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Cancer Risk of Asbestos Exposure

I. J. Selikoff

Environmental Sciences Laboratory, Mount Sinai School of Medicine of the City University of New York, New York, New York 10029

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CARCINOGENICITY OF ASBESTOS

Asbestosis

Comparatively few studies of asbestos-associated disease were undertaken prior to the late 1920's. In 1927, however, renewed attention was focused on the effects of inhalation of the fibrous dusts (Cooke 1927; Seiler 1928), and within the short span of 3 years the principal features of asbestosis were delineated (Merewether and Price 1930).

We have since learned much about this pneumoconiosis. Perhaps the most important feature we have come to appreciate is the long period of clinical latency between onset of exposure and subsequent appearance of radiologically evident changes. This can be appreciated by a review of the findings in an investigation of asbestos-insulation workers in the New York metropolitan area (Selikoff et al. 1965b). In 1963, 1117 of 1258 such workers were examined. Of the 725 workers with less than 20 years from onset of exposure, most had normal X rays (Table 1). It was only after the 20-year point had passed that abnormalities were commonly seen.

Pleural Abnormalities

A second important finding was that pleural changes were common among workers exposed to asbestos (Jacob and Bohlig 1955; Selikoff 1965). Unlike with other dust exposures (such as to coal, silica, beryllium) where pleural abnormalities are not commonly seen, the opposite was found to be the case with asbestos. Table 2, which gives the extent of roentgenographic abnormalities of the pleura found among the same 1117 men, demonstrates that fibrosis and/or calcification were commonly seen. When present, they, too, followed the "20-year rule." Few such abnormalities were observed when there was less than 20 years from onset of work (Selikoff 1965).

Table 1
X-ray Changes in Asbestos-insulation Workers

Years from onset of exposure	No. examined	Percent normal	Percent abnormal	Asbestosis (grade)		
				1	2	3
40+	121	5.8	94.2	35	51	28
30–39	194	12.9	87.1	102	49	18
20–29	77	27.2	72.8	35	17	4
10–19	379	55.9	44.1	158	9	0
0–9	346	89.6	10.4	36	0	0
Total	1117	51.5	48.5	366	126	50

Data from Selikoff et al. (1965b).

Lung Cancer

In 1935, the situation changed, although it is difficult, being this far removed, to evaluate fully whether those concerned with asbestos disease at the time perceived the onset of a shift in emphasis. In that year, both Lynch and Smith (1935) and Gloyne (1935) reported instances of lung cancer in patients who also had asbestosis, raising the possibility of an etiologic association between the two conditions. Additional reports of similar random cases followed, but it was difficult to be certain whether a true association was present. Nor did the report of the Chief Inspector of Factories of Great Britain in 1955 fully resolve the question. Although he noted that 17.8% of the cases known to the Factory Department to have died with asbestosis also had lung cancer (far more than would have been anticipated in light of the general British experience at that time), selective bias in the collection of cases could not be ruled out (Chief Inspector of Factories 1956).

The matter was clarified in 1955 as a result of a brilliant investigation by

Table 2
Roentgenographic Evidence of Pleural Abnormalities among 1117 Asbestos-insulation Workers

Years from onset of exposure	No. examined	Normal pleura	Abnormal pleura	
			fibrosis	calcification
40+	121	28	65	70
30–39	194	96	62	67
20–29	77	47	25	8
10–19	379	340	36	5
0–9	346	342	4	0

Data from Selikoff (1965).

Table 3
Expected and Observed Deaths among 632 Asbestos-insulation Workers in New York and New Jersey 20 or More Years after Onset of First Exposure (January 1, 1943–December 31, 1962)

Cause of death	Expected[a]	Observed
All causes	196.16	253
Total cancer, all sites	31.44	95
lung cancer	6.02	42
pleural mesothelioma	N.A.[b]	3
peritoneal mesothelioma	N.A.	1
cancer of stomach, colon, rectum	9.71	29
all other cancer	15.71	20
Asbestosis	N.A.	12
All other causes	164.72	146

Data from Selikoff et al. (1964).
[a] Nine men died before reaching 20 years from first employment. Expected deaths are based upon white male age-specific death-rate data of the U.S. National Office of Vital Statistics from 1949 to 1962. Rates for 1943–1948 were extrapolated from rates for 1949–1955.
[b] Rates are not available (N.A.), but these are rare causes of death in the general population.

Richard Doll. He investigated the experience of a group of heavily exposed asbestos-factory workers employed for at least 20 years. Among the 113 men, 0.8 deaths from lung cancer would have been expected had their experience been the same as that of other British men during those years. Instead, 11 such deaths occurred. Although the number of cases was small, the sharp increase in the relative number of lung cancer deaths provided convincing evidence of a relationship between asbestos exposure and lung cancer.

