual incidence rates for mesothelioma in geographical areas with shipyards and/or other important asbestos industries or uses are of the order of 200/1 million or higher, for men aged 45 or over.

The most relevant data on the incidence of mesothelioma in exposed populations are derived from cohort studies of occupational groups. But

only studies with long follow-up (30-40 years) can provide comprehensive information, although even these might not include all the cases. It has been estimated, from the relatively limited number of such studies, that between 5% and 11% of all deaths in asbestos-exposed workers are due to mesothelioma (16)(26)(43)(45)(61)(62)(63). In a cohort of 632 asbestos insulation workers observed prospectively from January 1, 1943 to December 31, 1976, 38 out of a total of 478 deaths were due to mesothelioma (see Table VIII-26) (60). The mortality experience of a large cohort of 17,800 asbestos workers in the United States and Canada (Table VIII-27) observed from 1967 to 1977 indicates that 175 out of 2,270 deaths were due to mesothelioma. In a cohort of amosite asbestos factory workers employed from 1941-1945, and observed until 1977, 16 out of 594 deaths were due to mesothelioma (Table VIII-28) (62). In another cohort of 689 asbestos factory workers employed before January 1939, and observed from 1959 through 1975, 26 out of 274 deaths were due to mesothelioma (48)(60). Newhouse reported the mortality experience of workers in an East London asbestos factory, 1931-1970; out of a total of 461 deaths, 35 were due to mesothelioma (43).

The importance of long-term observation is shown in Tables VIII-29, VIII-30, and VIII-31.

Two further problems are: 1) the correct assessment of all those at risk for developing mesothelioma in various occupations, or who have had such exposure even for short periods of time sometime during the last 40-50 years; and 2) quantification of the risk for "bystander" exposure, neighborhood or other types of environmental exposure (buildings, schools, etc.), and household-family exposure.

Although no firm data are as yet available for these types of asbestos exposure, according to the information available on cases occurring after short (several weeks) and relatively low levels of exposure, it has to be assumed that the risk is of the same order of magnitude as that for occupationally-exposed groups.

PATHOLOGY, PATHOGENESIS, AND PATHOPHYSIOLOGY

The pathology of mesothelioma is largely determined by the potential of the mesothelial cells to produce tumors of epithelial, mesenchymal, or most commonly a mixed type. This potential is related to the embryologic origin of the mesothelium, which is derived from coelomic epithelium developed from the mesoderm and underlined by mesenchymal tissue (27).

The macroscopic features of pleural mesothelioma are those of a gray-white or yellow-gray mass, varying in extent from a part of the lung's surface to a complete, or almost complete, encasement of the lung. The tumor has a rapid growth rate, extending along the serosa, with a tendency to grow along the interlobar fissures. Both the parietal and visceral pleura are involved; often the tumor seems to have originated in the visceral pleura (for example, in the minor fissure).

Two types of mesothelioma can be observed: 1) the scirrhous type, presenting as a hard sheet, with variable thickness often exceeding one inch, rapid encasement and compression of the lung, partial or total obliteration of the pleural cavity, and contraction of the hemithorax; and 2) the encephaloid type, presenting as large tumor masses, often multiple, sometimes with extremely rapid growth (seen on chest x-rays as "scalloping").

Continuous spread—with local invasion of the pericardium, mediastinum, chest wall, diaphragm, and, through it, the liver and peritoneum, or into the controlateral pleura—is frequent. The underlying lung can be invaded directly, into the pulmonary parenchyma immediately underlying the pleura, or by spread into septal and perivascular lymphatics, with lymph node involvement in about 50% of cases. Distant metastases, thought in the past to be rare, are, on the contrary, quite frequent, affecting the brain, liver, kidney, adrenals, thyroid, lung, or other organs in more than 50% of cases. Tumor growth along the needle biopsy track or surgical scar after thoracotomy is common.

Microscopic features are characterized by diversity of appearance, not only from case to case, but also in the same tumor, where both epithelial (or tubulo-papillary) and mesenchymal (or fibrosarcomatous) areas can be observed. According to the microscopic pattern, mesothelioma can be classified into four types: 1) epithelial or tubulo-papillary, with the epithelial cells usually cuboidal or flattened, tending to form tubular and papillary structures, separated by a more or less abundant matrix; 2) mesenchymal or fibrosarcomatous, appearing as a spindle cell sarcoma, but sometimes with extensive areas of acellular collagen; 3) mixed, the most frequent form, containing both epithelial and fibrosarcomatous areas; 4) the undifferentiated type, with polygonal, less often spheroidal cells, with large nuclei and scanty mitotic figures. These cells resemble those of the tubulo-papillary

Table VIII-26

EXPECTED AND OBSERVED DEATHS AMONG 632 NY-NJ ASBESTOS INSULATION WORKERS OBSERVED PROSPECTIVELY JANUARY 1, 1943 - DECEMBER 31, 1976

Number of Men	**632**	
Man-years of observation	**13,925**	
	Deaths 1.1.43-12.31.76	
Cause of death	*Expected**	*Observed*
Total deaths, all causes	328.9	478
Total cancer, all sites	51.0	210
Lung cancer	13.3	93
Pleural mesothelioma	**	11
Peritoneal mesothelioma	**	27
Cancer of esophagus	1.4	1
Cancer of stomach	5.4	19
Cancer of colon - rectum	8.3	23
All other cancer	28.06	36
Asbestosis	**	41
All other causes	262.6	227

*Expected deaths are based upon age and sex-specific U.S. death rates of the National Center for Health Statistics, 1949-1975 actual rates, 1943-1948 extrapolated from 1949-1955 rates, and 1976 extrapolated from 1967-1975 data.
**These are rare causes of death in the general population.

Table VIII-27

DEATHS AMONG 17,800 ASBESTOS INSULATION WORKERS IN THE UNITED STATES AND CANADA JANUARY 1, 1967 — JANUARY 1, 1977

Number of Men	**17,800**		
Man-years of observation	**166,855**		
	*Expected**	*Observed*	*Ratio*
Total deaths, all causes	1,660.96	2,270	1.37
Total cancer, all sites	319.90	994	3.11
Lung cancer	105.97	485	4.58
Pleural mesothelioma	**	66	—
Peritoneal mesothelioma	**	109	—
Cancer of esophagus	7.01	18	2.57
Cancer of stomach	14.23	22	1.55
Cancer of colon - rectum	37.86	59	1.56
All other cancer	154.83	235	1.52
Asbestosis	**	162	—
All other causes	1,351.06	1,114	0.82

*Expected deaths are based upon white male age-specific mortality data of the U.S. National Center for Health Statistics for 1967-1975 and extrapolation to 1976.
**These are rare causes of death in the general population.

Table VIII-28

EXPECTED AND OBSERVED DEATHS
AMONG 933 AMOSITE FACTORY WORKERS EMPLOYED
1941-1945, OBSERVED TO DECEMBER 31, 1977

	Deaths 1941-1977		
	Expected[a]	*Observed*	*Ratio*
Total deaths	368.62	594	1.61
Cancer, all sites	73.35	195	2.66
Lung cancer	19.16	100	5.22
Pleural mesothelioma	[b]	8	—
Peritoneal mesothelioma	[b]	8	—
G.I. cancer	21.55	32	1.48
All other cancer	32.64	47	1.44
Asbestosis	[b]	30	—
Other noninfectious respiratory disease	8.47	19	2.24
All other causes	286.80	350	1.22

[a] Expected deaths based upon age-specific death rate data for New Jersey white males in corresponding years. In 4 cases, ages were not known; omitted from calculations. 39 men partially traced and 890 traced to death on December 31, 1977.

[b] Death rates not available, but these have been rare causes of death in the general population.

type.

A property of mesothelial cells is the production of acid mucopolysaccharides, especially hyaluronic acid, which stains strongly with colloidal iron, but not with periodic acid Schiff (PAS). This last characteristic is useful in differentiating mesothelioma from adenocarcinoma; the latter usually gives a positive stain with PAS. The hyaluronidase test (digestion of hyaluronic acid by the enzyme) is useful in a limited number of cases, since the tubulopapillary type of the tumor is the only form which consistently produces hyaluronic acid. Therefore a negative hyaluronidase test does not exclude the diagnosis of mesothelioma.

