PART B - HEALTH EFFECTS OF ASBESTOS

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1. Executive Summary

Ambient asbestos levels are not expected to cause any acute health effects or to result in asbestosis, a frequently disabling lung disease. However, asbestos is an undisputed human and animal carcinogen, and has been documented to cause cancer in humans in both occupational and nonoccupational settings. While most experimental and epidemiologic studies have involved exposure to chrysotile, amosite and crocidolite, DHS staff members believe that fibrous anthophyllite, tremolite and actinolite should also be considered as human or potential human carcinogens.

In numerous studies of cohorts exposed occupationally, asbestos has been unequivocally associated with increased risks for several types of neoplasms, particularly lung cancer and pleural and peritoneal mesothelioma. Similar and other tumor types have also been produced in animals exposed to asbestos via inhalation and intraperitoneal or intrapleural administration. There is mixed evidence as to whether asbestos is genotoxic. Although the mechanism of asbestos carcinogenicity is unknown, there is no compelling evidence that this process is characterized by a threshold. There is inadequate information about respiratory tract deposition, clearance and fiber degradation in humans to permit pharmacokinetic modeling in the risk assessment.

Other serious chronic health effects of asbestos exposure (e.g., reproductive effects) have not been extensively studied, but there is no evidence suggesting a causal association.

Health risks posed by nonoccupational exposure to asbestos have been the subject of recent quantitative risk assessments conducted by Nicholson (1985), the National

Academy of Sciences (NRC, 1984), the Ontario Royal Commission on Matters of Health and Safety Arising from the Use of Asbestos in Ontario (1984), and the Consumer Product Safety Commission (1983). DHS adapted linear models developed and/or used by earlier investigators to estimate risks of mesothelioma and lung cancer to the general population. The models extrapolate risks observed in numerous occupationally exposed cohorts to lower levels of asbestos found in the general environment. In this case the range of extrapolation was four to five orders of magnitude. Results are presented in Table 1-1.

Table 1-1: ESTIMATED LIFETIME RISKS OF LUNG CANCER AND MESOTHELIOMA DUE TO CONTINUOUS EXPOSURE TO 0.0001 FIBERS/CC OF ASBESTOS (EXPRESSED AS CASES PER MILLION POPULATION)

Exposure Group	Lung Cancer	Mesothelioma
Male Smokers	11 (110)	24 (120)
Female Smokers	5 (50)	32 (160)
Male Nonsmokers	2 (15)	32 (160)
Female Nonsmokers	1 (6)	38 (190)

Numbers in parentheses represent approximate upper confidence limits. The analysis corrected for competing causes of death using lifetables constructed from recent California vital statistics. Since risks for lung cancer and for other causes of death are dependent on smoking status, the lifetables were modified to account for age- and gender-specific smoking prevalence. Thus, risks are presented by gender and smoking status. Health and Safety Code Section 39650 directs DHS to "utilize scientific criteria which are protective of public health consistent with current scientific data." In view of this directive, DHS staff members' recommended risk values do not routinely include the lower confidence interval, which, under the assumptions of the models used, is likely to be an underestimate. In this document we present the best estimates and approximate upper confidence limit estimates and explain that such lifetime cancer risk values represent a range of conservative estimates and are unlikely to be exceeded by actual risks.

Our results are compatible with those calculated in previous risk assessments and with current mesothelioma incidence data from the San Francisco-Oakland SEER Program. Subject to qualifications noted in the main body of the document, our estimates for mesothelioma suggest that exposure to ambient asbestos may account for a small to a substantial percentage (i.e., from about 10 to 60%) of the recent incidence of this disease.

DHS staff members recommend the use of excess lung cancer lifetime risk values between 11 and 110 per million for each 0.0001 fibers/cm^{3*} of asbestos exposure. For mesothelioma, recommended lifetime risk values are between 38 and 190 for each 0.0001 fibers/cm^{3*} of asbestos exposure. These recommendations are based on best estimates and approximate upper confidence limits for the groups theoretically at highest risk for lung cancer and mesothelioma: male smokers and female nonsmokers, respectively. (Female nonsmokers are not more susceptible to asbestos-related carcinogenesis. Rather, their higher theoretical risk follows from their greater longevity and consequent exposure for a longer period of time.) The above values represent theoretical lifetime risks of cancer, assuming continuous average daily exposure to 0.0001 fibers/cm^3 throughout life.

The range between best estimates and approximate upper confidence limits represents several sources of uncertainty, including principally the statistical uncertainty related to the sizes of the cohorts studied epidemiologically and the uncertainty due to the lack of reliable data on cohort exposures. Other major uncertainties involve the validity of high to low dose extrapolation and whether synergism in carcinogenesis (e.g., between asbestos exposure and cigarette smoking) occurs at low

doses. Uncertainty also arises because of sampling variablity, including interconversions between past industrial exposure measurements and fiber counts measurable by current techniques.*

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*Fibers/cm^3 = asbestos fibers ≥ 5μm in length, ≥ 0.3 μm in width, with a length/width ratio of ≥ 3:1. These fibers can be measured by phase contrast microscopy (PCM) and for historical reasons represent the basis for all recent asbestos risk assessments. Such fiber counts can be converted to total fibers measurable by transmission electron microscopy (TEM) by multiplying by 100 to 1,000. Thus, 0.0001 (PCM) fibers/cm^3 = 0.01 to 0.1 TEM fibers/cm^3 = 10,000 to 100,000 TEM fibers/m^3.

2. Physico-Chemical Properties

The physico-chemical properties of asbestos have been extensively reviewed elsewhere (Wagner, 1980; NRC, 1984). Only those properties known to be relevant to asbestos' ability to induce disease will be discussed below, following a brief summary of asbestos' mineralogical classification.

a. Mineralogical Classification

Asbestos is a generic name applied to a family of fibrous silicates which is divided into two mineralogical groups, serpentines and amphiboles. The most abundant type of asbestos is chrysotile, which is the only member of the family belonging to the serpentine group. Chrysotile is composed of curly fibers that can shear into smaller fibrils. Its crystalline structure in cross-section looks like rolled-up scrolls, whose configuration is due to layered sheets of silicates with outer magnesium and hydroxide ions.

Unlike chrysotile's curled shape, amphiboles crystallize in straight double chains, resulting in a needle-like structure. Amphiboles are typically more brittle than chrysotile and tend to cleave longitudinally. The amphiboles of greatest commercial importance are crocidolite and amosite, whose individual fibrils tend to be thicker than those of chrysotile. Other amphibole asbestos varieties, which are similar structurally, but differ in chemical composition, include tremolite, anthophyllite and actinolite.

b. Size and Aspect Ratio*

The physical dimensions of asbestos fibers, represented by their size distribution and aspect ratios, affect respirability, deposition, clearance, cytotoxicity, and carcinogenicity. As noted in Section 3, fibers with a diameter greater than 3 microns will be unlikely to reach the deep lung, but will be either filtered by the nasal passages or deposited in the ciliated airways, from which they will generally be cleared rapidly. Where the aspect ratio is greater than three, the fiber length becomes relatively unimportant in determining the site of deposition except at the level of the respiratory bronchioles, where the fibers may penetrate the mucosa (Timbrell, 1965,1970; Morgan and Seaton, 1984). Amphiboles, which are usually less than three microns in diameter and which have a needle-like appearance, have been shown to reach the respiratory bronchioles and alveoli in substantially larger concentrations than chrysotile fibers, which are curlier and possess a greater aerodynamic diameter, causing the latter to deposit in larger airways (NRC, 1984).

The size distribution of inhaled fibers affects the extent to which they will be retained or cleared from the lung. In animal experiments, shorter, thinner fibers appear to be preferentially retained (when compared to the size distribution of fibers to which the animals had

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*Aspect ratio is defined as fiber length / diameter.

been exposed) (NRC, 1984). Shorter fibers (less than 10 microns in length) are also more likely to be engulfed by macrophages and other scavenger cells, which will protect other cells in the alveolated airways from the cytotoxic effects of asbestos. Increasing fiber length is associated with resistance to phagocytosis and with greater in vitro cytotoxicity (NRC, 1984).

The macrophage response to the presence of asbestos fibers in the deep lung is believed to be responsible for the evolution of fibrosis and asbestosis. Longer, incompletely digested fibers are thought to play a pivotal role in the etiology of this condition. While the mechanism of asbestos carcinogenesis is unknown, fiber length and diameter appear to be critical factors in the experimental induction of mesothelioma (See Section 9.d., "Influence of Fiber Dimensions on Carcinogenicity").

c. Durability

Large numbers of asbestos fibers may be preserved intact in the lungs and other tissues for decades after exposure. The biological persistence of these fibers may be a sine qua non for their chronic toxicity. While retained asbestos fibers are remarkably durable, some physical degradation does take place. For instance, magnesium affecting chrysotile's surface charge and structural integrity can be leached out, causing fragmentation and faster clearance than is observed with the amphiboles. Fragmentation increases the number of fibers per unit mass (NRC, 1984).

d. Surface Area and Charge, Chemical Composition

Increasing the fiber surface area increases macrophage cytotoxicity and other deleterious biological effects (NRC, 1984). It is unclear how such an increase (as occurs when commercial asbestos is broken up during processing or usage) would affect carcinogenicity. Asbestos fibers' ability to cause cell lysis depends at least in part on the surface charge (NRC, 1984). The chemical composition of different asbestos varieties appears to exert mainly indirect pathogenic effects through its influence on other physical properties.

3. Deposition and Clearance

Deposition of particles in the lungs is influenced by the particles' physicochemical characteristics and by a variety of host factors, including ciliary and macrophage function, airway geometry, breathing patterns, and immunologic effects. A model developed for aerosol deposition by the Task Group on Lung Dynamics of the International Commission on Radiological Protection indicates that most nonfibrous dust particles greater than 5 microns in diameter will be filtered by the nasopharynx and will not reach the lower portion of the respiratory tract (Brain and Valberg, 1974, 1979) Most respirable particles are 3 microns or less in diameter.

An inhaled fiber behaves similarly to a spherical particle with an equivalent aerodynamic diameter, the latter defined as a sphere with a density of

1 g/cm^3 having the same falling speed as the fiber (NRC, 1984). The falling speed is the principal determinant of whether a fiber or particle will deposit in the large airways (Morgan and Seaton, 1984). A fiber's falling speed has been reported to be proportionate to its diameter squared (Timbrell, 1965, 1970). Since inhaled fibers tend to align themselves parallel to the walls of the airways, fiber length is relatively unimportant in determining the deposition site when the aspect ratio is $\geq$ 10:1 (Timbrell, 1965). This explains why fibers ranging up to 100 microns in length have been found in alveoli. (In the small airways, however, fiber length influences whether fibers will penetrate the respiratory bronchioles.) The curliness of chrysotile not only gives it a greater mean aerodynamic diameter than the amphiboles, but also fosters a more random orientation with respect to the airways, causing deposition to occur at sites higher in the respiratory tract. This general statement applies more to chrysotile fibers that are relatively intact than to the short, thin fibrils that are found after extensive milling and other industrial processing.

Many small inhaled fibers (mean aerodynamic diameter $\leq$ one micron) will be exhaled, failing to be deposited by impaction, sedimentation or diffusion. As the aerodynamic diameter increases (about 2 μm) more fibers are deposited in the lower respiratory tract. At even larger aerodynamic diameters (about 2.5 to 3μm), impaction in the upper respiratory tract becomes important and decreases the amount of material that can enter the lower respiratory tract. While most deposited fibers will subsequently be cleared, large numbers of

asbestos fibers are permanently retained in the lung and pleura, resulting in continuous in situ exposure (See section 7.a.).