Since 1955, the occurrence of lung cancer as a consequence of occupational exposure to asbestos has been amply confirmed. In approximately 20% of all the deaths of asbestos workers studied, this neoplasm has been identified as the cause. In one investigation, the mortality experience of asbestos-insulation workers in the New York metropolitan area was studied. As of January 1, 1943, 632 men were registered members of this trade's union in the area. By December 31, 1962, 262 of these men had died, 253 after reaching 20 years from first employment (Table 3). Although 6.02 deaths from lung cancer were expected, 42 occurred. By December 31, 1974, 451 men were deceased; 89 had died of lung cancer, whereas 12.2 had been anticipated (Table 4) (Selikoff et al. 1964; Selikoff 1976b).

Dr. E. C. Hammond and I are also studying the cancer experience of asbestos-insulation workers in the United States and Canada as a whole. As of January 1, 1967, there were 17,800 men on the union's rolls.[1] By December 31, 1975, 2003 of these men had died (against 1483.38 expected).

[1] International Association of Heat and Frost Insulators and Asbestos Workers, AFL-CIO, CLC.

Table 4
Expected and Observed Deaths among 632 Asbestos-insulation Workers in New York and New Jersey (January 1, 1943–December 31, 1974)

Cause of death	*Expected*[a]	*Observed*
All causes	305.20	451
Total cancer, all sites	52.02	200
lung cancer	12.20	89
pleural mesothelioma	N.A.[b]	10
peritoneal mesothelioma	N.A.	25
cancer of stomach, esophagus	6.46	20
cancer of colon	7.64	23
Asbestosis	N.A.	37
All other causes	253.18	214

Data from Selikoff (1976b).

[a] There were 632 members on the union's rolls on January 1, 1943. Nine died before reaching 20 years from onset of first exposure. Expected deaths are based upon white male age-specific death-rate data of the U. S. National Office of Vital Statistics from 1947 to 1973. Rates for 1943–1948 were extrapolated from rates for 1949–1955, and those for 1974 were extrapolated from rates for 1969–1973.

[b] U. S. death rates are not available (N.A.), but these are rare causes of death in the general population.

Table 5
Expected and Observed Deaths among 17,800 Asbestos-insulation Workers in the United States and Canada (January 1, 1967–December 31, 1975)

Cause of death	*Expected*[a]	*Observed*
All causes	1483.38	2003
Total cancer, all sites	281.49	867
lung cancer	92.28	427
pleural mesothelioma	N.A.[b]	52
peritoneal mesothelioma	N.A.	92
cancer of esophagus	5.77	16
cancer of stomach	12.71	22
cancer of colon, rectum	33.87	53
cancer of larynx	4.45	9
cancer of oropharynx	7.41	17
all other cancers	125.00	179
Asbestosis	N.A.	141
All other causes	1201.89	995

[a] Expected deaths are based upon white male age-specific mortality data of the U. S. National Office for Health Statistics for 1967–1974 and extrapolated for 1975.

[b] Rates are not available (N.A.), but these are rare causes of death in the general population.

Table 6

Deaths among 933 Workers Employed in an Amosite-Asbestos Factory, Starting at 5 Years from Onset of First Exposure (1941–1945) and Ending December 31, 1974

Cause of death	*Expected*[a]	*Observed*	*Ratio*
All causes	285.62	483	1.69
Total cancer, all sites	50.10	157	3.13
lung cancer	12.45	83	6.67
gastrointestinal cancer	12.05	24	1.99
pleural mesothelioma	N.A.[b]	5	—
peritoneal mesothelioma	N.A.	5	—
asbestos-related cancer	24.50	117	4.78
other cancer	25.60	40	1.56
Asbestosis	N.A.	28	—
All other causes	235.52	298	1.27

Data from Selikoff (1976b).

There were 128 workers omitted from these calculations: 33 had prior asbestos exposure; 38 died in the first 5 years after onset of first exposure; 49 were not completely traced; and 8 had other asbestos employment after the 5 years from exposure onset point.

[a] Expected deaths are based upon white male age-specific death-rate data of the U. S. National Office of Vital Statistics, 1949–1972. Rates for 1946–1948 were extrapolated from rates for 1949–1955, and those for 1973–1974 from rates for 1968–1972.

[b] U. S. death rates are not available (N.A.), but these are rare causes of death in the general population.

Although 92.28 deaths from lung cancer were anticipated, 427 occurred (Table 5). Similar results were obtained in an investigation of a cohort of 933 workers employed in an amosite-asbestos factory during World War II (1941–1945) and followed to December 31, 1974 (Selikoff 1976b). Although 285.62 deaths were expected, 483 occurred; 12.45 deaths from lung cancer were anticipated, but 83 occurred (Table 6).