The pathogenesis of mesothelioma is not yet completely understood. Nevertheless, the following facts of major theoretical and practical consequence have been established:

- mesothelioma may result from exposure to crocidolite, chrysotile and/or amosite; the evidence is derived from epidemiologic and experimental animal studies.
- relatively low levels and short duration of exposure can produce mesothelioma.
- while a dose-response relationship may exist, it has not been quantitatively clarified, and therefore available information can only be interpreted to indicated that any asbestos exposure, given a long enough period of follow-up, may induce mesothelioma.
- the hypothesis according to which polycyclic aromatic hydrocarbons adsorbed on asbestos fibers are important in the induction of mesothelioma has not been confirmed, nor has that attributing a similar effect to adsorbed trace metals (19).
- cigarette smoking has no etiologic relationship with mesothelioma.
- in experimental studies, intrapleural administration of asbestos, but also of similarly sized fibers of fibrous glass and fibrous aluminum oxide, resulted in pleural mesothelioma (66)(67)(68). This seems to indicate that fibrous characteristics, rather than the chemical composition, are crucial for this specific carcinogenic effect.
- a special selectivity in the distribution of asbestos fibers, relevant to the problem

Table VIII-29

EXPECTED AND OBSERVED DEATHS AMONG 689 ASBESTOS FACTORY WORKERS, EMPLOYED BEFORE JANUARY 1, 1939 DURING THE SEVENTEEN YEARS FROM JANUARY 1, 1959 THROUGH DECEMBER 31, 1975

	1959-1964		1965-1970		1971-1975		1959-1975		
	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs./Exp.
All causes	59	52.41	123	69.85	92	65.93	274	188.19	1.46
Cancer, all sites	21	10.47	45	14.70	33	14.73	99	39.92	2.47
Lung cancer	6	2.96	18	4.65	11	4.92	35	12.53	3.91[a]
Pleural mesothelioma	1	n.a.	5	n.a.	7	n.a.	14	n.a.	—
Peritoneal mesothelioma	1	n.a.	6	n.a.	4	n.a.	12	n.a.	—
Cancer of esophagus, stomach, colon and rectum	4	2.23	5	2.92	3	2.83	15	7.99	1.88
Cancer, all other sites	9	5.28	11	7.13	8	6.98	23	19.40	1.19
All respiratory disease	14	3.01	10	4.56	18	4.60	42	12.16	3.45
Asbestosis	12	n.a.	8	n.a.	15	n.a.	35	n.a.	—
Other respiratory	2	(b)	2	(b)	3	(b)	7	(b)	—
All other causes	24	38.93	68	50.59	41	46.60	133	136.11	0.98
Person-years of observation	3,962		3,411		2,273		9,646		

(a) Pleural mesothelioma included with cancer of bronchus in calculating ratio since expected rates are based upon "cancer of lung, pleura, bronchus, trachea."
(b) This rate is virtually identical with that of "all respiratory disease."
n.a.—not available.

Table VIII-30

MORTALITY EXPERIENCE AMONG 17,800 ASBESTOS INSULATION WORKERS IN THE UNITED STATES AND CANADA 1967-1977: OBSERVATIONS IN 2,270 CONSECUTIVE DEATHS

	Number of men	17,800							
	Man-years	166,855							
	Duration from onset of work exposure (years)								
Cause of death	*Total*	*<10*	*10-14*	*15-19*	*20-24*	*25-29*	*30-34*	*35-39*	*40-44*	*45+*
All causes	2,270	51	85	188	320	388	340	253	203	442
Cancer, all sites	994	7	17	59	125	193	186	128	95	184
Lung	485	0	7	29	59	104	112	66	39	69
Pleural mesothelioma	66	0	0	2	6	15	10	16	4	3
Peritoneal mesothelioma	109	0	0	3	3	18	22	18	16	29

Table VIII-31

EXPECTED AND OBSERVED DEATHS AMONG 933 AMOSITE ASBESTOS FACTORY WORKERS EMPLOYED 1941-45 OBSERVED TO DECEMBER 31, 1977

		Deaths of lung cancer and mesothelioma				
Time from onset (years)	*Man-years*	*Lung cancer*			*Mesothelioma*	
		Exp.	*Obs.*	*Ratio*	*Pleural*	*Peritoneal*
<5	4,331	0.95	0	—	0	0
5-9	4,095	1.78	3	—	0	0
10-14	3,784	2.57	13	5.06	0	0
15-19	3,362	3.19	20	6.27	0	0
20-24	2,837	3.49	18	5.16	1	0
25-29	2,250	3.59	25	6.96	2	4
30-34	1,553	3.16	17	5.38	5	3
35+	192	0.41	4	—	0	1
	22,404	19.14	100	5.22	8	8

of mesothelioma induction, has been demonstrated by Roe et al. (54). After subcutaneous injection in mice (experiments with three types of asbestos), wide dissemination from the site of injection and a highly selective distribution were observed; the main sites of asbestos accumulation were the visceral and parietal pleura and the serosal surface in the abdominal cavity.

- the fiber size (cross-sectional diameter and length) seems to be important, since smaller fibers penetrate deeply into the periphery of the lung and subpleural areas (21)(22)(67)(68)(70)(75).

The evidence for marked effects, including the carcinogenic mesothelioma inducing effect of small fibers (length less than 5 um) has emerged relatively recently (122)(24)(75). This is important in view of the fact that handling or treating asbestos as well as use of asbestos products gen erates fragmentation (both longitudinally and transversely) of fibers resulting in a larger number of shorter and thinner fibers or even fibrils. Chrysotile is especially prone to undergo such

fragmentation.

CLINICAL DESCRIPTION

Symptoms

Chest pain (unilateral) and shortness of breath are the most common presenting symptoms. The chest pain may be diffuse and dull or it may be of the pleuritic type; it often progresses to be severe. Shortness of breath may rapidly progress, especially with the development of a pleural effusion.

Other relatively frequent symptoms are loss of appetite, weight loss, fatigue, and in some cases fever; cough is infrequent.

Physical Signs

Pleural effusion occurs in the majority of cases, with dullness on percussion and decreased breath sounds. Rapid recurrence after aspiration of pleural fluid is the rule. The pleural fluid may be serous and clear but sometimes is hemorrhagic.

Retraction of the affected hemithorax, and shifting of the mediastinum to the side of the lesion may occur.

Natural History

Rapid tumor growth—often after pleural biopsy, i.e., needle biopsy or thoracotomy—with subcutaneous tumor nodules may involve the chest wall, the ribs and vertebrae, the mediastinum (sometimes with superior vena cava syndrome), and/or the pericardium with pericardial effusion. Distant metastases to the liver or other intra-abdominal organs, sometimes with ascites, can be clinically detected.

The metastatic spread of mesothelioma is much more frequent than previously thought and has been shown to occur in the majority of cases in which an autopsy was performed; both lymph node metastases and distant hematogenous metastases can be found. Spread of the mesothelioma to the opposite pleural cavity, and also to the peritoneum, is frequent; most often this is the result of a local invasive process, through the mediastinum or through the diaphragm.

The natural history of the disease is that of a rapid downhill course; death occurs in the majority of cases after an interval of months to one or two years. The mean survival from first diagnosis does not exceed 12 months. Although all therapeutic methods have been used, often in combination (surgery, radiotherapy, chemotherapy), no significant difference in survival of patients with pleural mesothelioma has been consistently achieved.

Laboratory Investigations

Radiographic changes are characteristically unilateral and progressive. The two main modalities of radiologic changes in pleural mesothelioma are: 1) unilateral pleural effusion; 2) large, nodular, protuberant opacities projecting from the pleura into the pulmonary parenchyma. Most often a combination of these changes is found.

Aspiration of the pleural fluid may be helpful in revealing underlying solid tumoral opacities. Extension of the tumoral growth over the apical pleura and into the mediastinal pleura is frequent. PA chest radiographs should be complemented by oblique views of the chest whenever a suspicion of pleural mesothelioma arises. Other radiographic evidence of asbestos-related parenchymal and/or pleural changes may or may not be present. Pleural plaques or calcifications are a useful marker of past asbestos exposure.

Pulmonary function studies are irrelevant for the diagnosis of mesothelioma.