Fibers deposited in the ciliated airways are carried by the mucociliary escalator to the pharynx and are then coughed up or swallowed within 2 to 8 hours. Swallowed fibers are excreted in the feces, or may penetrate the gastrointestinal mucosa. Those deposited in the lung parenchyma can be phagocytosed by macrophages, then transported to the mucociliary escalator or to the pulmonary interstitium and then to the lymphatics. From the lymphatic channels the fibers may be transported to sites throughout the body.

Asbestos fibers may also be taken up by type I pneumocytes within an hour after deposition, and may subsequently be translocated to basement membrane, interstitial cells, and connective tissue within the lung (Brody and Hill, 1981). This process is more common for fibers longer than the diameter of alveolar macrophages (>12 microns) (Lippmann et al., 1980). Longer fibers can injure the macrophage membrane, releasing cytotoxic enzymes and causing a loss of mobility.

Two other pulmonary mechanisms that protect against asbestos toxicity involve the formation of asbestos bodies (described in section 7.a.) and long-term in situ fiber degradation, which is effective mainly for chrysotile (Morgan and Seaton, 1984). Unlike the amphiboles, chrysotile has a tendency to partially dissolve in weakly acidic solutions, facilitating clearance.

In animals exposed to short fibers of chrysotile or amphibole asbestos, it has been reported that initial deposition patterns are similar throughout the lung, yet chrysotile appears to be cleared more quickly (Royal Commission, 1984; Lippmann et al., 1980). Within the lung, the initially uniform distribution of fibers is modified over time by fiber movement to the lung periphery, where fiber-containing cells aggregate in subpleural foci. Fibers may migrate to the peritoneal cavity and abdominal viscera not only via mucociliary clearance and swallowing, but also by transdiaphragmatic translocation or lymphatic and/or hematogenous transport (CPSC, 1983).

Other relevant animal studies, recently reviewed by Nicholson (1985), are summarized below (Morgan et al. 1975, 1977, 1978, 1979, and Evans et al. 1973). Deposition and clearance of fibers in rats were followed after a 30-minute inhalation exposure through a nose-breathing apparatus, using radioactive samples of chrysotile, amosite, anthophyllite, crocidolite, and a synthetic asbestos fluoramphibole. The percentage of fibers deposited ranged from 31 to 68%. From 51 to 67% of the fibers deposited in the respiratory system above the trachea were cleared rapidly and were found in the gastrointestinal tract at termination of the exposure. Fibers in the lower respiratory tract appeared to show two-stage clearance. The faster stage, with a half-life of six to ten hours, is believed to be due to macrophage movement. The slower stage involves clearance from the alveolar spaces and has a half-life of 60 to 80 days. Other studies by the same group, however, have suggested that this clearance process may have only one component.

Wagner et al. (1974) determined the lung content of fibers in rats exposed to different types of asbestos for varying periods over their lifetimes. They found that concentrations of amosite, anthophyllite, and crocidolite fibers increase over time while that of chrysotile fibers rapidly reaches an equilibrium between deposition and clearance.

4. Carcinogenicity

a. Human

Asbestos has been consistently demonstrated to be carcinogenic in animals and humans and is recognized as a human carcinogen by the International Agency for Research on Cancer (IARC, 1977; NRC, 1984; Royal Commission, 1984). In occupational cohort mortality studies, exposure to the three principal commercial forms of asbestos -- chrysotile, amosite, and crocidolite -- has been repeatedly linked with increased risks for lung cancer, mesothelioma and, to a lesser extent, other neoplasms, particularly gastrointestinal and laryngeal cancer (IARC, 1977; NRC, 1984). Occupational exposure to anthophyllite has been associated with an increased risk for lung cancer. Cigarette smoking acts synergistically with occupational exposure to asbestos in increasing the risk of lung cancer, but not mesothelioma. (Hammond et al., 1979; NRC, 1984)

Tremolite and actinolite are often contaminants of other ores and have not been extensively studied with respect to their biological effects in humans or animals. However, DHS staff members believe that these minerals should be considered as if they pose a carcinogenic risk to humans, based on the following rationale: (1) They are amphiboles and can occur in physical phases similar to the well-characterized carcinogens amosite and crocidolite; (2) Lungs of chrysotile miners with mesothelioma have been reported to contain substantially greater numbers of tremolite/actinolite/anthophyllite fibers than of chrysotile (Churg et al., 1984); (3) While tremolite can occur in different physical phases, when it

does occur as fine fibers there is some evidence that it is associated with lung cancer and mesothelioma (Wagner et al., 1982; Baris et al., 1979).

b. Animal

Many studies using laboratory animals have been conducted to investigate the carcinogenic potential of various forms of asbestos administered by inhalation, by ingestion (in food or drinking water), and via intraperitoneal and intrapleural injection or deposition. The animal studies have recently been reviewed by Condie (1983), NRC (1984), and Nicholson (1985). Therefore, only a brief description of these studies is presented below and in Tables 4-1 and 4-2.

The animal studies clearly indicate that asbestos is carcinogenic in a variety of species when administered by inhalation or directly into the peritoneum or pleural space. Results of bioassays where asbestos was ingested are inconclusive. In view of the unequivocal findings of carcinogenicity of asbestos in animals, the following discussion presents only a summary description of most of the relevant bioassays. (As noted in section 9, no animal data were used to derive a dose-response curve primarily because only one dose level was used in most of these experiments and the doses used were expressed on a mass basis, whereas fiber counts would have been more helpful for purposes of quantitative risk assessment.)

TABLE 4-1: SUMMARY OF ANIMAL INHALATION STUDIES

Author	Species	No.	Fiber Type	Experimental Detail	Results
Gross et al, 1967	Rat	132T 55C	Chrysotile	Mean concentration 86 mg/m^3 for 30 hours/week for their lifetime. Some treated and control rats given 0.05 ml intratracheal installation of 5% NaOH.	72 treated rats survived 16 months or longer. 10/41 without NaOH and 15/31 with NaOH developed thoracic tumors (adenocarcinomas, squamous cell carcinomas, fibrosarcomas, and a mesothelioma). No control animal developed malignant tumors (0/39).
Reeves et al, 1971	Rat Rabbit Mouse Hamster	219T,C 106T,C 139T,C 214T,C	Chrysotile, amosite and crocidolite	Exposed to one fiber type at a concentration of about 48 mg/m^3 16, hours/week for up to 2 years.	2 lung squamous cell carcinomas found in 31 rats examined after exposure to crocidolite. No tumors found in rats exposed to other fiber types or in any species exposed to any of the fiber types.
Reeves et al, 1972	Rat Gerbil Mouse Rabbit Guinea Pig	69T*, 12C 68T, 12C 30T, 10C 20T, 12C 32T, 12C	Chrysotile, amosite and crocidolite	Exposed to one fiber type at a concentration of about 49 mg/m^3, 16 hours/week for up to 2 years. Actual fiber counts were 864, 1105, and 54 fiber/ml for amosite, crocidolite and chrysotile, respectively.	The incidences of malignant thoracic tumors in rats exposed to chrysotile, amosite, and crocidolite were 3/43, 4/46, and 3/46, rspectively. Two of 18 chrysotile-exposed mice had malignant lung tumors, but so did one of 6 control mice. No other tumors were reported.
Wagner et al, 1974	Rat	19 to 52T 48 to 58C	UICC samples of amosite, anthophyllite, crocidolite, Canadian and Rhodesian chrysotile	Exposure varied from 9.7 to 14.7 mg/m^3 of the different fiber types. Exposure was 7 hours/day, 5 day/week for 1 day, 3, 6, 12, or 24 months. Animals were sacrificed at 24 months.	All fiber types induced adenocarcinoma and squamous cell carcinoma in the lung. Incidences were 11/146, 16/145, 16/141, 17/137, and 30/144, for the respective fiber types. Mesotheliomas were also induced. No tumors found in control animals. In general tumor incidence increased with length of exposure.

TABLE 4-1: SUMMARY OF ANIMAL INHALATION STUDIES (cont'd)

Author	Species	No.	Fiber Type	Experimental Detail	Results
Wagner et al, 1977	Rat	----	Superfine chrysotile	Exposed to 10.8 mg/m^3 for 37.5 hours/weeks. Exposure lasted 3, 6, or 12 months.	One of 24 rats exposed for 12 months had an adenocarcinoma of the lung. No tumors found in control animals exposed to nonfibrous talc.
Davis et al, 1978	Rat	Approx 40T* 20 C	Chrysotile, amosite and crocidolite	Exposed to 2 or 10 mg/m^3 chrysotile, 5 or 10 mg/m^3 crocidolite, or 10 mg/m^3 amosite. Exposure for 35 hours/week for about 45 weeks and sacrificed at 29 months.	Eight of 40 rats exposed to high dose chrysotile had lung tumors and 1 out 43 had lung tumors in the low dose group. Mesotheliomas were found in one animal in each low dose chrysotile group. Amosite-exposed and control rats did not have lung tumors.

* For each fiber type
+ For each fiber type and exposure concentration
T = Treated animals
C = Control animals

TABLE 4-2: SUMMARY OF ANIMAL INGESTION STUDIES

Author	Species	No.	Fiber Type	Experimental Detail	Results
Gross et al, 1974	Rat	40T 65C	Crocidolite	Given as 0.15% of diet. Exposure and study lasted 78 weeks.	No tumors were found in treated animals.
Cunningham et al, 1977	Rat	10,40T 10,40C	Chrysotile	Given as 1% of diet. Exposed for 24 months. 10T and 10C sacrificed at 24 months, others at 30 months.	In the small group 6 malignant tumors found compared to 1 in the control group. In the larger groups both had 11 malignant tumors.
Smith et al, 1980	Rat	60T* 120C	Amosite, taconite tailings	Given in drinking water at concentrations of 0.5, 5, and 50 mg/liter. Exposure and study lasted 23 months.	Two stomach tumors and one mesothelioma found in the mid-dose amosite group. No tumors found in the high-dose group.
Donham et al, 1980	Rat	240T 121C	Chrysotile	Given as 10% of diet for the for the entire 32 months of the study.	Three colon tumors found in both treated and control groups. One mesothelioma was found in the treated group.
Gibel et al, 1976	Rat	50T 50C	Filter material with chrysotile	Lifetime dosage of 20 mg/day	In the treated group there were 4 kidney, 1 lung, and 4 liver tumors and 4 lymphomas. The control group had 4 liver tumors.

TABLE 4-2: SUMMARY OF ANIMAL INGESTION STUDIES (cont'd)

Author	Species	No.	Fiber Type	Experimental Detail	Results
McConnell et al, 1983a	Hamster	251 to 254T* 126 to 128C*	Amosite, short-range chrysotile (SR), intermediate range chrysotile (IR).	Given as 1% of diet for their lifetime starting with the mothers of the test animals.	Increased adrenal cortical tumors in groups given SR and IR when compared to pooled control but not when compared to temporal control. Not considered related to treatment.
McConnell, 1983b	Rat	250T* 117 to 118C*	Amosite, Tremolite (nonfibrous)	Given as 1% of diet for their lifetime, starting with the mothers of the test animals.	Increase in incidence of C-cell carcinomas of the thyroid and monocytic leukemia in amosite treatment group. Not considered related to treatment.

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* Per group.
T = treated animals
C = control animals

Inhalation Studies

Gross et al. (1967) exposed male rats to airborne chrysotile over their lifetimes and found that a large number of treated animals developed malignant lung tumors and 1 developed mesothelioma. Reeves et al, (1971, 1974) did not find any rats in their first study that were exposed to about half the chrysotile airborne concentration given by Cross et al. to develop malignant lung tumors and only a small percentage developed tumors in their second study. Low incidences of malignant lung tumors were found in crocidolite-exposed rats in both studies by Reeves et al. Amosite did not induce any malignant lung tumors in rats. other species including rabbits, guinea pigs, hamsters, and gerbils, exposed to these asbestos fiber types did not develop lung tumors. Two respiratory tumors were found in mice exposed to crocidolite but one control mouse had the same tumor type.