That approximately one in five asbestos workers who were exposed under conditions which existed in the past now die of lung cancer is a critical problem. This is especially true because of the large number of individuals concerned—the U. S. Public Health Service has estimated that there are now approximately one million men and women in the United States who are currently employed as asbestos workers or who were formerly so employed (Wagoner 1976). To the extent that the conditions of their exposure were similar to those of the cohorts studied, we may look forward to an extraordinary number of asbestos-related lung cancer deaths in the next three to five decades, unless methods are discovered to prevent or treat this neoplasm (Selikoff and Hammond 1973).

Pleural Mesothelioma

The experience of the past 20 years has given us good reason to reflect on the observation that the mesothelial lining of the chest—the pleura—could

show abnormal changes following asbestos inhalation. In 1953, Weiss reported a primary malignancy of the pleura in an asbestos worker. This warranted interest since pleural mesothelioma was known to be uncommon. It is difficult to be sure as to exactly how uncommon it was as it had not been coded separately in the International Classification of Causes of Death, despite its definition as a separate pathological entity by Klemperer and Rabin (1931). A review of the published autopsy data suggests that it might have been present in approximately 1 in 1000 to 1 in 10,000 deaths (Hochberg 1951).

As with lung cancer, additional case reports followed. The case for an association was strengthened considerably by the results of a provocative study by Wagner et al. (1960). They described 47 cases of pleural mesothelioma found in the northwestern part of the Cape Province, South Africa —an area with numerous, small, crocidolite-asbestos mines and mills. Although detailed occupational histories were not available for many of the cases and although it was difficult to ascertain the population base from which they were derived, careful probing into the life histories of the individuals provided evidence that 45 of the 47 had had the opportunity, decades before, of being exposed to asbestos, many as a result of what would now be called "environmental" exposure. Epidemiologic studies soon showed that the suggestion of an etiologic association between asbestos exposure and the subsequent development of mesothelioma was valid; asbestos workers frequently died with mesothelioma, whereas people not known to have worked with asbestos did not (Selikoff et al. 1965a).

Peritoneal Mesothelioma

As with primary pleural neoplasms, the first description of an association between peritoneal mesothelioma and asbestos exposure was reported more than 20 years ago (Leichner 1954). Again, additional cases soon came to light, and by 1965 it was evident that this neoplasm also had to be added to the list of cancers that could be induced by asbestos (Selikoff et al. 1965a; Enticknap and Smither 1964). Among insulation workers in the United States and Canada, for example, we found that 93 of the 2003 deaths in the period 1967–1975 were ascribed to peritoneal mesothelioma—4.64% of all deaths (Table 5). Taken together with the deaths from pleural mesothelioma, this means that 7.19% of all deaths in this group of asbestos workers were due to mesothelioma, an extraordinary association for an otherwise rare tumor. For another cohort of asbestos-factory workers, it has been projected that 7–11% of all deaths will be caused by this neoplasm (Newhouse and Berry 1976), a percentage 100 to 1000 times that which might be expected ordinarily.

Parenthetically, peritoneal mesothelioma has been found more often than pleural mesothelioma in several asbestos-worker cohorts. By contrast, pleural mesothelioma seems to be much more common where there has been less intimate exposure, as with environmental, family contact, or neighborhood exposures.

Gastrointestinal Cancer

In 1964, when analyzing the experiences of asbestos-insulation workers in the New York metropolitan area, we found a modest increase in gastrointestinal cancer, with 9.71 such neoplasms expected and 29 observed (Selikoff et al. 1964). Similar observations have now been made by others (Elmes and Simpson 1971), and we continue to find increased incidences of cancer of the esophagus, stomach, colon, and rectum among other cohorts of insulation workers (Selikoff et al. 1973). The increase, however, is more modest than that seen with bronchogenic carcinoma or pleural and peritoneal mesothelioma (Tables 3–5).

Other Neoplasms

Upon entrance into the body, asbestos fibers commonly spread to various organs. It has been of interest, therefore, to inquire whether there is increased frequency of other neoplasms in addition to those detailed in the foregoing. It is difficult to be certain about this, since many of the neoplasms in which there would be interest are in general seen only rarely, and much experience is needed before one can evaluate whether or not there is an increased incidence.

The results of our prospective study of the mortality experiences of the cohort of 17,800 asbestos-insulation workers in the United States and Canada, from January 1, 1967 to December 31, 1975, representing observations made in 150,975 man-years of observation, have been analyzed with regard to a number of less common neoplasms. Although these experiences are fewer than one would wish, there appear to be significant increases in cancer of the buccal cavity and of the pharynx. There were 7.41 cancers of these sites expected; 17 occurred. Similar observations were made with regard to the larynx, with 4.45 deaths anticipated and 9 observed (Table 7).