Pleural fluid aspiration, while often necessary to alleviate respiratory distress, is of limited diagnostic use. Cytology of the pleural effusion is often fraught with the difficulty of distinguishing between mesothelial malignant cells and "atypical" mesothelial cells. The detection of hyaluronic acid in the pleural fluid is useful, although it can be found with other malignant tumors of the pleura; a negative result does not discard the diagnosis (6)(25)(76).

Needle biopsy specimens are insufficient for tissue diagnosis, since tissue specimens so obtained might not include malignant changes (although such changes may well be present in adjacent areas of the pleura) and since there is marked variability of pathologic changes.

Thoracotomy with surgical pleural biopsy, although providing adequate tissue specimens for diagnostic purposes, is often followed by local extension of tumor growth into the chest wall.

Treatment

There is no effective therapeutic approach, although surgery to reduce the tumor mass (9), radiotherapy (17)(57)(71), chemotherapy, single drugs (7)(18)(29)(30)(40), or combinations of two, three, or four drugs, and all possible combinations of these methods have been attempted (35).

Wanebo et al. reported on 66 cases with

malignant mesothelioma (78). For the epithelial type, pleurectomy combined with irradiation and chemotherapy seemed to be more effective; in the fibrosacromatous type, surgery resulted in longer survival.

Prognosis

The disease is fatal, and progression is usually rapid, with marked deterioration over short periods of time. In exceptional cases, longer survival (several years) can occur even in the absence of any therapeutic procedure.

DIAGNOSTIC CRITERIA

The diagnostic criteria for pleural mesothelioma are:

- a history of asbestos exposure in the past. Occupational exposure (even for short periods) or household or neighborhood exposure has to be actively searched for and can be established in the vast majority of cases if histories are taken by a physician with experience in occupational medicine (11).
- long latency period, usually more than 20 years from onset of exposure, most often between 30 and 40 years.
- clinical symptoms: unilateral chest pain and/or significant increase in dyspnea over a short period of time (weeks or months).
- physical findings: consistent with pleural effusion.
- radiographic abnormalities presenting as pleural effusion or pleural thickening often with large nodular opacities projecting from the pleura. Rapid increase in pleural thickening or the the appearance of irregularities of the pleura are highly suspicious. Rapid progression of radiologic changes.
- tissue diagnosis on an adequate specimen (thoracotomy with pleural biopsy). Microscopic findings consistent with the epithelial (tubulopapillary), mesenchymal (fibrosarcomatous), or mixed or undifferentiated type.

The complexities and difficulties of the pathologic diagnosis have been discussed. The finding of hyaluronic acid in the pleural fluid of tissue specimen is useful, but the diagnosis cannot be discarded when the test is negative.

In the differential diagnosis of pleural mesothelioma, the following problems are of practical importance: (a) Benign pleural effusions may occur in a patient with present or past asbestos exposure. The clinical course is usually indicative, since benign pleural effusions tend to resolve spontaneously over several weeks. Nevertheless, such a "benign pleural effusion" has been observed, in some cases, to be a precursor of pleural mesothelioma. (b) Pleural fibrosis is a common finding in persons with present or past asbestos exposure; the prevalence increases with time since onset of exposure. In cases with extensive pleural fibrosis, especially when the width on chest x-ray exceeds 10 mm, the differential diagnosis between pleural fibrosis and pleural mesothelioma may be difficult. The presence of similar pleural changes on previous x-ray films makes the diagnosis of mesothelioma less likely; repeat chest x-ray films after several weeks are necessary when no previous chest x-ray are available. (c) The differential diagnosis between pleural mesothelioma (*primary* malignant tumor originating in the pleura) and secondary involvement of the pleura by a malignant tumor, either lung cancer or another primary malignant tumor with metastatic spread to the pleura, has been given much attention. In the case of lung cancer, sputum cytology and fiber optic bronchoscopy with bronchial biopsy, in addition to the radiologic appearance, contribute to the differential diagnosis. The proportion of cases which remain undecided is small. The possibility of a malignant primary tumor originating in another site, with metastatic spread to the pleura is investigated by the routine clinical work-up. Patients with no other detectable primary tumor but with clinical and radiologic features of mesothelioma have, with a high degree of probability, pleural mesothelioma. The absolute certainty of this differential diagnosis is reached only after postmortem examination.

In reviewing the experience accumulated over the last 20 years, it becomes obvious that pleural mesothelioma has been largely underdiagnosed in the past. This has been established in prospective cohort studies of asbestos-exposed workers (28)(33)(34)(38)(44)(47)(60); in many studies investigating diagnostic accuracy in series of reported mesothelioma cases (15); and in systematic reviews of all pathology material—as in Scotland where 80 undiagnosed cases were discovered (39).

In the 1967-1977 cohort study of 17,800 asbestos insulation workers in the United States and Canada, out of a total of 2,270 consecutive deaths, 60 were recorded on the death certificate as mesothelioma (31 pleural, 29 peritoneal). Review of medical records, including pathology reports, chest x-ray films, postmortem examinations (when available) and independent review of tissue specimens by experienced pathologists resulted in a diagnosis of mesothelioma in 175 cases (66 pleural, 109 peritoneal). The death certificate accuracy was 47% for pleural mesothelioma and 27% for peritoneal mesothelioma (Table VIII-32). In another cohort of 689 asbestos workers, 11 cases of mesothelioma (4 pleural, 7 peritoneal) were recorded on death certificates for the period 1959-1975. Review of medical records and pathology material resulted in a diagnosis of mesothelioma in 26 cases (14 pleural, 12 peritoneal), with the death certificate accuracy only 28% for pleural mesothelioma, and 58% for peritoneal mesothelioma (Table VIII-33).

In the majority of pleural mesothelioma cases it is possible to establish the diagnosis intravitam. The greater awareness of population groups with present or past exposure, of the Department of Health, Education and Welfare, of other governmental agencies, and of the medical community are expected to result in earlier diagnosis. This is a prerequisite for future meaningful attempts of therapy.

The requirement of postmortem examination for the definitive diagnosis is necessary for the complete assessment of mesothelioma incidence from an epidemiologic point of view, although it is expected that a higher index of suspicion will substantially reduce the difference between the number of cases diagnosed while alive and those in which the diagnosis is reached only after postmortem examination.

METHODS OF PREVENTION

The prevention of pleural mesothelioma is dependent on the reduction of exposure to asbestos fiber to the minimum possible level, since this adverse health effect has been specifically associated with low level and short-term exposure. In December 1976, NIOSH, based on a "Reexamination and Update of Information on the Health Effects of Occupational Exposure to Asbestos," recommended to the DHEW and OSHA that the standard be reduced to 0.1 fibers /cm^3. This was based on the lowest concentration at which asbestos fibers can be reliably identified by phase contract microscopy.

RESEARCH NEEDS

Critical problems where research is needed:

1. Determine mechanisms of carcinogenicity (mineral fibers; potential effect of other mineral fibers, such as zeolites, titanite fibers, etc.).
2. Define, to the extent that it is at all possible, the lowest level of asbestos exposure which may result in mesothelioma. This is of paramount importance for the acceptable standard.
3. Establish the role(s) of immune mechanisms in individual susceptibility for mesothelioma.
4. Determine mechanisms of carcinogenicity in peritoneal mesothelioma, including the significance of ingestion of fibers. This is important since water may be polluted with mineral fibers from various sources, and the risk of mesothelioma from such a situation has not yet been assessed.
5. Establish mesothelioma therapy.

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Table VIII-32

MORTALITY EXPERIENCE AMONG 17,800 ASBESTOS INSULATION WORKERS IN THE UNITED STATES AND CANADA 1967-1977: OBSERVATIONS IN 2,270 CONSECUTIVE DEATHS

	Accuracy of death certificate categories				
		Death Certificate		*Ascertained*	
Cause of death	*Expected*	*Number*	*o/e*	*Number*	*o/e*
Cancer, all sites	319.90	888	2.77	994	3.10
Cancer, lung	105.97	403	3.80	485	4.57
Pleural mesothelioma	—	31	—	66	—
Peritoneal mesothelioma	—	29	—	109	—
Cancer, esophagus	7.01	16	2.28	18	2.56
Cancer, stomach	14.23	19	1.34	22	1.55
Cancer, colon	37.86	58	1.50	59	1.56
Cancer, pancreas	17.46	48	2.75	22	1.26
Cancer, liver	7.50	18	2.40	5	0.66
Cancer, brain	10.34	19	1.84	14	1.35
Asbestosis	—	108	—	162	—
Chronic obstructive lung disease	58.58	127	2.17	66	1.13

Death certificate accuracy: Cancer, 89%; lung cancer, 83%; G.I. cancer, 94%; pleural mesothelioma, 47%; peritoneal mesothelioma, 27%.