Wagner et al. (1974) compared the carcinogenic effect of 5 different UICC (Union Internationale Contre le Cancer) asbestos samples, amosite, anthophyllite, crocidolite, chrysotile (Canadian), and chrysotile (Rhodesian). Exposure length varied from 1 day to 24 months, although all animals were followed for their lifetimes. Malignant lung tumors were found in some rats from all five asbestos exposure groups and all but the group exposed to Rhodesian chrysotile had at least one rat with a mesothelioma. Rhodesian chrysotile was the most potent, while amosite was the least potent asbestos sample, based on an air mass concentration. Total cumulative exposure (all asbestos exposure groups combined) averaged over the animals' lifetime appears to be directly related to the incidence of malignant tumors, except in the one-day exposure group, where the incidence of malignant tumors was unexpectedly high. In a later study, Wagner et al. (1977) exposed rats to a

superfine chrysotile. Only one animal exposed for 12 months developed a malignant lung tumor.

Davis et al. (1978) exposed rats to chrysotile, crocidolite, and amosite. Twenty percent of the animals exposed to the high concentration of chrysotile developed malignant lung tumors. One out of 40 animal exposed to the low concentration of chrysotile developed a peritoneal mesothelioma. Neither amosite nor crocidolite induced malignant lung tumors in the rats. However, one animal exposed to the low crocidolite concentration did develop a pleural mesothelioma.

In separate studies, Shabad et al. (1974) and Smith et al. (1970) examined whether intratracheal injection of chrysotile would induce lung cancer in rats or hamsters, respectively. Chrysotile alone failed to induce any tumors in either species except when co-administered with benzo(a)pyrene.

Ingestion Studies

Several long-term ingestion studies have been conducted on asbestos. Cunningham et al. (1977) and Gross et al. (1974) fed diets containing chrysotile to rats. Neither study indicated that ingested chrysotile induced an increased incidence of intestinal tumors. Smith et al. (1980) reported that amosite given to male and female hamsters via their drinking water did not significantly increase the incidence of cancer, although, a peritoneal mesothelioma, a pulmonary carcinoma, and two early squamous cell carcinomas of the nonglandular stomach were found in this group of treated animals.

Donham et al. (1980) reported equivocal results in a lifetime rat feeding study using a diet containing 10% chrysotile. There was evidence of penetration of asbestos into the colonic mucosa and possible cytotoxicity to the colonic tissues, which they suggested may be related to induction of peritoneal mesothelioma. Gibel et al. (1976) reported an increase in malignant tumors of the lung, kidney, liver, and reticuloendothelial system in rats fed asbestos filter material, however, there was no increase in intestinal tumors.

McConnell et al. (1983a,b) reported on a number of studies conducted by the National Toxicology Program (NTP) in which hamsters and rats were fed diets containing different types of asbestos. Hamsters given chrysotile had an increase in adrenal cortical tumors and rats given amosite had increased incidences of C-cell carcinomas of the thyroid and monocytic leukemia. None of these tumors were considered treatment-related.

Intrapleural or Intraperitoneal Administration Studies

A number of studies have shown that intrapleural administration of asbestos results in the development of mesothelioma (Donna 1970, Reeves et al. 1971, Pylev and Shabad 1973, Shabad et al. 1974, and Smith and Hubert 1974). Chrysotile, amosite, anthophyllite, and crocidolite have all induced mesothelioma when administered intrapleurally to rats, rabbits, and/or hamsters.

Wagner et al. (1973) demonstrated a dose-response relationship between the amount of asbestos (superfine chrysotile or crocidolite) administered intraperitoneally and the incidence of mesothelioma in treated rats. Stanton and Wrench (1972) showed that commercial asbestos fibers as well as glass and other mineral fibers implanted onto the pleural surface of rats were able to induce formation of mesotheliomas. These authors concluded that the effect was related to the fiber's physical size. When asbestos samples were ground in a ball mill to produce shorter length fibers, the latter were less likely to induce cancer. Stanton et al. (1981) suggest that the carcinogenic potential of a fiber material can best be estimated by the number of fibers $\leq$ 0.25 μm in diameter and $\geq$ 8 μm in length (see "Influence of fiber dimensions on carcinogenicity", infra).

Maltoni and Annoseia (1974) found that intraperitoneal injection crocidolite into Sprague-Dawley rats resulted in over 60% developing mesothelial tumors. Amosite failed to induce any tumors when injected intraperitoneally into rats. Pott and Friedrichs (1972) and Pott et al. (1976) reported that several commercial varieties of asbestos, as well as other fibrous materials, induced peritoneal mesotheliomas in mice and rats injected intraperitoneally. Pott (1980) has proposed a model for the relative carcinogenicity of mineral fibers based on their length and diameter. The most potent fibers are those with a length of between 5 and 40 μm and a diameter of between 0.05 and 1 μm.

5. Genotoxicity

The mutagenicity of asbestos has been examined in a number of in vitro assay systems. Reports of these studies have been reviewed by NRC (1984) and Nicholson (1985). The following summarizes the review by NRC (1984).

Asbestos has not shown any activity in bacterial mutagenicity assays. The negative results may be from a lack of asbestos uptake by the bacteria. Asbestos was also not mutagenic in rodent liver epithelial cells; however, chrysotile, crocidolite, and amosite were considered to have given a weak positive mutagenic response at the hypoxanthine-guanine phosphoribosyltransferase (HGPRT) locus in Chinese hamster lung fibroblasts. Chromosomal aberrations and chromatid breaks have also been reported to occur in rodent cells incubated with chrysotile or crocidolite. Sister chromatid exchange (SCE) in Chinese hamster ovary cells was reported to be increased after exposure to amosite and crocidolite. However, no increase in SCE was observed in the V79-4 Chinese hamster lung cell line or cultured mesothelial cells exposed to crocidolite and chrysotile, respectively. Human cells appear to be relatively resistant to DNA damage by asbestos, although chromatid and chromosome breaks were reported to be increased in one study using freshly isolated human lymphocytes exposed to Rhodesian chrysotile.

6. Reproductive Effects

In comparison to the enormous number of studies on asbestos' carcinogenic effects, almost none have been directed towards its potential reproductive effects. Based on very limited data (one study of CD-1 mice), there is no evidence for a teratogenic effect of asbestos (Schneider and Maurer, 1977).

7. Other Health Effects

Exposure to asbestos can result in pulmonary changes varying in severity from no clinical impairment to progressive cardiorespiratory failure. These effects include: (1) the presence of asbestos fibers and asbestos bodies in the lung parenchyma; (2) development of pleural thickening and pleural plaques; (3) the occurrence of benign pleural effusions; and (4) interstitial fibrosis or asbestosis. All of these have been extensively reviewed elsewhere and are discussed only briefly herein (See Morgan and Seaton, 1984; Rom, 1983; CPSC, 1983; NRC, 1984). The first three are generally considered markers of asbestos exposure, while the last is often associated with functional impairment and disability.

a. Retained Asbestos Fibers and Asbestos Bodies

Large numbers of asbestos fibers have been reported to be present in the lungs of the general population as well as in those of individuals with occupational exposure. Electron microscopy has shown the presence of asbestos fibers (chrysotile and amphiboles) in the lungs of urban dwellers to be a nearly universal phenomenon. In one study of 21 urban dwellers with no

identifiable asbestos exposure, an average of 130,000 fibers per gram of wet lung was reported (by electron microscopy)(Churg and Warnock, 1980). In another study using electron microscopy, virtually all samples of lung tissue taken from residents of New York City were shown to contain asbestos (CPSC, 1983).

Light microscopic counts of more than 100,000 fibers per gram of dried lung are typical of persons with an identifiable (usually occupational) exposure. Persons with mesothelioma usually fall within this range, while in individuals with asbestosis fiber counts generally exceed 3,000,000 fibers per gram (Morgan and Seaton, 1984).

A small percentage of retained asbestos fibers are coated with mucopolysaccharide and protein with ferritin granules, identifiable by the light microscope as asbestos bodies. The latter are believed to be created by lung macrophages and appear to exert a protective effect against fibrosis (Morgan and Seaton, 1984). Formation of such bodies represents a generic response to the presence of fibers (e.g., glass, talc), but the core of most such coated fibers, particularly in urban dwellers, is probably asbestos (CPSC, 1983). Asbestos bodies have been reported to be present in 20-60% of routine autopsies, with higher counts in persons who have lived in urban areas close to industrial users and sources of asbestos. A higher prevalence is found in asbestos-exposed workers, as would be expected. While asbestos fibers and asbestos bodies commonly aggregate in areas of fibrosis, the presence of these entities unaccompanied by other sequelae is considered an indication of exposure to asbestos, but not a disease or disability (CPSC, 1983).

b. Pleural Thickening and Pleural Plaques

Inhaled asbestos can produce fibrosis of the pleura, resulting in thickening and/or plaque formation. Typically these developments are detected in X-ray examinations rather than because of patient symptomatology. The radiographic presence of calcified plaques on the diaphragm and the pleura is an excellent marker for asbestos exposure, even in persons with nonoccupational exposure. Pleural thickening and plaque formation generally do not cause clinical impairment (CPSC, 1983; NRC, 1984; Royal Commission, 1984).

The clinical significance of pleural plaques and lesser degrees of pleural thickening is considered to be minor when viewed in isolation from lung parenchymal involvement (NRC, 1984). It has been suggested that the presence of pleural abnormalities may be predictive of subsequent functional impairment, but it is difficult to assess the validity of this observation independent of the duration and intensity of asbestos exposure (CPSC, 1983).

Pleural abnormalities have been reported in a large percentage of household contacts of asbestos workers, presumably due to contamination from the workers' clothes (Anderson et al., 1979). While dyspnea was present in a small number of individuals with radiographic pleural abnormalities, the prevalance of symptoms was not significantly different from a control group (Anderson et al., 1979). In some cases it is clear that extensive fibrotic involvement of the pleura can lead to disabling restrictive lung disease (Royal Commission, 1984; NRC, 1984). At present, however, the principal

importance of pleural changes is in their utility as a marker of exposure (CPSC, 1983).

c. Pleural Effusions

Pleural effusions are uncommon in the U.S. among individuals with no identifiable asbestos exposure. In contrast, such effusions are probably the most common complication of occupational asbestos exposure occurring within 20 years following initial exposure (Epler et al., 1982). Such effusions can be benign or due to pulmonary or pleural malignancy. Benign effusions tend to be small and asymptomatic, often leaving a residual pleural thickening, and may represent the etiologic explanation for the latter. The condition appears to be dose-related (Epler et al., 1982). Because such effusions are rarely disabling, they have been considered to be markers of asbestos exposure (Royal Commission, 1984).

d. Asbestosis

Diagnostic criteria for asbestosis include a history of asbestos exposure, characteristic X-ray findings, decreased lung function, crackles heard on auscultation of the chest, and progressive symptoms of diffuse pulmonary fibrosis, including breathlessness, cough, sputum production, and eventual cardiopulmonary failure (Morgan and Seaton, 1984). Symptoms usually progress even after cessation of exposure. All types of asbestos are capable of causing asbestosis. Mortality from asbestosis is still substantial among occupationally exposed persons, but has not been reported among individuals without occupational exposure (Royal Commission, 1984;

Nicholson, 1985). In their study of household contacts of asbestos workers, Anderson et al. (1979) found that while 35% of the study population (compared with 5% of controls) had radiographic abnormalities, only about 8% (versus 0.3% of controls) had radiographic signs consistent with findings of asbestosis. A few of these individuals were also symptomatic, but "(w)ith only a few exceptions, household contact clinic participants were unaware that they had any asbestos-associated disease...(and) considered themselves to be in good health; the clinical examinations generally confirmed this." (p. 395) In addition, samples in other asbestos workers' homes indicated significant contamination at levels substantially higher than ambient urban air (Nicholson et al., 1980).