Experimental Studies

Laboratory investigations of the carcinogenic potential of asbestos have produced many observations of interest, providing information on a number of

Table 7
Expected and Observed Deaths from Selected Neoplasms among 17,800 Asbestos-insulation Workers in the United States and Canada (January 1, 1967–December 31, 1975)

Site	Expected*	Observed	Ratio
Cancer of buccal cavity or pharynx	7.41	17	2.29
Cancer of larynx	4.45	9	2.90

* Expected deaths are based upon white male age-specific mortality data of the U. S. National Office for Health Statistics for 1967–1974 and extrapolated for 1975.

important questions. In perhaps the most extensive and detailed such study (Wagner et al. 1974), it was found, for example, that all fiber types studied (amosite, anthophyllite, chrysotile, crocidolite) produced neoplasms. In other investigations, the interesting question of the importance of fiber size has been raised (Stanton and Wrench 1972).

CURRENT PERSPECTIVES

The main outlines of the occupational asbestos-associated cancer problem were largely defined by the mid-1960's. It was clear then that exposure to asbestos could constitute an important hazard and that such exposure need not be more than might occur in some environmental circumstances. Taken by itself, this would be an important enough problem. However, the further dimension of widespread community concern was added as the result of several critical observations made at about the same time.

First, Thomson et al. (1963) demonstrated in 1963 that asbestos bodies were found frequently at autopsy among individuals from the general population. Shortly thereafter, this observation was extended by the demonstration that asbestos fibers were also found in the lungs of urban dwellers (Langer et al. 1971). Although it was understood that these observations only demonstrated previous exposure to asbestos and carried no necessary prognostic significance concerning disease hazard, there was unease at finding that fibers which could cause serious neoplastic disease in some people (asbestos workers) at some exposure levels (occupational exposures) were also present in a very large majority of urban residents, albeit at much lower concentrations (Selikoff and Hammond 1968).

The second observation that attracted attention was that of Kiviluoto (1960), who demonstrated that pleural calcification was found frequently among residents living near an asbestos mine and mill in Finland. Pleural calcification was interpreted appropriately only as indicating prior exposure, decades before, to asbestos air pollution from the mine and mill. Again, it did not necessarily indicate, as a consequence, a substantial environmental cancer hazard. Still, the pleural-reaction evidence based on radiological changes demonstrated that nonoccupational community exposure to environmental asbestos contamination could result in at least one tissue change (pleural calcification). The possibility existed that other changes (neoplasm) might result.

The third observation was that of Wagner et al. (1960), who brought the matter a step farther by demonstrating that, at least in some environmental circumstances, such a result (mesothelioma) could occur.

Taken together, these three findings provided a background for considering that asbestos neoplasia might be a much wider and more pervasive problem than an occupational hazard alone.

Dose–Disease Response

An important difficulty in evaluating the quantitative relationship between amount of exposure and subsequent risk of asbestos-associated disease has been the long period of clinical latency (see below) between onset of effective

exposure (i.e., the amount necessary to cause disease) and subsequent appearance of such disease, including asbestosis and cancer. Since few measurements were made in the 1920's, 1930's, and 1940's, and virtually none in relation to work exposure of individuals with whom we were later to be concerned in the 1950's, 1960's, and 1970's, it has been difficult to correlate quantitative measurements of exposure and risk of disease (Nicholson 1976). Some measurements have been available for risk of asbestosis (British Occupational Hygiene Society 1968), and more general, but perhaps more pertinent, evaluations have been made for cancer risk. The latter include two useful sets of observations.

Newhouse and Thompson (1965) analyzed 76 cases of mesothelioma in the files of the London Hospital. As expected, 31 cases had a history of having worked with asbestos; however, 45 did not. Of the 45 cases, 9 had presumed exposure resulting from residence within households of asbestos workers, and 11 had lived within a half mile of an asbestos plant in London. Although no quantitative dose–disease-response relationships could be derived from these data, since the population bases from which they were derived were not known, it nevertheless was proposed that an exposure gradient was demonstrated.

Recently, more direct information has become available. Among the 933 workers employed in the amosite-asbestos factory during World War II (see above), employment was limited for some and prolonged for others. Beginning in 1941, a number worked for as little as a day or a week, some worked for 1–3 months (often while waiting to go into military service), and still others worked for the full 13 years until the plant closed in 1954. Some information exists, albeit indirect, that exposures were poorly controlled, with levels often reaching 50 fibers/ml or more. By the end of 1974, it was found that the lung cancer risk of this group of workmen was considerable, with 12.45 such deaths expected and 83 observed. However, closer analysis showed that the extent of this risk varied with the duration of exposure (and therefore dose). The mortality ratio of observed-to-expected deaths was, for example, 3.87 for those with 3 months' work or less, whereas those with 1 or more years of exposure showed a mortality ratio of 10.56 (Table 8) (Selikoff 1976b).