Table VIII-33

RELATION BETWEEN DIAGNOSIS OF CAUSE OF DEATH AS RECORDED ON THE DEATH CERTIFICATE AND AS ASCERTAINED BY REVIEW OF ALL AVAILABLE INFORMATION, IN 274 DEATHS AMONG 689 ASBESTOS WORKERS OBSERVED JANUARY 1, 1959 - DECEMBER 31, 1975

	Death certificate	*Ascertained*
Cancer, all sites	94	99
Cancer of lung	36	35
Pleural mesothelioma	4	14
Peritoneal mesothelioma	7	12
Mesothelioma — unspecified site	7	0
Cancer of esophagus, stomach, colon, and rectum	12	15
All other cancer	28	23
All respiratory disease	43	42
Asbestosis	26	35
Pneumoconiosis	8	0
All respiratory disease	9	7
All other causes	137	133

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Statement By

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Before the

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control

April 26, 1990

I am pleased to testify on the science and the health effects caused by exposures to asbestos. I am currently Assistant Director of the National Institute for Occupational Safety and Health (NIOSH). I have been involved with the study of occupational exposures to asbestos since 1970. I am also the primary author of the NIOSH recommended standard for occupational exposure to asbestos, the asbestos monograph published by the International Agency for Research on Cancer, and numerous articles on asbestos in the scientific literature. I have attached a copy of my complete curriculum vitae.

Asbestos is a generic term referring to a group of naturally occurring fibrous minerals that are commercially prized for their thermal and insulative properties, in addition to their flexibility, durability and tensile strength. Because of these characteristics, asbestos is highly persistent in the human body once inhaled or ingested.

Based on studies of workers who were heavily and regularly exposed to asbestos before general government regulation of the workplace, we know that asbestos causes specific diseases such as asbestosis, an irreversible and progressively disabling lung disease which impairs breathing, and mesothelioma, an invariably fatal cancer of the lining of the chest, pericardium, or abdominal cavity. Asbestos is one of the leading causes of lung cancer in non-smokers. Asbestos exposure for smokers increases the risk of lung cancer approximately 55 times that of those who are not exposed to asbestos and who do not smoke. Asbestos is also associated with an increased risk of gastrointestinal and other cancers.

The conclusion drawn by many experts, in this and other countries, and best summarized in the 1987 Supplement of the World Health Organization's International Agency for Research on Cancer, is that "... occupational exposure to chrysotile, amosite and anthophyllite asbestos and to mixtures containing crocidolite results in an increased risk of lung cancer, as does exposure to minerals containing tremolite and actinolite and to tremolitic material mixed with anthophyllite and small amounts of chrysotile. Mesotheliomas have been observed after occupational exposure to crocidolite, amosite, tremolitic material and chrysotile asbestos. Gastrointestinal cancers occurred at an increased incidence in groups occupationally exposed to crocidolite, amosite, chrysotile or mixed fibres containing crocidolite, although not all studies are consistent in this respect. An excess of laryngeal cancer has also been observed in some groups of exposed workers. No clear excess of cancer has been associated with the presence of asbestos fibres in drinking water. Mesotheliomas have occurred in individuals living in the neighbourhood of asbestos factories and mines, and in people living with asbestos workers."

Recent reports have appeared in the scientific literature to suggest that different forms of asbestos are not equally pathogenic (Mossman and Gee, 1989 and Mossman et al., 1990). However, there is a great deal of uncertainty associated with these findings and equally important contradictory evidence. Results from research involving animal bioassays present a strong case that there is no safe form of asbestos. Wagner et al. (1979), then with the United Kingdom's Medical Research Council, have shown that a commercial grade, predominantly short-fiber Canadian chrysotile (a purportedly less hazardous form of asbestos), and an ingredient used primarily in paint and in plastic tile fillers, induces mesotheliomas when injected intrapleurally into rats, and induces primary lung neoplasms in rats exposed by inhalation. Not only has chrysotile been found to be as potent as crocidolite and other amphiboles in inducing mesotheliomas when injected intrapleurally (Wagner et al., 1973), it has been found equally potent in inducing pulmonary neoplasms through inhalation

exposures (Wagner et al., 1974). Chrysotile also appears to be more potently fibrogenic and carcinogenic than amphiboles, in relation to the quantity of dust deposited and retained in the lungs of rats (Wagner et al., 1974).

There is the hypothesis that chrysotile is less hazardous because of its chemical and biological reactivity. In fact chrysotile fibers are much more chemically and biologically reactive than amphibole fibers (Davis et al., 1978; Davis et al., 1986a; and Davis et al., 1986b). In contact with body tissues, chryostile fibers lose their structural elements and divide into smaller fibrils, making their recognition difficult by the usual analytical methods. In fact, many of the fibers are removed from the lungs to other organs in the body and up through the bronchi. These findings also support the hypothesis that chrysotile fibers cause cellular injury, fibrosis and lung cancer. These fibers are less readily detected in the tissue after the damage is done. The concentration of dust in the lungs of rats exposed to Canadian chrysotile (Wagner et al., 1974) was only 1.8% to 2.2% of the dust concentration in the lungs of animals exposed to amphiboles, after 24 months of inhalation exposure. Yet the lung tumor incidences and degree of pulmonary fibrosis were similar among groups of rats exposed to different forms of asbestos.

At this time, there is no compelling evidence to justify different public health policy for different asbestos fiber types. The reason for higher incidence of lung cancer and mesothelioma in workers exposed to amphiboles is probably related to higher concentrations of respirable fibers during their exposures (NIOSH, 1979). Furthermore, most commercially exploited deposits of chrysotile are contaminated with some type of the amphibole form of asbestos (Bartlett, 1988 and Campbell, 1988).

Other international expert groups have reached similar conclusions regarding the uncertainty of the hypothesis that some forms of asbestos may be less hazardous. In a recently released document from an expert panel convened by the World Health Organization in 1989, the panel concluded: "it is difficult to substantiate this difference [in pathogenicity] firmly after standardization for exposure levels, type of industry, duration of employment, etc." This conclusion agrees with the findings of the 1984 report of the Canadian Royal Commission on Matters of Health and Safety Arising from the Use of Asbestos in Ontario. The Commission recommended that textile manufacturing using a form of asbestos purported to be less hazardous (chrysotile) be banned, and concluded that "all fiber types can cause all asbestos-related diseases."

The Centers for Disease Control (CDC) through NIOSH has recently submitted to Occupational Safety and Health Administration (OSHA) on April 8, 1990 a reiteration of its previous testimony of June 21, 1984, that " . . . there is no safe concentration for exposure to asbestos." Not even the lowest exposure limit for asbestos could assure all workers absolute protection from exposure-related cancer. OSHA projects that at the current occupational standard for asbestos of 0.2 fibers/cc over a working lifetime, 67 cancers for every 1,000 exposed workers can be expected to develop (OSHA, 1986). In the April 8, 1990 submittal to OSHA, CDC through NIOSH also reaffirmed its position that there is no scientific basis for differentiating between types of asbestos fibers for regulatory purposes. The scientific evidence to date suggests that fiber morphology (size and shape) is the most critical factor in the pathogenicity of the material and as such the most prudent public health policy is to regulate asbestos based upon its morphology and not on its mineralogic source.

I would be happy to answer any questions the subcommittee may have.

American Journal of Public Health

Reprint

Occupational Exposure to Chrysotile Asbestos and Cancer Risk: A Review of the Amphibole Hypothesis

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ABSTRACT

Objectives. This article examines the credibility and policy implications of the "amphibole hypothesis," which postulates that (1) the mesotheliomas observed among workers exposed to chrysotile asbestos may be explained by confounding exposures to amphiboles, and (2) chrysotile may have lower carcinogenic potency than amphiboles.

Methods. A critical review was conducted of the lung burden, epidemiologic, toxicologic, and mechanistic studies that provide the basis for the amphibole hypothesis.