8. Thresholds

a. Cancer

For toxicologic purposes, a threshold dose is one below which a specified outcome does not occur. The self-propagating, clonal nature of tumor growth and development from a single damaged cell, however, suggests that the effective dose for carcinogenesis may be so low as to be indistinguishable from zero. While threshold models (based on pharmacokinetics, DNA repair mechanisms, recurrent cytotoxicity) have been proposed, none has been convincingly demonstrated.

An "epigenetic mechanism" that could theoretically embody threshold doses has been invoked to explain the carcinogenic action of substances that do not directly produce genetic damage in short-term tests. However, neither short-term tests nor nonlinearities in dose-response curves from animal bioassays or epidemiologic studies can reliably distinguish between "genetic" versus "epigenetic" carcinogenesis, primarily because of the limited sensitivities of the experimental methodologies. DHS staff members agree with the conclusion of the International Agency for Research on Cancer (1983) that there is insufficient evidence at present to justify creating separate classes of carcinogens (based on mechanism) for which different risk assessment methods would be used. Thus, in the absence of compelling evidence to the contrary, DHS treats carcinogenesis as a nonthreshold phenomenon. The mechanism of asbestos carcinogenesis is unknown and there is no evidence to suggest the existence or location of a threshold.

b. Asbestosis

The disabling clinical manifestations of asbestosis are a consequence of extensive fibrosis of the lung due to the presence of asbestos fibers. It is probable that a pulmonary fibrotic response occurs at low levels of exposure. However, the development of symptoms characteristic of asbestosis appears to require the fibrotic destruction of a substantial lung volume, which in turn depends on the inhalation of quantities of asbestos not typically encountered outside of the occupational setting. Lesser degrees of fibrosis may often occur without any symptomatology because of the large reserve capacity of the lung.

The Consumer Product Safety Commission, reviewing the evidence available to 1983, concluded that the incidence of asbestosis is proportional to the cumulative exposure. The studies reviewed involved occupational cohorts with high-level exposures, which, when extrapolated to low doses, could be consistent with either a "threshold" at cumulative exposures of 10 fiber-yr/cc or less or a nonthreshold model. Indicating that the existence of a threshold for asbestosis could not be proved or disproved by existing data, the panel stated that it knew of "no reports of disabling asbestosis occurring among persons whose maximum exposure to asbestos was of the order of 1 fiber/ml or less. Hence...(citing Finkelstein, 1982) 'the major risk at lower exposures will be due to cancer rather than to asbestosis'" (CPSC, 1983). Others have shared this conclusion (Morgan and Seaton, 1984; Royal Commission, 1984). DHS staff members concur, based on the absence of reports of asbestosis

occurring at low levels of exposure and on grounds of biological plausibility.

9. Quantitative Risk Assessment

The outcomes of interest in this quantitative risk assessment are lung cancer and mesothelioma, since both are considered to be nonthreshold processes posing potential population risks at ambient concentrations of asbestos. Asbestosis was not included in the risk assessment because it is not considered to pose such a risk to the general population (See section 8, "Thresholds"). Other cancers (e.g., gastrointestinal cancer) were not included because: (1) increased risks for these tumors have not been consistently detected in epidemiologic studies; (2) in those investigations disclosing an elevated risk for these cancers, the magnitude of the risk is substantially lower than that for lung cancer and mesothelioma; (3) for gastrointestinal cancer, although there is a positive dose-response trend with asbestos exposure, the data are insufficient to establish a functional dose-response model (Nicholson, 1985), and numerous experimental studies involving ingestion of asbestos by animals have not confirmed a causal relationship. Some investigators have recently concluded that the excess cases of gastrointestinal cancer observed in a few epidemiological studies are artifacts due to misclassification of cause of death (Doll and Peto, 1985).

DHS' risk assessment relies extensively on work done by the Consumer Product Safety Commission (1983), the National Academy of Sciences (NRC, 1984), Nicholson (1985), and the Ontario Royal Commission (1984). These

risk assessments have been based exclusively on the results of occupational epidemiologic studies: this assessment is similar in that regard. The relevant studies have been extensively reviewed elsewhere and are presented here only in tabular format (See Tables 9-1 and 9-2).

As noted earlier (section 4.a), asbestos has been indisputably demonstrated to be carcinogenic in humans in a variety of occupational settings. Tables 9-1 and 9-2 are not comprehensive and include only studies used in the quantitative risk assessment. Although individual study details are provided only in summary form, even a cursory review of the standardized mortality ratios (SMRs) in Table 9-1 and the numbers of pleural and peritoneal mesotheliomas in Table 9-2 indicates that there is strong evidence for asbestos carcinogenicity in humans.

TABLE 9-1: SUMMARY ASPECTS OF EPIDEMIOLOGIC STUDIES

USED IN QUANTITATIVE RISK ASSESSMENT FOR LUNG CANCER

Study	Cohort Occupation	Fiber type	Cohort Number	Sex	Follow-up	Lung Cancer Mortality Expected	Observed	SMR
Finkelstein, 1983	Asbestos Cement mfg.	Chrysotile, Crocidolite	241	M	1963-80	3.3	20	606
Selikoff et al., 1979	Insulation	Chrysotile, Amosite	17,800	M	1967-76	93.7	390	416
Seidman et al., 1979	Insulation mfg.	Amosite	820	M	1961-76	21.9	83	380
Dement et al., 1982, 1983a,b	Textile products mfg.	Chrysotile	1,261	M	1940-75	9.8	33	336
Henderson and Enterline, 1979	Asbestos mfg.	Chrysotile, Amosite, Crocidolite	1,075	M	1941-73	23.3	63	270
Newhouse and Berry, 1979	Asbestos products mfg.	Chrysotile, Crocidolite, Amosite	4,600	M	1936-75	43.2	103	238
Newhouse and Berry, 1979	Asbestos products mfg.	Chrysotile, Crocidolite, Amosite	922	F	1936-75	3.2	27	843
Nicholson et al., 1979	Mining	Chrysotile	544	M	1961-77	11.1	25	225

TABLE 9-1 (Continued)

Peto, 1977, 1980	Textile products mfg.	Chrysotile	822	M	1933-74	22.9	49	214
McDonald et al., 1984	Friction products	Chrysotile	3,177	M	1938-77	49.1	73	149
Weill et al., 1979	Asbestos Cement mfg.	Chrysotile, Crocidolite	5,645	M	1940-74	49.2	51	104
Berry and Newhouse, 1983	Friction products	Chrysotile, Crocidolite	7,474	M	1942-80	139.5	143	103
Berry and Newhouse, 1983	Friction products	Chrysotile Crocidolite	3,708	F	1942-80	11.3	6	50
Rubino et al., 1980	Mining	Chrysotile	952	M	1946-75	8.7	9	103
McDonald et al., 1980	Mining	Chrysotile	9,767	M	1926-75	184	230	125
McDonald and Liddell, 1979	Mining	Chrysotile	...	M	...	...	...	...

TABLE 9-2: SUMMARY ASPECTS OF EPIDEMIOLOGIC STUDIES USED IN QUANTITATIVE RISK ASSESSMENT FOR MESOTHELIOMA

Study	Cohort Occupation	Fiber type	Cohort Number	Sex	Follow-up	No. Mesotheliomas Pleural	Peritoneal
Selikoff et al., 1979	Insulation	Chrysodile, Amosite	17,800	M	1967-76	63	112
Peto, 1980	Textile mfg.	Chrysotile	822	M	1933-74	9	0
Seidman et al., 1979	Insulation mfg.	Amosite	820	M	1961-76	7	7
Finkelstein, 1983	Asbestos Cement mfg.	Chrysotile Crocidolite	241	M	1963-80	6	5
Newhouse and Berry, 1976	Asbestos products mfg.	Chrysotile, Crocidolite, Amosite	---	---	---	---	---

The reasons for excluding animal bioassay data from this analysis are threefold. First, there are numerous epidemiologic studies of populations occupationally exposed to asbestos, at least fourteen of which contain or have been supplemented with exposure data adequate for purposes of quantitative risk assessment. Second, while there have also been many animal bioassays involving exposure to asbestos, almost all have used only one dose level, which makes the use of the usual low-dose extrapolation models inappropriate. In addition, inhalation studies with multiple dose levels have specified doses on a mass basis, i.e., mg/cm^3, which displays considerable variability (up to 3 orders of magnitude) vis-a-vis PCM fiber counts (Schneiderman et al., 1981). The principal reason to utilize an animal bioassay risk assessment in this context would be to take advantage of controlled exposure data in order to narrow the range of uncertainty in the exposure-response relationship. However, existing studies are not suitable for this purpose. Third, a risk assessment based on animal data could, at best, be used to confirm the estimates based multiple human studies. If the former produced risk estimates substantially greater than or less than those derived from human studies, they would only add a caveat to the interpretation of the latter.

a. Models Used in Risk Assessment

Risk estimates for both lung cancer and mesothelioma were developed using a linear, nonthreshold model. The data upon which these models are based (i.e., the results of occupational epidemiological studies)

are consistent with such a model, but do not rule out nonlinear dose-response relationships. For example, Nicholson has noted that the results of linear extrapolation cannot be distinguished from those derived using the logit, log-probit, or multistage models within the observable range for occupational asbestos exposures (Nicholson, 1981). Previous risk assessments have relied on a linear model because it is biologically plausible, conservative, and mathematically tractable (Royal Commission, 1984; NRC, 1984; Nicholson, 1985, 1981; CPSC, 1983). DHS staff members have found this rationale persuasive.

In previous documents DHS has applied the multistage model to animal, not human, data. This model could be applied to epidemiological data as well, since it was originally derived from studies of cigarette smoking in humans. Dr. Kenny Crump used the multistage to model the risk of mesothelioma from occupational asbestos exposure (as described in his comments on a proposed federal Occupational Safety and Health Administration [OSHA] asbestos standard, previously submitted in this administrative record as an attachment to the comments of the Asbestos Information Association). His mesothelioma risk estimates were notably lower than those derived by OSHA using a model similar to that employed by DHS. In so doing, Dr. Crump utilized newly developed software which DHS has ordered, but not received.

DHS staff decided to use these models to estimate risks of mesothelioma and lung cancer in part because of the above-noted reasons, in part because at least six other organizations or teams of investigators with far greater resources and time at their disposal had fitted these models

to the epidemiologic data, and in part because the software used by Dr. Crump was unavailable to DHS staff. The models were critically reviewed by DHS staff and were subjected to minor modifications. As can be seen in Table 9-8, our risk estimates are not dramatically different from those developed by the National Academy of Sciences, the Consumer Product Safety Commission or Dr. Nicholson (for the Environmental Protection Agency).

While previous asbestos risk assessments have used the same basic models, each has incorporated some methological modifications. Not surprisingly, however, the effects of such modifications on risk estimates are relatively minor (see Tables 9-8 and 9-9). Our description of the models most closely parallels that of the Ontario Royal Commission (although the latter estimated risks from occupational and not from ambient levels of exposure).

The models providing the best fit to the results of epidemiologic studies predict relative risks for lung cancer and absolute risks for mesothelioma. Fitting the models to the data produces several constants (see below), which are then used in predicting risks due to low ambient levels of asbestos exposure. DHS staff members relied on others' work (Nicholson, 1985; CPSC, 1983; NRC, 1984; Royal Commission, 1984) in deriving these constants and did not duplicate this aspect of the risk assessment. Although there are potential difficulties in adopting others' calculations, the consistency of our results with previous risk assessments and with actual incidence data for mesothelioma (See

Sections 9.g. and 9.h.) suggests that this issue is of greater theoretical than practical importance. The general characteristics of the models are discussed in the following subsections, and the results are presented subsequently.

i. Lung Cancer Model

1) Excess Relative Risk

Since there is a significant background incidence of lung cancer in the general population, the model used to predict lung cancer incidence due to asbestos exposure incorporates the concept of excess relative risk. If relative risk (RR) is the ratio of disease incidence experienced by an exposed population divided by that experienced by an unexposed population, then excess relative risk can be considered as RR - 1, which takes the background incidence into account.