There is reason to believe that the dose–disease-response relationships for the several kinds of asbestos-associated diseases do not necessarily follow the same pattern. For asbestosis, there is much evidence that extensive disease is very unlikely to occur at low levels of exposure (e.g., in "neighborhood" circumstances). Pleural mesothelioma, on the other hand, may occur at levels of asbestos exposure below those necessary to yield radiologically evident asbestosis. At the moment, there is inadequate information to warrant a judgment concerning dose–disease-response relationships for lung cancer. We know a good deal about lung cancer incidence in relation to the more intense occupational exposures, but population-based studies have not yet been completed with regard to lung cancer incidence among individuals with less than intense exposure, as in family or neighborhood circumstances. There is little knowledge concerning dose–disease-response patterns for gastrointestinal cancer, since this has been investigated only among occupationally exposed groups.

Table 8

Expected and Observed Deaths Subsequent to First Year after Onset of First Exposure among 870 Amosite-asbestos-factory Workers First Employed in 1941–1945 and Observed to December 31, 1973

	3 Months or less			*3–11 Months*			*More than 1 year*		
	expected	*observed*	*ratio*	*expected*	*observed*	*ratio*	*expected*	*observed*	*ratio*
Total deaths, all causes	99.75	112	1.12	94.34	170	1.80	110.55	216	1.95
Cancer, all sites	16.92	28	1.65	16.29	46	2.82	18.99	81	4.27
lung cancer	4.13	16	3.87	4.00	16	4.00	4.64	49	10.56
pleural mesothelioma	N.A.[a]	0	—	N.A.	2	—	N.A.	2	—
peritoneal mesothelioma	N.A.	0	—	N.A.	1	—	N.A.	4	—
stomach	1.46	1	0.68	1.47	3	2.04	1.73	5	2.89
colon, rectum	2.38	4	1.68	2.27	7	3.08	2.67	5	1.87
Asbestosis	N.A.	1	—	N.A.	2	—	N.A.	23	—
All other causes	82.83	83	1.00	78.05	122	1.56	91.56	112	1.22
Number of workers		249			294			327	
Person-years of observation		5747			6305			7061	

Data from Selikoff (1976b).

The data in this table excludes 63 men. Ten died during their first year of employment, 34 could not be traced after the first year, and 19 had prior occupational exposure to asbestos. Of the 870 men, 18 were partially traced and 16 had subsequent asbestos work. These remained in the calculations until lost to observation or until onset of subsequent asbestos work. Expected deaths are based upon white male age-specific death-rate data of the U. S. National Office of Vital Statistics, 1949–1971. Rates for 1941–1948 were extrapolated from rates for 1949–1955, and those for 1972–1973 from rates for 1967–1971. Distribution is by duration of employment.

[a] U.S. death rates are not available (N.A.), but these are rare causes of death in the general population.

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Despite these variables, it appears clear that, taken as a whole, there is an important dose–disease-response gradient for asbestos, with disease much more likely to occur as a result of heavier exposure and less likely to occur with less intense exposure.

Dose–Induction Period

Just as higher doses are associated with the greater likelihood of asbestos-related cancer, there also seems to be substantial variation in the time of appearance of neoplasms according to the dose received. Initial information regarding this has begun to appear. Although this information still requires confirmation, it suggests that even with brief (albeit intense) exposures excess cancers will appear, but that this increased risk will not be observed for some time. Thus, again among the amosite-factory workers, we have found a statistically significant increased risk of lung cancer 15 years after onset of first exposure among workers with 5 or more years of work experience. In contrast, among those with a month or less of employment, an increased ratio of observed-to-expected deaths from lung cancer was not observed until 30 or more years had passed.

Comparatively little information is presently available for mesothelioma, but I would expect that similar data will be found for these neoplasms as well. Should this be so, a practical consequence would be that in any evaluation of environmental mesothelioma risk, observation periods of 30–50 years will be necessary. Occupational cancers, resulting from more intense exposures, will occur more rapidly; environmental neoplasms, only after a longer time.

Period of Clinical Latency

Laced through the foregoing discussions has been the importance of the period of clinical latency in asbestos-associated disease. Quantitative information is now becoming available to document this perspective and to emphasize the fact that one can hardly expect to be able to evaluate fully the effects of asbestos exposure without having the opportunity for adequate duration of observation. Tables 9–11 analyze the experiences of asbestos-insulation workers in the United States and Canada with regard to time of death from lung cancer and pleural and peritoneal mesotheliomas in relation to the elapsed time from onset of first exposure.

No mesotheliomas were seen in less than 15 years from onset of exposure, and comparatively few in less than 20–25 years from onset. Similar observations obtained for lung cancer. For mesothelioma, only 0.65% of 307 deaths (occurring in 83,538 man-years of observation) were from pleural mesothelioma and only 0.98% were from peritoneal disease. In contrast, 2.90% of 1696 deaths were caused by pleural mesothelioma (in 67,437 man-years of observation) after 20 years from onset, and 5.31% of all deaths were due to peritoneal mesothelioma after the 20-year mark.