Results. Mechanistic and lung burden studies do not provide convincing evidence for the amphibole hypothesis. Toxicologic and epidemiologic studies provide strong evidence that chrysotile is associated with an increased risk of lung cancer and mesothelioma. Chrysotile may be less potent than some amphiboles for inducing mesotheliomas, but there is little evidence to indicate lower lung cancer risk.

Conclusions. Given the evidence of a significant lung cancer risk, the lack of conclusive evidence for the amphibole hypothesis, and the fact that workers are generally exposed to a mixture of fibers, we conclude that it is prudent to treat chrysotile with virtually the same level of concern as the amphibole forms of asbestos. (*Am J Public Health.* 1996;86:179–186)

Introduction

Chrysotile is the predominant type of asbestos produced and consumed in the world today, and it accounted for over 98.5% of US asbestos consumption in 1992.[1] Although asbestos consumption has declined in North America and Europe, sales in other countries (e.g., Southeast Asia, South America, and Eastern Europe) have increased primarily due to the use of asbestos-based construction materials.[2]

Chrysotile is a serpentine (curly) form of asbestos that is distinguished from other amphibole forms of asbestos (i.e., crocidolite, amosite, tremolite). It has been hypothesized that (1) the mesothelioma risk observed among workers exposed to chrysotile asbestos may be explained by the relatively low concentrations (<1%) of tremolite fibers in commercial chrysotile asbestos fibers and (2) that chrysotile asbestos may be less potent than amphiboles in the induction of asbestosis and lung cancer. This has been dubbed the amphibole hypothesis.[3] It has even been suggested that exposure to chrysotile asbestos in the absence of tremolite may present little or no carcinogenic hazard.[4]

The arguments advanced to support the amphibole hypothesis have been primarily based on pathologic studies of burdens of asbestos fibers in human lungs and on toxicologic, mechanistic, and epidemiologic studies. This article presents a critical review of these arguments and of the literature on the carcinogenic hazards associated with exposure to chrysotile asbestos and considers the implications of these findings for the development of occupational health policies.

Lung Burden Studies

The development of methods that involve electron diffraction and energy dispersive analysis of x-rays (EDAX)[5] has made possible the measurement of the amounts of different fiber types in the lung. The results from lung burden studies have provided the primary basis for the advancement of the amphibole hypothesis.

Case studies of individuals who have worked in industries using or producing chrysotile asbestos revealed an unexpectedly high proportion of amphibole (primarily tremolite) fibers, considering the relatively low percentage of amphibole fibers in commercial chrysotile asbestos.[6] In one of the earliest studies, Pooley observed a greater number of amphibole fibers than chrysotile fibers in 7 of 22 patients with asbestosis who had worked in the Canadian chrysotile mining industry.[7] Rowlands et al. also reported a nearly equal concentration of tremolite fibers and chrysotile fibers in the lungs of 47 workers employed as miners or millers in Quebec.[8] Similarly, in population-based studies the percentage of chrysotile fibers found in the lungs has been surprisingly low considering the fact that chrysotile is the major source of exposure for the general population.[9]

Most case–control studies that evaluated the potential relationship between

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Editor's Note. See related annotation by Cullen (p 158) in this issue.

TABLE 1—Summary of Epidemiological Cohort Studies of Workers Exposed to Predominantly Chrysotile Asbestos

Study	Industry	Lung Cancer Deaths		Mesothelioma Cases	
		Observed	Expected	Observed	Deaths, %
Acheson et al.[27]	Gas masks	6	4.8[a]	1	0.6
Cheng and Kong[28]	Textiles, friction materials, and cement	21	6.7*	0	0
Dement et al.[29]	Textiles	126	64.0*	2	0.2
Finkelstein[30]	Electrical conduit pipe	6	3.7	1	1.0
Finkelstein[31]	Automotive	11	7.9	1–2[b]	1.0–1.9
Hughes et al.[32,c]	Cement manufacturing	70	53.2	1	. . .
Huilan and Zhiming[33]	8 asbestos factories	65	15.6[a]*	2	0.4
McDonald et al.[34]	Friction products	73	49.1*	0	0
McDonald et al.[35,36,d]	Mining and milling	518	389.7*	28	0.4
Piolatto et al.[37]	Mining	22	19.9	2	0.5
Shiqu et al.[38]	Mining	6	. . .	3	4.5
Weiss[39]	Paper and millboard	4	4.3	0	0
Total		922[e]	618.9	41.0	0.3

Note. SMR = the standardized mortality ratio, which is the ratio between the observed and expected.
[a]The expected number is for cancer of the lung and pleura combined.
[b]One or two cases of mesothelioma were reported. Only one was included in the totals.
[c]Results are for workers exposed only to chrysotile from one of two plants studied. The total number of deaths was not reported; thus, the percentage of mesothelioma deaths could not be estimated.
[d]Observed and expected numbers exclude observations from the asbestos factory.
[e]The Shiqu et al. study was not included in the total number of lung cancer cases because expected numbers were not reported.[37]
*Significantly different from the observed number, $P < .05$ (two tailed).

mesothelioma risk and lung concentrations of the different fiber types of asbestos demonstrated a clear relationship with amphibole lung burdens but failed to find a relationship with lung chrysotile concentrations.[10–14] McDonald et al. reported an association between mesothelioma and lung concentrations of long (≥ 8 μm) chrysotile fibers in univariate analyses but not in multivariate analysis, which controlled for the other fiber types.[15] Rogers et al. reported a significant association between mesothelioma risk and lung concentrations of short chrysotile fibers (<10 μm) in multivariate models and a significant trend for lung concentrations among mesothelioma case and control subjects who had only chrysotile detected in their lungs.[16]

The interpretation of the results from the studies of lung burden is complicated by differences in the respiratory clearance rates of the different forms of asbestos. Experimental studies demonstrated that chrysotile fibers are cleared far more rapidly from the lungs than are amphibole fibers.[17–19] The retention half-life of chrysotile in human lungs is unknown, but a half-life of 90 days has been reported in experimental studies of baboons.[20] If the half-life for chrysotile is similar for humans and baboons, then clearly the vast majority of the dose received in early years would not be reflected in the lung burdens measured at the time of autopsy. This is of particular concern for mesothelioma, which has been estimated to have a latency period of at least 20 years.[21] For example, assuming a 90-day half-life and first-order kinetics, only approximately $1/(8 \times 10^{22})$ of the dose received 20 years earlier would be predicted to be present in the lungs at the time of the autopsy. Hence, lung burdens of chrysotile may be a poor measure of the integrated exposures to chrysotile.

The high degree of correlation between the lung concentrations of the different fiber types, which has been noted by several investigators, further complicates the interpretation of the lung burden analyses.[15,16,23] Churg reported that the correlation coefficient between the numbers of chrysotile and crocidolite fibers in lungs of asbestosis patients was .88 ($P < .05$).[23] Rowlands et al. reported a stronger correlation between cumulative asbestos exposure and lung fiber counts for tremolite than between cumulative asbestos exposure and lung burdens of chrysotile in their study of Quebec miners and millers.[8] The high degree of correlation might explain the negative findings in some of the case-control studies if amphibole exposures are simply acting as a surrogate for integrated lifetime chrysotile exposure in these studies. As Churg et al. suggested, "It may be true that the tremolite serves as a better measure of past chrysotile than the chrysotile itself."[19]

Finally, studies of fiber counts in extrapulmonary sites raise serious questions about the validity of using lung burden studies for assessing mesothelioma risk. Several investigators reported cases in which short chrysotile fibers were the predominant fiber found in the pleura, pleural plaques, or pleural fibrotic tissue when amphiboles were the predominant fiber found in the lung.[22,24–26] These results suggest that chrysotile may be preferentially translocated to the pleura and that the fiber counts found in the lung may not accurately reflect the concentrations found at the site for mesothelioma induction.

Epidemiologic Studies

Lung Cancer

There have been 12 retrospective cohort mortality studies of workers who were predominantly exposed to chrysotile asbestos fibers. Results for mortality from lung cancer (and mesothelioma) from the most recent updates of these cohorts are summarized in Table 1. Mortality from lung cancer was greater than expected in nearly all of the studies. Combining the results from these studies, there were 928 observed and 618.9 expected lung cancer deaths, resulting in a pooled standardized mortality ratio for lung cancer of 1.50 (95% confidence interval [CI] = 1.40, 1.60). The observed excesses of lung cancer mortality did not appear to be explained by differences in cigarette smoking habits in the studies that had information on tobacco consumption.[28,33,35,36,40,41] Collectively, these studies provide strong evidence that exposure to chrysotile asbestos is associated with an excess risk of lung cancer.