2) Linear Model

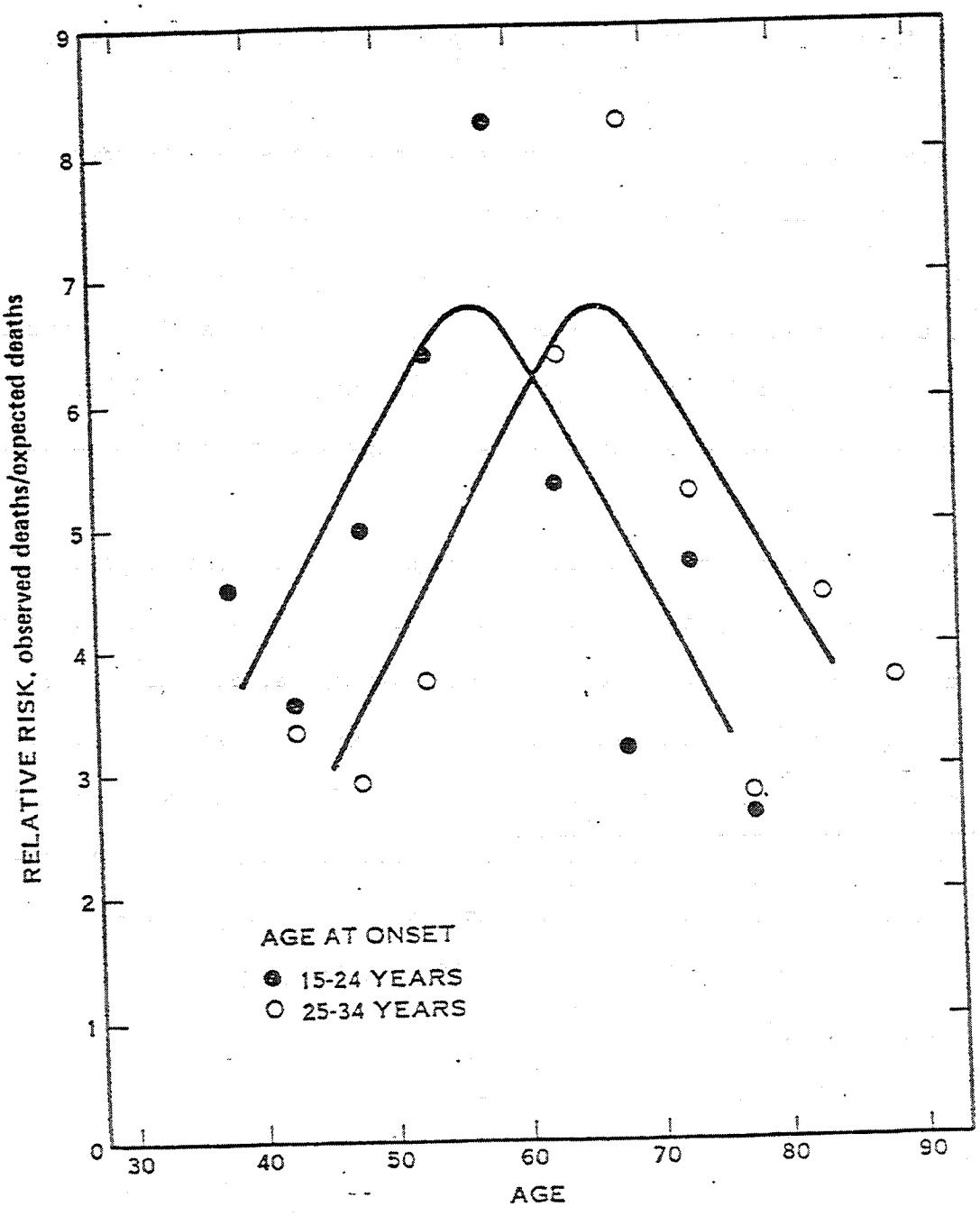
Data from multiple occupational epidemiological studies are consistent with a dose-response relationship in which the relative risk of lung cancer increases linearly with cumulative dose (Nicholson, 1985; NRC, 1984; Royal Commission, 1984). Although the dearth of human data on deposition and clearance make the estimation of dose somewhat problematic, for practical purposes it will be assumed that

cumulative dose is equivalent to the mathematical product of duration of exposure (in years) times its intensity (in fibers/cc). Implicit in a dose-response relationship proportionate to cumulative exposure is the notion that the effects of a given cumulative exposure will not be influenced by the manner in which it occurred. For example, a cumulative exposure of 20 fiber-years/cc is predicted to produce identical effects for a 5-year exposure at 4 fibers/cc or a 10-year exposure at 2 fibers/cc.

3) Considerations of Time and Age

Expressing risk as a function of cumulative exposure also implies that exposures at younger ages will not affect lung cancer risk more than exposures at older ages. This proposition cannot be empirically validated from occupational cohort data for exposures occurring earlier than age 15. However, support for the idea that risk is independent of age at first exposure comes from the data of Selikoff et al. (1979). Insulation workers first exposed between ages 15 and 24 showed a pattern of relative risk increasing after a lag time of about 10 years and decreasing after several decades, which quite closely approximated the experience of a cohort first exposed between ages 25 and 35. When relative risk is plotted as a function of age, the slopes for these cohorts are similar, except that the curves are separated by a period of about 10 years, corresponding to the approximate difference in the average age of first exposure (Figure 9-1).

FIGURE 9-1: RELATIVE RISK OF DEATH FROM LUNG CANCER IN TWO COHORTS OF INSULATION WORKERS



Source: Nicholson (1985).

The decline in relative risk 30-40 years after initiation of exposure is suggested by data from several other cohorts, but is not unequivocally or consistently demonstrable (Royal Commission, 1984; Walker, 1984; Selikoff et al., 1979; Seidman et al, 1979). This delayed decline may be due to cohort selection effects, such as premature deaths of asbestos-exposed smokers, increased susceptibility of some workers to asbestos-related diseases such as asbestosis, or clearance of chrysotile from the lungs (CPSC, 1983). The trailing off of excess risk is not taken into account in the risk assessment model because it is not consistently well-characterized by epidemiologic data and because it is unknown whether the principles responsible for the decline are likely to be operative at very low exposure levels (Royal Commission, 1984).

As noted above, there appears to be a delay of about 10 years after the onset of exposure before the expression of an increase in relative risk (Selikoff et al., 1979; Seidman et al., 1979). In the context of occupational exposures, increased intensity of exposure does not appear to decrease the length of the latency period (Doll and Peto, 1985). Although an exact duration of the latency between onset of exposure and expression of disease cannot be ascertained for the general population, a 10-year lag period has been incorporated in the model.

4) Dependence on Background Lung Cancer Rate

It is necessary to incorporate the background lung cancer rate in order to transform excess relative risk to an expression of excess lung cancers due to asbestos exposure. The relatively short survival of nearly all lung cancer patients justifies DHS' assumption that cancer mortality rates are equivalent to incidence rates. In this risk assessment, the background mortality rates were taken from the San Francisco-Oakland Surveillance Epidemiology and End Results (SEER) Program for the years 1979 - 1983. These rates were readily accessible and, while not necessarily representative of California as a whole (since mainly urban areas are included), were considered more representative than those used in other published risk assessments (e.g., 1978 Canadian national lung cancer mortality rates).

The background lung cancer rates are age-, gender-, and smoking-specific. Age- and gender-specific rates were available directly from the SEER data. These rates were made smoking-specific using California smoking patterns from 1984 weighted by a relative risk factor for lung cancer of 10.4, which was taken from Doll's and Peto's British doctors study (CDC, 1985; Doll and Peto, 1976). One consequence of stratifying the background lung cancer rates by smoking status is that the risks predicted for smokers will be dramatically higher than for nonsmokers. This is consistent with the observation that smoking and occupational asbestos exposure

interact synergistically to cause lung cancer (Hammond et al., 1979).

Several assumptions about smoking patterns and lung cancer mortality are made in this risk asessment. First, smoking patterns are assumed to be constant, although DHS recognizes that changes are occurring--e.g., young females constitute an increasing percentage of smokers, which may increase the future background incidence of lung cancer, and low-tar cigarettes are more popular than in past decades, which may have the opposite effect on background rates. Second, mortality from lung cancer is not anticipated to decrease appreciably from improvements in treatment: in other words, lung cancer mortality is not assumed to be significantly lower than lung cancer incidence. Third, it is assumed that upon becoming an ex-smoker, the excess risk of lung cancer declines to the level experienced by non-smokers.

5) Lung Cancer Constant of Proportionality

In this linear model a proportionality constant ("C_l") derived from epidemiologic studies is used to relate excess lung cancer mortality to cumulative exposure. C_l represents the fractional increase in relative risk per unit of cumulative exposure in units of (fiber-years/cc)$^{-1}$. The value of C_l varies from study to study and reflects to some extent the carcinogenic potency of the fiber types and dimensions to which the cohorts were exposed.

The proportionality constant represents the ratio of lung cancer mortality to cumulative exposure for each cohort studied. Values for C_l were obtained by linear regression of (excess) relative risk on cumulative dose (See Appendix D for examples of such linear regressions). Where regression could not be done because multiple data points were not available, C_l was derived using a single value for excess relative risk divided by the average cumulative exposure.

DHS tabulated a range of values for C_l from prior risk assessments. (Royal Commission, 1984; NRC, 1984; CPSC, 1983; Nicholson, 1985). As can be seen in Table 9-3, there is a wide range of values for C_l. Different C_l values were obtained for some studies analyzed by more than one panel, which may be largely explained by the use of different conversion factors (from mppcf to fibers/cc), resulting in different exposure estimates, and by adjustments made for perceived biases.