With but few exceptions, serious risk begins after 20 years from onset of first exposure and continues from that point on.

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Table 9
Deaths from Lung Cancer among 17,800 Asbestos-insulation Workers in the United States and Canada (January 1, 1967–December 31, 1975)

Attained years from onset of first exposure	No. of men	Man-years of observation	Deaths from lung cancer		
			expected[a]	observed	ratio
<10	8189	25,974	0.65	0	—
10–14	8527	26,361	2.54	6	2.36
15–19	9402	31,203	7.89	29	3.68
20–24	8306	27,754	15.20	55	3.62
25–29	5768	17,616	18.13	87	4.80
30–34	3077	10,016	15.71	96	6.11
35–39	1657	4496	9.46	59	6.24
40–44	977	2845	7.17	37	5.16
45+	1362	4710	15.53	58	3.72
All men	17,800	150,975	92.28	427	4.63
<20 years	12,683	83,538	11.08	35	3.16
20+ years	11,470	67,437	81.20	392	4.83

[a] Expected deaths are based upon white male age-specific mortality data of the U. S. National Office for Health Statistics for 1967–1974 and extrapolated for 1975.

Table 10
Deaths from Pleural Mesothelioma among 17,800 Asbestos-insulation Workers in the United States and Canada (January 1, 1967–December 31, 1975)

Attained years from onset of first exposure	No. of men	Man-years of observation	Total deaths	Deaths from pleural mesothelioma		
				no.	deaths/1000 person-years	percent of all deaths
<10	8189	25,974	50	0	0	0
10–14	8527	26,361	77	0	0	0
15–19	9402	31,203	180	2	0.03	1.11
20–24	8306	27,754	289	4	0.14	1.38
25–29	5768	17,616	343	15	0.85	4.37
30–34	3077	10,016	298	9	0.89	3.02
35–39	1657	4496	201	8	1.78	3.98
40–44	977	2845	176	3	1.05	1.70
45+	1362	4710	389	10	0.21	2.57
All men	17,800	150,975	2003	51	0.34	2.55
<20 years	12,683	83,538	307	2	0.02	0.65
20+ years	11,470	67,437	1696	49	0.73	2.90

Table 11

Deaths from Peritoneal Mesothelioma among 17,800 Asbestos-insulation Workers in the United States and Canada (January 1, 1967–December 31, 1975)

Attained years from onset of first exposure	*No. of men*	*Man-years of observation*	*Total deaths*	*Deaths from peritoneal mesothelioma*		
				no.	*deaths/ 1000 person-years*	*percent of all deaths*
<10	8189	25,974	50	0	0	0
10–14	8527	26,361	77	0	0	0
15–19	9402	31,203	180	3	0.10	1.67
20–24	8306	27,754	289	3	0.11	1.04
25–29	5768	17,616	343	15	0.85	4.37
30–34	3077	10,016	298	17	1.70	5.70
35–39	1657	4496	201	14	3.11	6.97
40–44	977	2845	176	15	5.37	8.52
45+	1362	4710	389	26	5.52	6.68
All men	17,800	150,975	2003	93	0.62	4.64
<20 years	12,683	83,538	307	3	0.04	0.98
20+ years	11,470	67,437	1696	90	1.33	5.31

Multiple-factor Interactions

In 1967, the observation was made that lung cancer risk among asbestos workers seemed to be largely concentrated among those workers who also had a history of cigarette smoking. As of January 1, 1963, among the 370 survivors of the original cohort of 632 men who were members of the Insulation Workers' Union in the New York metropolitan area on January 1, 1943, there were 87 men who had no history of cigarette smoking and 298 with such a history. By 1967, 2.98 deaths from lung cancer were anticipated among the cigarette smokers, but 24 occurred. On the other hand, not one death from this neoplasm was seen among the 87 nonsmokers, despite the fact that among those who died much asbestos was found in their lungs. Thus there was evidence that lung cancer among these asbestos workers was not due to asbestos alone—none of the nonsmoking asbestos workers died of lung cancer—or to the smoking alone, since only about three such deaths would have occurred among men of the same age in the general population. The combination of the two—smoking plus asbestos—was associated with the extraordinary increase in the observed over expected death rates. It was calculated that asbestos workers who smoked cigarettes had approximately a 92 times greater risk of dying of lung cancer than men who neither smoked nor worked with asbestos, and it was proposed that asbestos greatly increased the lung cancer risk of cigarette smokers (Selikoff et al. 1968).