There is little, if any, evidence to suggest that the excess in lung cancer mortality observed in these cohorts may be attributable to tremolite contamination. In fact, this hypothesis is strongly contradicted by the fact that the lung cancer response in the studies of populations with relatively pure chrysotile exposures is similar to that in studies of cohorts with amphibole or mixed exposures. Estimates of the increase in excess relative risk per unit of exposure (i.e., potency) for lung cancer based on cohort studies by industry and fiber type are presented in Table 2. Variations in risk according to

industry type appear to be far more remarkable than variations according to fiber type. The potencies for lung cancer risk are similar among the cohorts with pure chrysotile and mixed exposures in the textile industry and are generally higher than the potencies observed among workers in the mining or asbestos products industries. The studies of asbestos products industry workers all show very low potencies, with the lowest unit risks observed among friction product workers. One study of cement workers, which provided separate analyses for workers exposed to chrysotile asbestos and workers exposed to a mix of chrysotile and crocidolite fibers, produced remarkably similar potency estimates for these two groups.[32] Among the studies of miners, lung cancer potency was substantially lower among workers in the Quebec mining industry who were exposed to chrysotile ores than among crocidolite or tremolite miners.

It has been suggested that the high lung cancer mortality observed among South Carolina textile workers might be explained by exposure to mineral oils.[47] However, Dement et al. demonstrated in case–control analyses that the risk of lung cancer observed in this cohort is unrelated to mineral oil exposure.[29,48] In addition, studies of workers exposed to mineral oils have generally not demonstrated an excess of lung cancer.[49] There is evidence that asbestos fibers in the textile industry were considerably longer than the fibers measured in chrysotile mining and milling and other industries.[50] Thus, differences in fiber dimensions would appear to be a more likely explanation than mineral oil exposures for the higher lung cancer rates observed in textile workers.

TABLE 2—Estimates of Asbestos Potency for Lung Cancer from Studies with Individual Exposure Estimates, by Industry and Fiber Type

Study	Industry	Fiber Type	Excess Relative Risk per Fiber/cc × Yr
Dement et al.[29]	Textiles	Chrysotile	0.031
McDonald et al.[12]	Mainly textiles	Chrysotile, amosite, crocidolite	0.017[a]
Peto et al.[42]	Textiles	Chrysotile, crocidolite	0.015[b]
McDonald et al.[43]	Mining	Tremolite	0.013
de Klerk et al.[44]	Mining and milling	Crocidolite	0.010
McDonald et al.[36]	Mining and milling	Chrysotile	0.0006[a,c]
Henderson and Enterline[45]	Asbestos products	Chrysotile, amosite, crocidolite	0.002[a]
Hughes et al.[32]	Cement products	Chrysotile,[a] chrysotile,[b] and crocidolite	0.0071,[a] 0.0076[b]
Berry and Newhouse et al.[46]	Friction products	Chrysotile	0.00058
McDonald et al.[34]	Friction products	Chrysotile	0.00053[a]

[a]A conversion factor of three fibers per cubic centimeter being equivalent to 1 million particles per cubic foot was assumed.
[b]Data are based on results for workers employed after 1951.
[c]Slope was estimated by fitting a linear relative risk Poisson regression model to the standardized mortality ratio results reported by McDonald et al.[36]

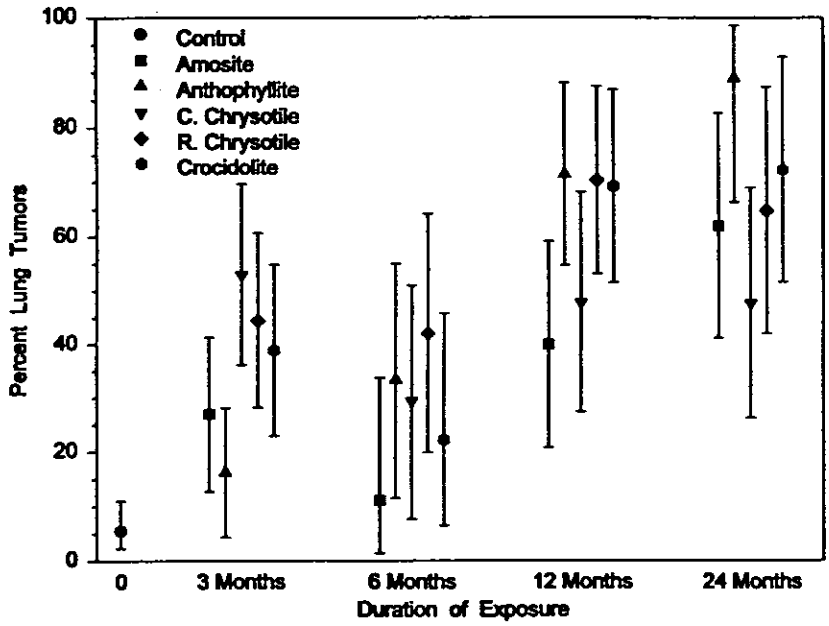
Mesothelioma

A total of 45 cases of mesothelioma (primarily pleural) were reported in the epidemiologic studies of workers who were predominantly exposed to chrysotile asbestos (Table 1). Although it has generally not been possible to estimate expected numbers of mesothelioma deaths, the percentage of deaths due to mesothelioma may be estimated and compared with background percentages. This percentage is 0.3% for all studies combined. In contrast, the percentage of deaths due to pleural malignancies (most of which are mesotheliomas) was only 0.02% in the United States in 1988.[51]

Although the evidence of excess mortality of mesothelioma among workers exposed to commercial chrysotile is compelling, the critical issue is whether this excess may be attributable to trace contamination by tremolite. All of the asbestos workers studied (Table 1) are likely to have potential exposures to tremolite, although in minute concentrations compared with their chrysotile exposures.

In a few studies the percentage of tremolite is known and varies. Contrasting the results from these studies provides some information on the plausibility of the amphibole hypothesis. Two cases of mesothelioma have been reported among chrysotile asbestos miners and millers in Zimbabwe, where the chrysotile ores are believed to be free of tremolite contamination.[52] Begin et al. noted that although exposure to tremolite may be as much as 7.5 times higher in Thetford than in Asbestos, the incidence of mesothelioma in these two Quebec mining towns was proportional to the size of their work forces.[53] He suggested that this fact may indicate that tremolite contamination may not be a determinant of mesothelioma risk in Quebec. In the most recent update of the study of Quebec miners and millers, McDonald et al.[36] presented separate exposure–response analyses for workers at the Thetford and Asbestos mines and mills. There is no indication in their findings that these two facilities exhibit a different exposure–response relationship for mesothelioma. On the other hand, McDonald and McDonald[54] recently reported that the average concentration of tremolite fibers in the lungs of miners was higher in one area of the Thetford mine, which also demonstrated a stronger association with mesothelioma risk than another area of the mine.

Informative comparisons may also be made between the proportion of deaths from mesothelioma observed in the South Carolina textile workers study and that observed in the Quebec miners and millers study. Based on lung burden studies, Sebastien et al. estimated that the proportion of tremolite in dust was probably 2.5 times higher in the Thetford mines of Quebec than in the Charleston textile facility.[47] The percentage of deaths due to mesothelioma in the most recent reports was one half as high in the South Carolina textile workers (0.2%) as it was among Quebec miners and millers (0.4%) (Table 1). However, in making this comparison one needs to consider the fact that the incidence of mesothelioma is known to increase exponentially with follow-up time,[55] and 72% of the Quebec miners and millers had died,[36] compared with 42% of the workers in the South Carolina study,[29] in the most recent updates of these cohorts. In the previous



Note. Data are from Wagner et al.[17]; approximate 95% confidence intervals for a binomial outcome have been added. C = Canadian; R = Rhodesian.