Table 9-3: LUNG CANCER PROPORTIONALITY CONSTANTS

DERIVED FROM EPIDEMIOLOGIC STUDIES

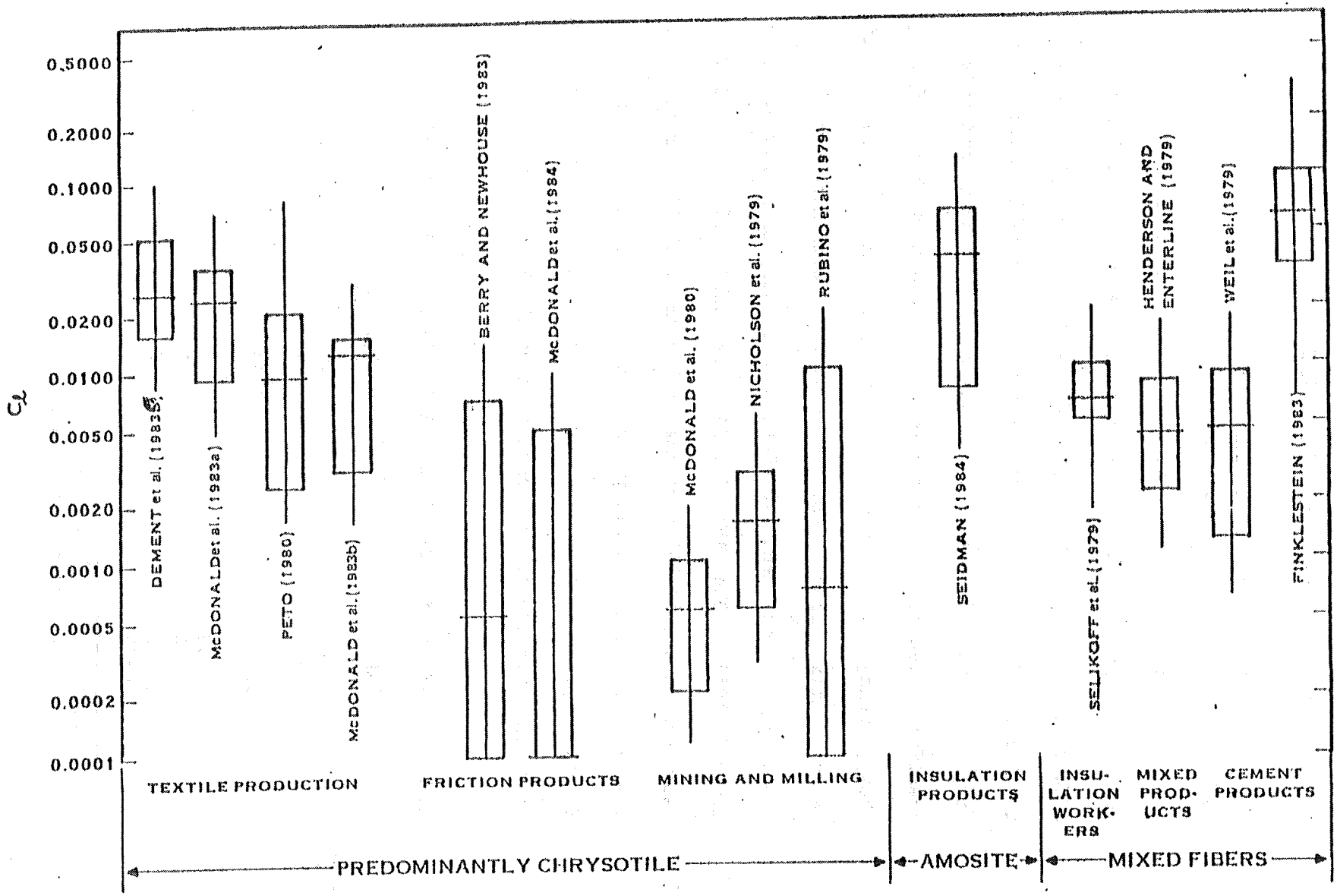
Study	Cohort Occupation	Fiber Type	Proportionality Constant (C_p) Nicholson	NRC	CPSC	Royal Commission
Selikoff et al., 1979	Insulation	Chrysotile, Amosite	.0075	.017	.010	.010
Henderson and Enterline, 1979	Asbestos manufacturing	Chrysotile, Amosite, some Crocidolite	.0049	.003	.005	.00069
Peto, 1980	Textile products mfg	Chrysotile	.011	.008	.01	.01
Dement, 1982, 1983a, b	Textile products mfg	Chrysotile	.028	.053	.023	.042
McDonald et al., 1980 McDonald and Liddell, 1979 Liddell et al., 1977	Mining and milling	Chrysotile	.0006	.0006	.0006	.00046
Seidman et al., 1979	Insulation mfg	Amosite	.043	.091	.068	---
Nicholson et al., 1979	Mining and milling	Chrysotile	.0017	.011	.0012	---
Finkelstein, 1983	Asbestos cement mfg	Chrysotile, Crocidolite	.067	---	.048	.042
Berry and Newhouse, 1983	Friction products mfg	Chrysotile, crocidolite,	.00058	---	.0006	.00058
Weill et al., 1979	Asbestos cement mfg	Chrysotile, crocidolite	.0053	---	.0031	---
Rubino et al., 1979	Mining and milling	Chrysotile	.0075	---	.017	---
Newhouse and Berry, 1979	Asbestos products mfg	Chrysotile, Crocidolite and Amosite	---	.084(female) .013(male)	---	---
McDonald et al., 1984	Friction products mfg	Chrysotile	.0001	---	---	---

Selection of an appropriate value or range of values for C_l involves several assumptions. DHS staff members do not consider that the C_l values derived from studies of asbestos miners and millers are generally applicable to environmental exposures. The low risk of lung cancer in these cohorts is thought to reflect the relatively unprocessed state of the asbestos, which would contain a high percentage of easily countable (by PCM) but largely non-respirable fibers (McDonald et al., 1984; Nicholson, 1985). Fibers more likely to be respirable and carcinogenic are generated by industrial processes that cause extensive fiber breakage. We assume that the latter would be more representative of the airborne asbestos to which most individuals in California may be exposed. Thus, the values for C_l from studies of miners and millers have been excluded from consideration.

DHS staff members used the median of the remaining C_l values as the best estimate. The median C_l for all non-mining or milling occupations is 0.01. Figure 9-2 illustrates 95% confidence intervals for values of C_l associated with variability in the numbers of lung cancer cases observed, along with adjustments made by Nicholson for possible biases and for uncertainty associated with the measurement of exposure. The upper bound in DHS' risk

assessment was calculated with C_2 set as 0.1, which was the highest 95% upper confidence limit estimated for any of the epidemiologic studies under consideration (See Figure 9-2). However, uncertainties associated with exposure data and other nonquantifiable biases make this upper bound only an approximate 95% confidence limit.

FIGURE 9-2: CONFIDENCE INTERVALS FOR VALUES OF C_ℓ



Values of C_ℓ, the fractional increase in lung cancer per f-y-ml of exposure in 14 asbestos exposed cohorts. The open bar reflects the estimated 95% confidence limits associated with measures of response. The line represents the uncertainties associated with measures of exposure, generally ± a factor of two.

6) Adjustment for Survival Probability

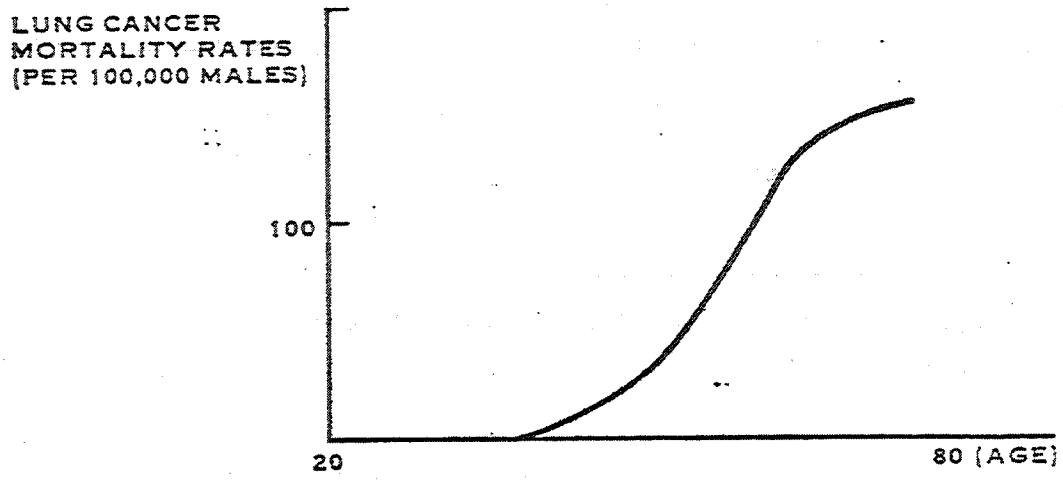
Members of the theoretical cohort used to calculate excess cancer risks will be subject to competing causes of death, which need to be taken into account in estimating lifetime cancer risks. The effect of adjusting for the probability of survival is illustrated in Figure 9-3. In DHS' risk assessment, probabilitites of survival to age 85 have been summarized in gender- and smoking-specific lifetables constructed by standard methods (Chiang, 1984), using 1980 census data for California and age-specific death rates from California vital statistics for 1979-80 (California Department of Health Services, 1982; Bureau of the Census, 1982) (See Appendix B). Although previous DHS risk assessments under AB1807 have used a hypothetical 70-year lifespan, the latter will underestimate risks when lifetables are used. Survival probabilities for smokers were calculated using relative risks of mortality for all causes of death (See Table 9-4).

TABLE 9-4: RELATIVE RISK OF ALL CAUSE MORTALITY FOR SMOKERS

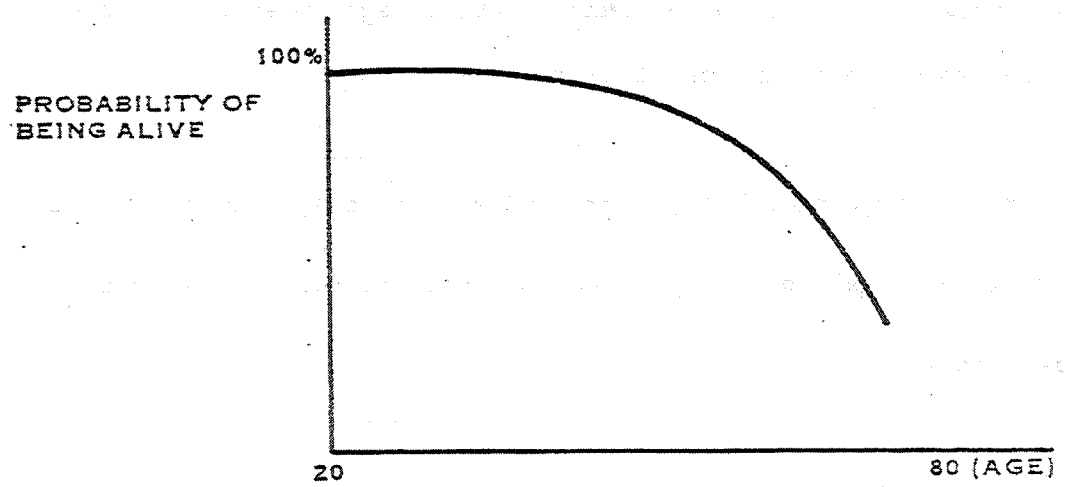
Age	Relative Risk
35-39	1.49
40-44	2.16
45-49	2.60
50-54	2.02
55-59	1.99
60-64	1.93
65-69	2.20
70-74	1.57
75-79	1.28
80-84	1.57

Source: Royal Commission, 1984
(Adapted from Doll and Peto, 1976)

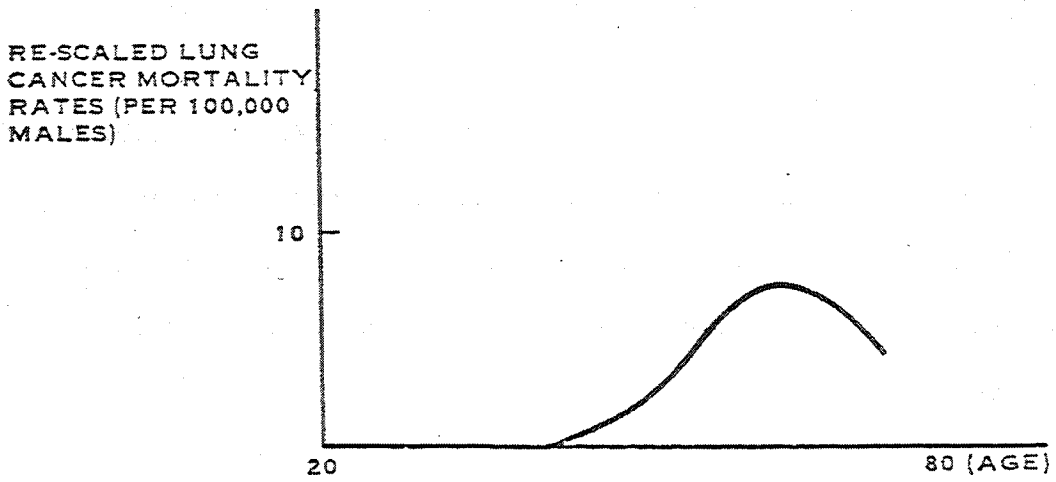
FIGURE 9-3: YEARLY PROBABILITY OF LUNG CANCER MORTALITY



LUNG CANCER RISK GRADIENT FOR NON-SMOKING MALES



SURVIVAL PROBABILITIES FOR NON-SMOKING MALES



LUNG CANCER RISK GRADIENT RE-SCALED FOR SURVIVAL

Source: Ontario Royal Commission, 1984, p. 459.