This observation has now been amply confirmed. Asbestos workers who have no history of cigarette smoking are not likely to die of lung cancer. Although their risk may be greater than that of nonsmokers in general (without

occupational exposure to asbestos), since the risk of the latter is comparatively low, even increasing it threefold would not result in a very important hazard, overall. Among cigarette-smoking asbestos workers, on the other hand, the already high risk associated with cigarette smoking when increased by the risk due to asbestos results in the extraordinary hazard of lung cancer that has been observed.

Parenthetically, neither pleural mesothelioma nor peritoneal mesothelioma has been associated with cigarette smoking among asbestos workers. These risks are present in both cigarette-smoking asbestos workers and those without such a history (Table 12). There were 0.38 deaths from pleural mesothelioma per 1000 man-years of observation among asbestos workers with a history of cigarette smoking and 0.39 for those with no history of cigarette smoking. Comparative rates for peritoneal mesothelioma were 0.73 for cigarette smokers and 0.83 for nonsmokers.

Cancer of the esophagus, interestingly enough, has shown a predilection for cigarette-smoking asbestos workers (as among cigarette smokers in general), but cancer of the stomach, colon, and rectum has not. Too few data are yet available to allow adequate evaluation for cancer of the pharynx and buccal cavity and of the larynx.

Family-contact (Conjugal) Disease

An important contribution was made by Newhouse and Thompson (1965) when they described nine cases of mesothelioma among individuals whose only known contact with asbestos was presumably by virtue of their residence within households of asbestos workers. Investigations have shown that such situations provide ample opportunity for exposure, by means of contamination of a household with dust brought home on the workmen's shoes, clothes, hair, etc. We have also found cases where employees of asbestos firms, proud of the materials being manufactured, would bring home some of the products made by their firms. By 1975, Anderson et al. (1976) had collected 33 reported cases of household-contact mesothelioma, to which they added 4 cases that they had seen.

Household-contact mesothelioma may well turn out to be an uncomfortably common problem in the future (given the likelihood of a longer period of clinical latency than for occupationally exposed cases!). In a current investigation of the wives and children who resided with the amosite-asbestos-factory workers during their period of employment (1941–1954), approximately one-third of those examined in 1975–1976 had radiological abnormalities on chest films. These abnormalities were of the type characteristically seen with asbestos exposure (parenchymal fibrosis, pleural fibrosis, pleural calcification). They were generally limited in extent and not accompanied by symptoms such as dyspnea. Nonetheless, they indicate that asbestos exposure was common in the workers' households, and in many cases to the extent necessary to result in radiological change (Anderson et al. 1976). The ultimate fate of these people cannot yet be predicted. Nevertheless, there is some concern, especially since four instances of mesothelioma have already been found (see above).

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Table 12
Distribution of Deaths from Lung Cancer and Mesothelioma among 17,800 Asbestos-insulation Workers in the United States and Canada According to Smoking Habits (January 1, 1967–December 31, 1975)

Smoking habits	*Man-years of observation*	*Deaths/1000 man-years of observation*		
		lung cancer	*pleural mesothelioma*	*peritoneal mesothelioma*
History of cigarette smoking	81,316	3.50	0.38	0.73
No history of cigarette smoking	17,909	0.33	0.39	0.83
Never smoked	12,756	0.31	0.16	0.71
Pipe and/or cigar	5153	0.39	0.97	1.16
Unknown	51,750	2.62	0.25	0.37

1779

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Neighborhood Exposure

The general observations of Wagner et al. (1960) and Newhouse and Thompson (1965) have been referred to above. Other reports have since appeared, including those of McEwen et al. (1971) and Greenberg and Lloyd-Davies (1974). That the problem might be more widespread than believed initially is suggested by recent observations in Turkey (Yazicioglu 1976).

Cases of disease associated with neighborhood exposure can and do occur; what is not known, however, is whether these are likely to be frequent or uncommon. Quantitative population-based data are needed before this aspect of the question can be clarified.

Bystander Disease

Harries (1968) reported five cases of pleural mesothelioma at the Royal Navy Dockyard in Devonport. Not one case involved an asbestos worker; the trades listed were welder, laborer, shipwright, boilermaker, and fitter. This called attention to the possibility that men working in the same areas where asbestos work was in progress could also be exposed to the same dust to a significant extent. Although they might be bystanders in one sense, they were not in another. Further experiences confirmed the initial observations. By 1973, 55 cases of mesothelioma had been recorded at Devonport. Only 2 of these were found in asbestos workers, whereas 53 were found in men engaged in other trades at the shipyard (Harries 1976).

The shipyard mesothelioma problem—lung cancer risk has not been studied—is likely to be a vexing one for many decades to come. In the United States, for example, some 4.5 million men and women were employed in shipbuilding and ship repair during World War II, and a shipyard work force of approximately 250,000 remained in the postwar years. In view of the considerable turnover in shipyard employees, it is likely that a very large number of workers have been employed in U.S. yards in the past 30 years. Many had considerable opportunity for indirect occupational asbestos exposure, and the potential for bystander disease is considerable. The construction industry may also be an important potential source for such disease.