FIGURE 1—Lung tumors in rats exposed to 10 mg/m³ concentrations of asbestos for 3, 6, 12, or 24 months.

update of the Quebec miners and millers study, the percentage that had died was 41% and the percentage of deaths due to mesothelioma was 0.2%, which is nearly identical to the percentage of deaths from mesothelioma in the most recent update of the South Carolina textile workers.[35] The fact that these percentages are so similar is even more remarkable when it is recognized that the fiber exposure levels were approximately ten times higher in the Quebec miners and millers than in the South Carolina textile workers.[47] Thus, comparison of the mesothelioma results from the study of Quebec miners and millers with those from the study of South Carolina textile workers does not provide support for the hypothesis that tremolite exposure explains the mesothelioma excess observed in these studies.

In contrast to the evidence for lung cancer, there is epidemiologic evidence indicating that exposure to chrysotile may be less potent than exposure to some amphiboles with regards to the induction of mesothelioma. Hughes and Weill estimated that the risk of mesothelioma was approximately five times lower among workers exposed to chrysotile fibers than among workers with mixed fiber exposure.[56] The percentage of deaths due to mesothelioma among South African asbestos miners was recently reported to be 4.7% among those exposed to crocidolite, which is substantially greater than the percentage of deaths due to mesothelioma observed in either the Quebec miners (0.4%) or the South Carolina textile workers (0.2%) exposed to predominantly chrysotile fibers.[57] The percentage of deaths due to mesothelioma was only slightly higher among South African miners exposed to amosite (0.6%) than among the chrysotile-exposed cohorts.[57] McDonald et al.[43] reported that the percentage of deaths due to mesothelioma was 2.4% among vermiculite miners who were predominantly exposed to tremolite fibers, which is approximately six times higher than the percentage (0.4%) reported in the study of Quebec miners and millers.[36] It must be recognized that the usefulness of these comparisons is limited by our inability to control for potential differences in exposure concentrations, fiber size distributions, and length of observation and are thus difficult to interpret. Nonetheless, the differences in mesothelioma response observed among chrysotile- and amphibole (primarily crocidolite)-exposed workers are so striking that alternative explanations for these differences appear unlikely.

Toxicologic Studies

Lung Cancer

Toxicologic studies demonstrated that all forms of asbestos can induce lung cancers in experimental animals. For example, the lung tumor response to 3- to 24-month exposures to Union International Contre le Cancer reference amosite, anthophyllite, Canadian chrysotile, Rhodesian chrysotile, and crocidolite is shown in Figure 1.[17] The overlapping 95% confidence intervals suggest that there is no significant difference in potency among the five types of asbestos (i.e., the amphiboles are not systematically more or less potent than the chrysotiles).

Davis and co-workers also compared the carcinogenic potencies of chrysotile and amphibole asbestos by exposing rats to 10 mg of amosite, crocidolite, and Zimbabwe chrysotile per m³ for 1 year. These investigators found that chrysotile actually produced more lung tumors than the other forms of asbestos.[58] These results obviously differ from those of Wagner et al.[17] and may point to the need to consider differences in fiber length when comparing the potencies of different types of asbestos. Davis et al. noted that 5% of the chrysotile in their study consisted of fibers greater than 20 μm in length vs 0.5% of the fibers for the amosite and crocidolite exposures.[58] Other studies by Davis et al. showed that long-fiber samples of amosite[59] and chrysotile[60] are considerably more active than short-fiber samples in inducing lung tumors.

Davis et al. also showed that tremolite,[61] crocidolite,[58] and long-fiber chrysotile[60] produce similar numbers of lung tumors. Figure 2 represents lung tumors due to amosite, crocidolite, chrysotile, or tremolite from the 1-year inhalation studies of Davis et al. and Davis and Jones, plotted against the exposure concentration in units of fiber count.[58-61] Inspection of Figure 2 suggests that the tumor incidence is strongly related to the concentration of fibers 5 μm or greater in length, regardless of which type of asbestos is involved.

More recently, Coffin et al.[62] reported the results from studies of rats exposed via intratracheal instillation of chrysotile or crocidolite. Although these investigators focused primarily on mesotheliomas, it is worth noting that (summed across all dose groups) intratracheal instillation of chrysotile asbestos produced

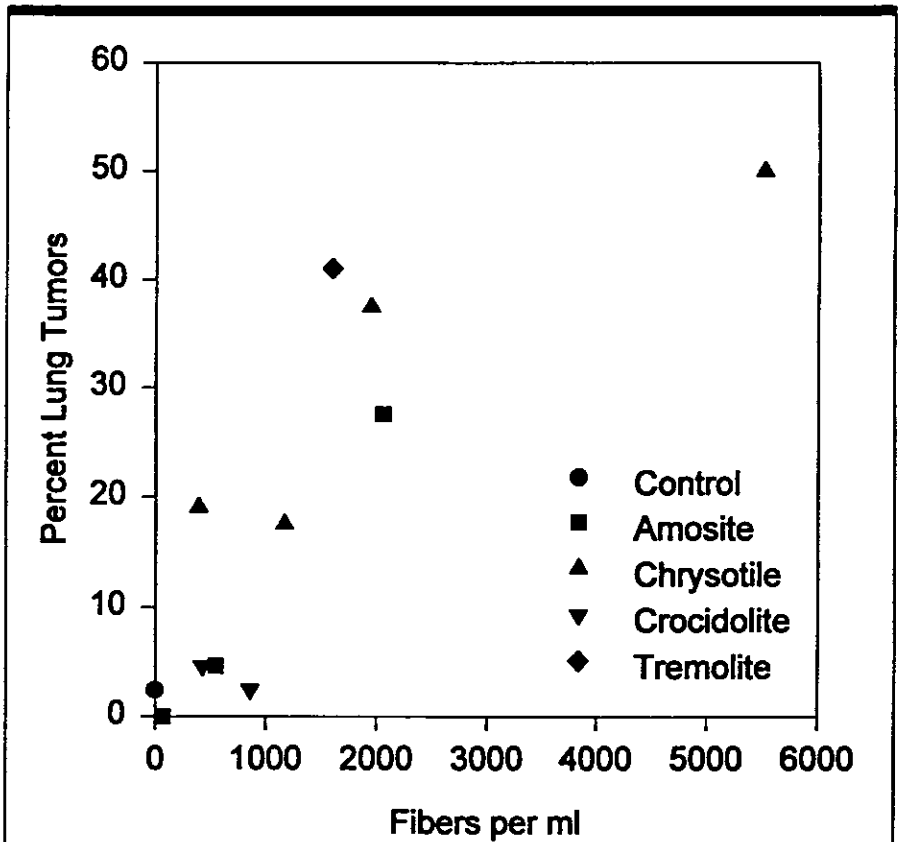
lung carcinomas in 18.3% of the animals tested vs 4.6% for crocidolite.[62]

Overall, the toxicologic data suggest that chrysotile asbestos is at least as potent, if not more so, as the amphibole forms in the induction of lung tumors on a per-milligram basis. The data shown in Figure 2 further suggest that the carcinogenic potencies of the various types are similar when the dosage is measured in terms of the number of fibers greater than 5 μm in length, as is customary in epidemiologic studies.

Mesothelioma

Rats exposed to asbestos by inhalation also develop mesotheliomas, albeit at a low incidence. Wagner et al.[17] exposed rats to 10 mg/m³ of Union International Contre le Cancer reference asbestos[63] for periods of 1 day to 2 years; the mesothelioma yields were amosite, 0.7%; anthophyllite, 1.4%; crocidolite, 2.8%; and Canadian chrysotile, 2.9%. No mesotheliomas were observed in control animals or animals exposed to chrysotile from Zimbabwe.[17] Similarly, Davis et al. and Davis and Jones reported small numbers of mesotheliomas in response to 1-year inhalation exposures to amosite, crocidolite, Canadian chrysotile, and Zimbabwe chrysotile.[58-60] The highest mesothelioma incidence in these studies, 7.5%, was produced by exposure to long-fiber chrysotile.[60] Although the low incidence rates and small numbers of animals make quantitative comparisons uncertain, it cannot be said that these studies provide convincing support for the amphibole hypothesis.