7) Summary of Lung Cancer Risk Model

Taking into account the variables discussed above, the annual excess deaths due to asbestos-caused lung cancer in a population of 1,000,000 can be expressed as:

$$IE(a) = C_{\ell} * F * (D-10) * 10^{6} * Lu(a) * S(a), \qquad (9\text{-}1)$$

Where:

IE(a) = annual excess cases of lung cancer at age interval (a) due to asbestos exposure beginning at birth.

C_{ℓ} = Constant of proportionality, expressed as percentage annual increase in relative risk of lung cancer per unit of cumulative exposure, $(\text{fiber-years/cc})^{-1}$.

F = Average level of continuous exposure to asbestos, expressed as fibers (≥ 5 microns in length, aspect ratio >3:1)/cc.

D = Duration of exposure in years. A lag time of 10 years is subtracted from duration to allow for a latency period preceding the expression of disease. Since we assume continuous exposure from birth, D = time since first exposure = age. Where D≤10, the risk is set to equal zero.

Lu(a) = Lung cancer mortality rate by age, gender, and smoking status at age interval (a).

S(a) = Cumulative probability of survival from birth to age (a).

The lifetime excess lung cancer mortality due to asbestos exposure can be expressed as:

$$IE\ (\text{lifetime}) = \sum_{a=0}^{85} IE(a) \quad \text{(by 5-year intervals).} \qquad (9\text{-}2)$$

Lifetime risk estimates based on the above formulas are presented in Section 9.g.

ii) Mesothelioma Model

The incidence of mesothelioma in the general population is so low that reliable values for expected numbers of cases cannot be calculated. Instead of estimating relative or excess risk for this neoplasm, the model predicts lifetime risks based on summation of annual incidence. In other words, this model predicts absolute rather than relative risks.

1) Dependence on Time Since First Exposure

Peto et al. (1982) demonstrated that mortality from mesothelioma among asbestos workers can be represented by a function that is a

product of a power function of time since first exposure (t^k), and a term that is linear in dose (or exposure). Fitting the model to data from five epidemiologic studies, Peto et al. estimated the exponent $k = 3.2 \pm 0.36$, although it was stated that any value of k between 3 and 4 would have fit the data equally well (1982).

It is obvious that risk estimates for mesothelioma will be quite sensitive to the value of k. It should be recognized, however, that within the range bounded by 3 and 4 the choice is somewhat arbitrary. Incorporating a lag or latency factor delays the expression of risk, so that some of the population at risk would die before they could develop cancer. The use of such a lag factor in the model results in lower values of k (2 to 3) when fitted to the epidemiologic data (Nicholson, 1985). Since DHS' model utilizes a lag to adjust for latency, we have designated $k = 3.0$. This value of k has also been utilized by CPSC (1983) and Nicholson (1985), both of whom also incorporated a latency factor in their models for the expression of mesothelioma risk.

2) Other Considerations of Time and Age

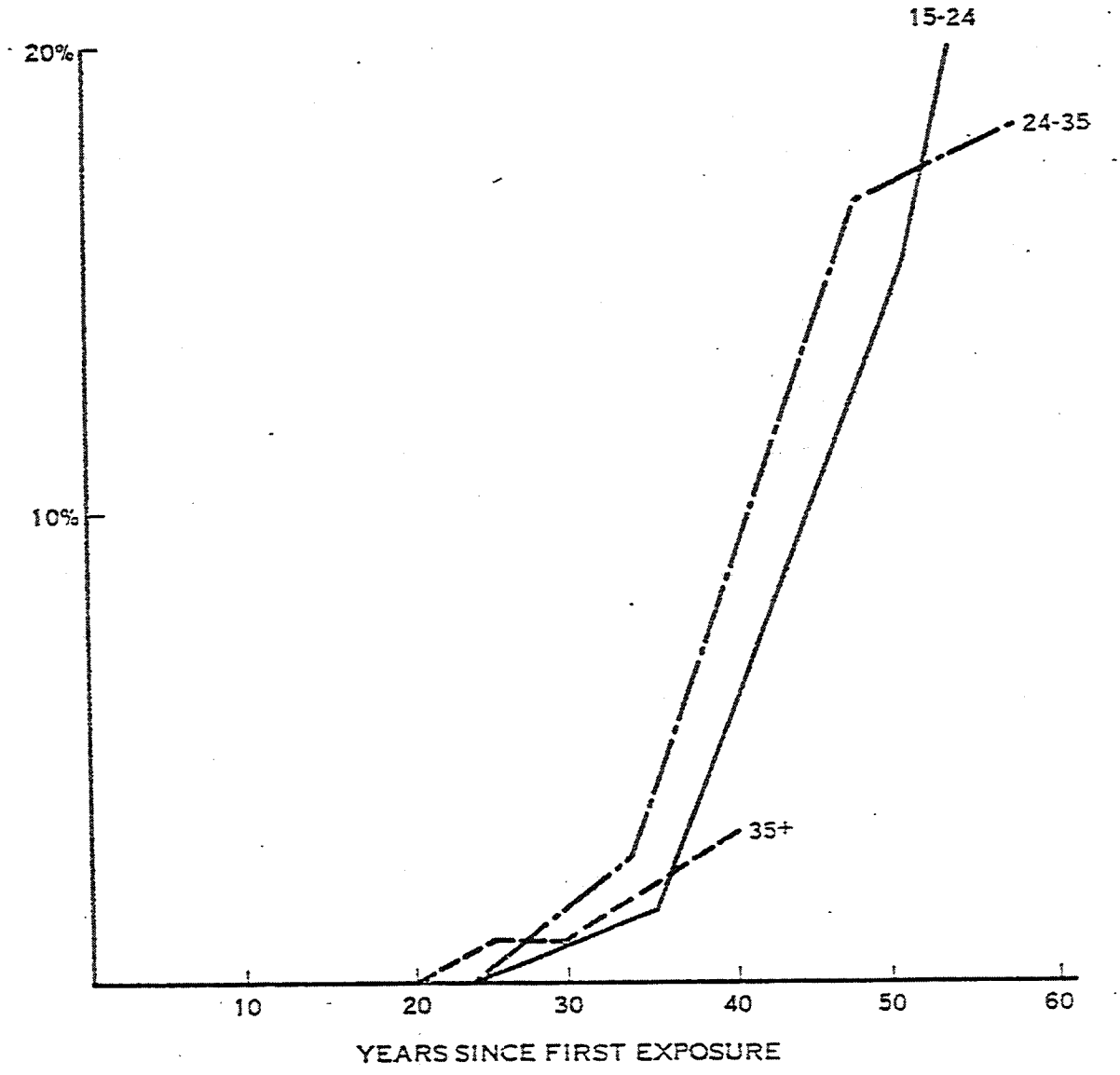
Data from Selikoff et al. (1979) demonstrate that the development of mesothelioma is independent of age at first exposure. Plotting mesothelioma mortality of occupational cohorts exposed at different ages against time since first exposure shows similar patterns of increasing incidence (Peto, 1982) (Figure 9-4). It should be noted that the increase in the risk of mesothelioma does not occur until

about 20 years after first exposure, suggesting a latency period of this length. Although the lower limit of the latter is unknown, mesothelioma is thought to have a latency period longer that most other cancers (Doll and Peto, 1985). Mesothelioma incidence data from 4 studies presented by Nicholson (1985) indicate that 98% (266/271) occurred 20 or more years after first exposure, while the remainder occurred 15-19 years after onset of exposure.

Risk patterns for mesothelioma after long periods (>50 years) of follow-up are not well-characterized by epidemiologic studies. Inferences drawn from occupational cohorts would be subject to the same limitations as were noted for long-term follow-up of lung cancer. Following the lead of the Ontario Royal Commission (1984), DHS staff members have not incorporated any factor to model a delayed decline in the risk of mesothelioma. This decision is supported by the observation that there is a continuous increase in mesothelioma incidence with age or years since first exposure among nonoccupationally exposed ("unexposed") residents of Los Angeles (Peto, 1982)(See Figure 9-5).

The model is consistent with an etiologic role for asbestos as an initiator or early-stage carcinogen. Although children are not assumed to be more vulnerable to carcinogenesis than adults, because of the rapid increase of risk with time since first exposure, early exposures are predicted to be the dominant factors in determining lifetime risks. (Data from industrial cohorts cannot yield direct

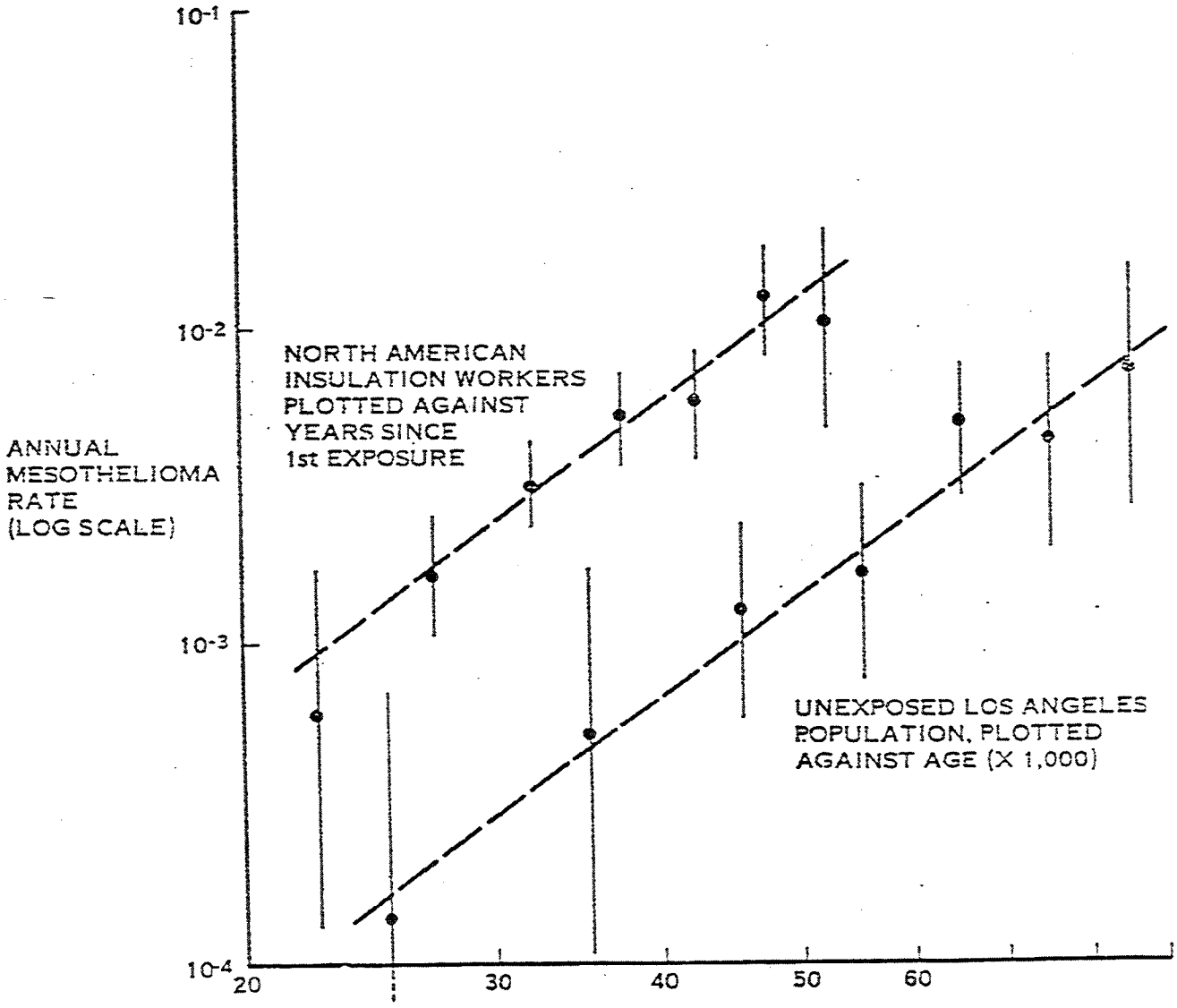
FIGURE 9-4: CUMULATIVE RISK OF MESOTHELIOMA MORTALITY IN THREE COHORTS OF INSULATION WORKERS



Source: Ontario Royal Commission, 1984, p. 469, citing evidence submitted by J. Peto. Based on data from Selikoff et al., 1979.

information about the biological activity of asbestos in children. If the latter are more susceptible to asbestos carcinogenesis than adults, then the risk estimates presented below may be too low.)