PUBLIC HEALTH CONSIDERATIONS IN THE CONTROL OF ASBESTOS-ASSOCIATED DISEASE

Primary Concern: Asbestos-related Cancer

Asbestosis is unlikely to be the major concern in the future with regard to asbestos-associated disease; rather, cancer will have the honor of first place. Although in current studies of cohorts of asbestos workers asbestosis still accounts for a considerable proportion of deaths (Tables 4–6), this reflects, to a large extent, the mostly uncontrolled exposures that occurred 20–40 years ago. Such exposures are unlikely to be seen frequently in the future.

On the other hand, we have a double responsibility in the next decades. First, we are left with a legacy of individuals with sufficient past exposure to

bear a significant risk of developing asbestos-associated cancers in the next 30 or 40 years (Selikoff and Hammond 1973). Second, we are not confident that a decrease in asbestos exposure sufficient to control the risk of extensive asbestosis will also be sufficient to control the risk of neoplastic disease, especially in view of the multiple-factor interaction with cigarette smoking, a common personal habit of men in general and industrial workers in particular. It would appear that workplace exposures will have to be reduced to levels below those which obtained in households of asbestos workers in the past or among those with indirect occupational (bystander) exposure.

Such exposure control will need to be maintained not only in asbestos mines and factories, but also in any surrounding where asbestos products are in use. For example, more than one million workers are employed in the United States in brake repair and brake maintenance work. Asbestos-dust exposures have been significant in such workplaces (Rohl et al. 1977), and evidence of asbestosis and mesothelioma has already been documented. Other uses of asbestos abound, and the control of such associated exposures will be required.

Low-level Exposure

The mention of end-product use and family contact and neighborhood contamination problems brings to mind a feature common to many environmental cancer agents: the factor of low-level intermittent or long-term exposure, which bears less risk than more intense occupational exposure but affects a vastly larger number of individuals. There are comparatively few asbestos workers. Many more people who are not asbestos workers may be exposed to the dust.

The low-level-exposure problem is therefore much more diffuse, but by no means less important. Much more information is needed to guide public-health control measures with respect to such exposures, since much of the data collected heretofore has been concerned with the more intense exposures generally found in the workplace. In particular, quantitative estimates are needed as to the extent and nature of family-contact disease, neighborhood and bystander disease, and disease that may be associated with end-product use. In the United States, this extension of emphasis can be seen in the facts that the Environmental Protection Agency and the Consumer Products Safety Commission, in addition to the Occupational Safety and Health Administration of the Department of Labor, are now concerned with asbestos regulation and control, and that basic research with regard to asbestos-related disease is currently very much the responsibility of the National Institute of Environmental Health Sciences as well as of the National Institute for Occupational Safety and Health.

Asbestos Contamination of Public Water Supplies

Until now, evidence concerning asbestos-related-disease hazard has been associated with inhalation of the dust. Little is known concerning the hazard of ingested asbestos, although the problem has been brought to sharp atten-

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tion with the contamination of Lake Superior by asbestos-content mine waste (Cook et al. 1974). Also, contamination of public water supplies by erosion from asbestos-cement pipe systems is now being investigated.

Maintenance, Repair, Demolition, and Waste Disposal

A special subset of end-product and bystander exposures includes those associated with maintenance and repair of materials containing asbestos once they are in use. A particularly difficult and worrisome problem is that associated with the maintenance and repair of asbestos insulation in refineries, chemical plants, factories, and buildings. In our experience, this has been a common source of unanticipated asbestos exposure, one worthy of close attention in the future. Furthermore, some 25 million tons of asbestos has been used in the United States from 1890 to 1970 (Bruckman and Rubino 1977). Much of this is still in our buildings, ships, railroad locomotives, and factories. In the next half century many of these will be subject to demolition, and the potential exposure to asbestos of workmen and the community at large should be studied carefully.

High-risk Groups

We have already identified many groups of workers, family contacts, and others who were exposed in the past to significant levels of asbestos dust and who are therefore at high risk of developing cancer in the future (Selikoff and Hammond 1975). The knowledge that such groups exist and can be identified immediately raises the question of whether it is now a public health responsibility to develop appropriate long-term surveillance programs for these people. Much can be done to make much less grim their rather unhappy prognosis. Perhaps an additional number of lung cancers could be cured if early diagnosis were available; in this, serial sputum cytology studies might be helpful. Cancers of the colon and rectum also can be cured to a greater extent with early detection. The course of asbestosis allows for much useful intervention, since death, when it occurs, is often the result of superimposed pulmonary infection. If anticipated and treated, this intercurrent disease can be properly managed, without fatal outcome. Mesothelioma so far remains resistant to all approaches, even with early diagnosis (Selikoff 1976a).

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