The mesothelioma-inducing potential of asbestos fibers that reach pleural surfaces has also been examined via implantation studies. Union International Contre le Cancer reference amosite, anthophyllite, crocidolite, Canadian chrysotile, and Zimbabwe chrysotile all produced mesotheliomas in rats after intrapleural inoculation.[64] Extensive studies by Stanton and co-workers suggest that all long, thin, durable fibers have the potential to induce mesotheliomas after surgical implantation and that fiber dimensions have much more influence on mesothelioma yield than any differences that may exist between types of asbestos.[65] However, it is certainly possible that different types of asbestos fibers may have differing probabilities of reaching pleural surfaces when inhaled into the lungs. Overall, the implantation studies suggest that chrysotile asbestos does have the potential to induce mesothelioma, but



Note. Data are from Davis et al. and Davis and Jones.[58-61] Controls are the pooled control animals from all four studies.

FIGURE 2—Lung tumors in rats exposed to 10 mg/m³ concentrations of crocidolite, amosite, chrysotile, or tremolite for 1 year.

these studies do not resolve the question of whether or not chrysotile is less potent in this regard than the amphibole forms.

Coffin et al. recently reported that both chrysotile and crocidolite produce mesotheliomas when administered intratracheally.[62] No consistent dose–response relationship was observed in these experiments, but (summing across all dose groups) chrysotile asbestos produced mesotheliomas in 9.5% of the animals vs 5.1% for crocidolite. This suggests that chrysotile may have greater mesothelioma-inducing potential than crocidolite on a per-milligram basis. However, the chrysotile preparation used in this experiment contained more fibers per milligram than the crocidolite preparation, as well as a larger proportion of long fibers. If the experimental exposures are expressed on the basis of the number of fibers greater than 5 μm in length, it appears that crocidolite produced nearly 12 times more mesotheliomas per fiber than chrysotile. It should be noted that the fiber preparations in the Coffin et al. experiments consisted primarily of short fibers, with median fiber lengths on the order of 1 μm for both chrysotile and crocidolite. If short fibers do in fact have some mesothelioma-inducing potential, the attribution of all mesotheliomas to the small fraction of the fibers that were greater than 5 μm in length may lead to an exaggerated estimate of the difference in potency of crocidolite vs chrysotile. In addition, reliance on the quantitative responses in this study should probably be limited due to the lack of dose–response. Nevertheless, these data do provide some support for the hypothesis that chrysotile may have lower mesothelioma-inducing potential than the amphibole forms of asbestos.

Mechanistic Studies

It has been hypothesized that the cytotoxic, genotoxic, and proliferative effects of asbestos are in part mediated by the production of reactive oxygen species released by alveolar macrophages in response to engulfment of long fibers and

that this process may be catalyzed by iron on the fiber surface. Furthermore, it has been suggested that the needle-like configuration, durability, and increased iron content of crocidolite render it more pathogenic than either amosite or chrysotile.[66] Experimental support for this hypothesis is primarily derived from in vitro studies, which suggest that iron could potentially act as a source of free radicals, an inhibitor of tumoricidal defense mechanisms, and a nutrient for unrestricted tumor cell replication.[67] However, comparison of the carcinogenic potencies of fibers in the rat in vivo does not support the hypothesis that carcinogenic potency is related to iron content. As discussed above, Wagner et al.[17] observed similar numbers of tumors in rats with crocidolite, amosite, and chrysotile, even though these fibers have an elemental iron content of 40%, 28%, and less than 1%, respectively.[67] The nonasbestos mineral erionite does not include iron as a constituent[68] but is nonetheless a potent mesothelioma inducer in rats.[69] Silicon carbide "whiskers," with an iron content of essentially zero, induce pleural tumors in rats after intrapleural implantation.[65] Therefore, no obvious correlation between iron content and carcinogenicity is apparent in the rat.

Summary

Our review of both the toxicologic and epidemiologic literature strongly supports the view that occupational exposure to chrysotile asbestos is associated with an increased risk of both lung cancer and mesothelioma. The hypothesis that these observations may be attributable to trace amounts (<1%) of tremolite contamination may seem to be primarily of academic interest, because chrysotile exposures in workers and the public are also contaminated with tremolite. However, the percentage of tremolite has been reported to range from 0.5% to 6.9% in one analysis of eight commercial chrysotile asbestos samples,[6] and it has been suggested that chrysotile from Zimbabwe[70] and other countries may be free of contamination by amphiboles. Hence, the amphibole hypothesis may be of some public health relevance.

In our view, the currently available scientific literature does not provide persuasive evidence for the hypothesis that tremolite contamination explains the mesothelioma excesses observed in the studies of chrysotile-exposed workers. The primary evidence for this hypothesis comes from pathologic studies in which lung burdens were measured. However, interpretation of these studies is hampered by the fact that chrysotile lung burdens are a poor reflection of integrated exposures and the fact that chrysotile exposure is highly correlated with lung burden of the amphiboles (e.g., tremolite). In addition, the pattern of asbestos fiber deposition in the lung does not appear to be consistent with the pattern of deposition in the target tissue (i.e., pleura). The previously reviewed empirical data from toxicologic studies and comparisons of mesothelioma mortality and lung cancer mortality between epidemiologic studies with differing levels of tremolite contamination do not provide support for this hypothesis. Mechanistic arguments that have been made to support the amphibole hypothesis, which are based on in vitro studies of iron content, appear to be contradicted by the lack of correlation between iron content and carcinogenic potency observed in experimental studies.

Whether chrysotile asbestos is less potent than the amphibole forms of asbestos is a question that has not yet been fully resolved. There is currently very little toxicologic evidence to support this hypothesis. There is evidence from epidemiologic studies that chrysotile may be less potent for mesothelioma induction than crocidolite. The proportion of deaths due to mesothelioma are strikingly lower in chrysotile-exposed miners and millers than in crocidolite miners. There is absolutely no epidemiologic or toxicologic evidence to support the argument that chrysotile asbestos is any less potent than other forms of asbestos for inducing lung cancer.

It should be recognized that comparisons of the potency of the different forms of asbestos are severely limited by uncontrolled differences in the bivariate distribution of fiber length and diameter (i.e., fiber dimensions). Experimental studies clearly demonstrated that fiber dimensions are a critical component of the carcinogenic potency of fibers.[65] This concern applies to most of the toxicologic studies in which exposure is determined on an equal mass basis and is particularly pertinent to the epidemiologic investigations. Historic exposures in most of the epidemiologic investigations were based on impinger samples that assessed the number of fibers, and conversion factors were applied to estimate the number of fibers longer than 5 μm. Concerns have been raised about the accuracy of these conversion factors and the potential impact of associated errors on the assessment of risk.[71] The current Occupational Safety and Health Administration (OSHA) method counts asbestos fibers that are longer than 5 μm and that have a length-to-diameter ratio of at least 3 to 1. This method implicitly assumes that fibers less than 5 μm in length are not carcinogenic and that all fibers greater than 5 μm in length are of equal carcinogenic potency. These assumptions are clearly inconsistent with the experimental data and most likely result in substantial misclassification of exposure in the epidemiologic studies.

Policy Implications

The American Conference of Governmental Industrial Hygienists and several countries (e.g., the United Kingdom) have adopted less restrictive standards for chrysotile asbestos than for the other forms of asbestos.[72] In our view, the currently available scientific evidence does not provide sufficient support for developing separate standards for the different forms of asbestos. As this article documents, the scientific evidence for the amphibole hypothesis is still tenuous. Furthermore, the fact remains that in practice workers in this country and other countries are not exposed to pure chrysotile, but rather to a mixture of chrysotile, tremolite, and other forms of asbestos. Thus, it is highly impractical to consider setting separate standards for the different forms of asbestos. Finally, even if one accepts the argument that chrysotile asbestos does not induce mesothelioma (which we do not), the risk of lung cancer (and asbestosis) can not be dismissed, and chrysotile appears to be just as potent a lung carcinogen as the other forms of asbestos. It is noteworthy that the risk of lung cancer is of greater concern than the risk of mesothelioma because in most studies there are at least two excess lung cancers for every mesothelioma observed (see Table 1). There is also the additional concern of asbestosis risk, which was not considered in this article but clearly adds to the risk associated with chrysotile exposure.

Therefore, given the clear evidence of a lung cancer risk, the lack of compelling evidence for the amphibole hypothesis, and the fact that workers are generally exposed to mixture of fiber types, we believe that it is prudent policy to treat chrysotile asbestos with virtually the same level of concern as the amphibole forms of asbestos. This view is consistent with the

past National Institute for Occupational Safety and Health Administration recommendation and the recently revised OSHA standard to limit occupational exposures for all forms of asbestos to 0.1 fiber/cc. □

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