FIGURE 9-5: MESOTHELIOMA RATES AS A FUNCTION OF AGE OR TIME SINCE FIRST EXPOSURE



Source: Peto, 1982.

3) Mesothelioma Constant of Proportionality

The model for mesothelioma also includes an empirical constant of proportionality ("C_m"), derived by fitting the model to epidemiologic studies with adequate exposure-response information. DHS has relied on prior work in this area and has used the median of the values presented in Table 9-5. The C_m values developed by the Ontario Royal Commission are not included here since they were derived with the exponent of t in the model fixed at 4.0, which resulted in a value of C_m 2 to 3 orders of magnitude lower than those derived by others using an exponent of 3 (CPSC, 1983; Nicholson, 1985) or 3.2 (NRC, 1984).

TABLE 9-5: MESOTHELIOMA PROPORTIONALITY CONSTANTS DERIVED FROM EPIDEMIOLOGIC STUDIES

Study	Cohort Occupation	Fiber Type	Proportionality Constant ($Cm \times 10^{-8}$)		
			Nicholson	NRC	CPSC
Selikoff et al.,1979	Insulation	Chrysotile Amosite	1.5	1.39	1.5
Peto, 1980	Textile Products Mfg.	Chrysotile	1.0	0.85	0.7
Seidman et al., 1979	Insulation Mfg.	Amosite	3.2	7.22	5.7
Finkelstein, 1983	Asbestos Cement Mfg.	Chrysotile Crocidolite	1.2	----	12.0
Newhouse and Berry, 1976	Asbestos Products Mfg.	Chrysotile Crocidolite Amosite	----	3.67	----

4) Adjustment for Survival

The mesothelioma model uses the same lifetables to adjust for population survival as were used in the lung cancer model. Although mesothelioma incidence is independent of smoking, non-smokers live longer than smokers and thus run a higher risk of mesothelioma. Therefore, separate lifetables for smokers and non-smokers were used to adjust for survival.

5) Summary of Mesothelioma Risk Model

Taking into account the variables discussed above, the annual deaths due to asbestos-caused mesothelioma in a population of 1,000,000 can be expressed as:

$$IM(a) = C_m * F * (T-20)^3 * 10^6 * S(a), \qquad (9\text{-}3)$$

Where:

IM(a) = annual mesothelioma deaths at age interval (a) due to asbestos exposure beginning at birth.

C_m = constant of proportionality (see above).

F = average level of continuous exposure to asbestos expressed as fibers (≥ 5 microns in length, aspect ratio >3:1)/cc.

T = time since first exposure in years. A lag time of 20 years is subtracted from time since first exposure to allow for a latency period preceding the expression of disease. Since we assume continuous exposure from birth, T = duration of exposure = age. Where T ≤ 20, mesothelioma risk is set to equal zero.

S(a) = cumulative probability of survival from birth to age (a).

Predicted lifetime mesothelioma mortality due to asbestos exposure can be expressed as:

$$IM(\text{lifetime}) = \sum_{a=0}^{85} IM(a) \quad \text{(by 5-year intervals).} \qquad (9\text{-}4)$$

Lifetime risk estimates based on the above formulas are presented in Section 9.g.

b. Limitations in Determining Dose-Response Relationships

Establishing dose- or exposure-response relationships from past human exposures to asbestos is subject to several significant limitations. The mathematical risk assessment models described above have been validated by fitting the data of numerous epidemiologic investigations. The principal difficulties arising from the use of the latter include: (1) uncertainty about exposure due to infrequent and inaccurate (by today's standards) measurements of past workplace concentrations of asbestos; (2) incomplete follow-up of the cohorts under study; (3) lack of data on workers' smoking habits, necessitating an assumption that the latter are not significantly different from those of the general population; (4) variability due to small numbers of deaths; (5) misclassification of causes of death, particularly mesothelioma, and (6) inappropriate choice of a control or reference population. The relative importance of each of these varies from study to study. As has been noted elsewhere, however, the most significant deficiency in all these

investigations is the lack of reliable exposure data for the cohorts under study.

Measurements of asbestos fibers in occupational settings were infrequent prior to 1965, so that quantification of exposure for the working populations studied epidemiologically has been somewhat problematic. Furthermore, pre-1965 measurements were made using midget impingers, which relied on bright field microscopy, resulting in an underestimation of fiber counts. Impinger counts, expressed as millions of particles per cubic foot (mppcf), included quantification of total dust particles, fibrous and nonfibrous alike.

Current techniques for measuring workplace concentrations of asbestos utilize membrane filters and phase contrast microscopy (PCM). These methods have been in common use only since 1964 in the U.S. and Great Britain, and have been standardized since the early to mid-1970s. For the convenience of PCM operators and in order to achieve greater precision, only fibers with a length $\geq$5 microns and with an aspect ratio $\geq$3:1 are counted. Although most asbestos fibers in the workplace and in the environment are shorter than 5 microns, it was believed at the time this convention was adopted that the longer fibers were more important clinically (i.e., in the development of asbestosis, not cancer). It should be noted that transmission electron microscopy (TEM), the method of choice for examination of environmental asbestos samples, can visualize 100 to 1,000 times more fibers per sample than PCM (See Appendix A).

Although it is well-known that PCM fails to detect the vast majority of airborne fibers, "there is incomplete awareness that the fraction counted is highly variable" (Nicholson, 1985). Depending on the fiber type, the industrial processes or products under consideration, the age of the materials, and so forth, the percentage of fibers longer than 5 microns in an aerosol may vary from 0.5% to 30%, nearly two orders of magnitude (Nicholson, 1985). Furthermore, PCM cannot detect 50% or more of asbestos fibers ≥5 microns because their diameter is less than 0.3 microns, the limit of resolution (Royal Commission, 1984).

Despite the obvious limitations of the PCM technique, the calculations and results of this risk assessment are expressed in terms of fibers (≥5 microns in length, aspect ratio >3:1)/cc, rather than total TEM fibers, mainly for historical reasons. Exposures in occupational epidemiologic studies (upon which quantitative risk assessments have been based) have either been measured in or, for pre-1965 measurements, converted to PCM fibers/cc. PCM fiber counts can be converted to total TEM fibers (Appendix A), and vice versa, though this has not been done herein except to select appropriate ambient concentrations as a basis for risk assessment (See Section 9.f., "Assumptions Regarding Exposure").

c. Fiber Type and Carcinogenesis

An issue of considerable practical importance in any risk assessment is whether to differentiate among fiber types in estimating risks of cancer. There is epidemiologic evidence suggesting that cancer risks

from chrysotile may be lower than those from the amphiboles. The potential regulatory significance of this observation lies in the commercial predominance of chrysotile. Most recent risk assessments have not, however, segregated the analysis on the basis of fiber type (NRC, 1984; CPSC, 1983; Nicholson, 1985). In evaluating the epidemiologic evidence, it should be borne in mind that mixed exposures, the lack of good quantitative exposure data, and the physical effects of different industrial processes on asbestos fibers make it difficult to compare individual studies.

Lung Cancer. Evidence that amphiboles may be more potent than chrysotile in producing lung cancer comes from several occupational cohort mortality studies involving asbestos mining, concrete pipe and shingle manufacturing, and maintenance work. SMRs for cohorts exposed to chrysotile alone were approximately half those for cohorts with mixed exposures or with exposure to crocidolite alone (Royal Commission, 1984). However, in one cohort mortality study of two asbestos textile operations, the ratio was reversed, even though average exposure levels at the factory using all three types of commercial asbestos were higher than those at the factory using chrysotile alone (Royal Commission, 1984). In addition, animal inhalational bioassays indicate that chrysotile is at least as effective in producing lung cancer as the amphiboles (IARC, 1977; Royal Commission, 1984). Thus, at least insofar as lung cancer is concerned, there is no compelling reason to differentiate between chrysotile and the amphiboles in this risk assessment.

Mesothelioma. Recent literature reviews have indicated that, for comparable industrial processes, exposure to amphiboles or to mixed fibers (amphiboles and chrysotile) appears to carry a significantly higher risk of mesothelioma than exposure to chrysotile alone (Howard, 1984; Royal Commission, 1984; NRC, 1984). This phenomenon may be partially due to the lower degree of chrysotile deposition in the deep lung, combined with faster clearance than the amphiboles (Wagner et al., 1982,1982a; Churg et al., 1984). It has been observed that the difference in mesothelioma risk is markedly more pronounced for peritoneal than for pleural mesotheliomas (CPSC, 1983; Royal Commission, 1984).

Although the epidemiological evidence is suggestive that mesothelioma is more likely to be caused by amphiboles than by chrysotile, DHS staff members do not believe that the risk assessment should be segregated by fiber type. First, there is limited evidence with respect to the airborne asbestos concentrations to which the study populations were exposed. The incidence of mesothelioma may therefore be more a function of fiber number (amphibole fibers tend to become airborne more easily and in greater numbers than do chrysotile fibers) than of fiber type (Royal Commission, 1984). Second, while some cases of mesothelioma occurring in persons exposed to chrysotile and one or more amphiboles have been attributed primarily to the latter, this conclusion is rather incautious from a public health standpoint. As Peto et al. (1982) have observed, "It may therefore be dangerously optimistic to attribute the substantial incidence of pleural mesothelioma among chrysotile factory workers to occasional crocidolite exposure, merely because mesothelioma is rare among chrysotile miners...The overall excess of lung cancer is

also relatively low among chrysotile miners." Finally, animal studies involving experimental induction of mesotheliomas have repeatedly shown that chrysotile is at least as potent as crocidolite and amosite in producing peritoneal as well as pleural tumors (Bolton et al, 1982; IARC, 1977; Royal Commission, 1984).

d. Influence of Fiber Dimensions on Carcinogenicity

Although the mechanisms of asbestos-induced carcinogenesis are obscure, there appears to be general agreement in the literature that longer, thinner fibers are likely to be more carcinogenic than shorter and/or thicker fibers (Royal Commission, 1984; CPSC, 1983). With respect to mesothelioma, this hypothesis has been tested by inoculating asbestos and a variety of non-asbestos fibers into animals' pleural spaces, resulting in the production of mesotheliomas (or pleural sarcomas), with the highest incidence occurring in animals inoculated with large numbers of long (>8 microns), thin (<0.25 microns) fibers (Stanton et al., 1981). In samples of lung tissue taken from exposed animals, avid phagocytosis of short, larger diameter fibers was reported. Short (<5 microns) fibers are reportedly cleared more efficiently from the lung than long fibers (probably by alveolar macrophages), which would give the former less of an opportunity to interact with susceptible host cells (Morgan, 1980).

While the above-noted "Stanton hypothesis" appears to have been generally accepted, its limitations should be acknowledged. First, it was developed as a model only for mesothelioma, though it may also be

applicable to other asbestos-induced tumors. Second, Stanton et al. (1981) noted that narrow dimensional ranges of sized fibers were unobtainable, that errors in the measurement of asbestos fibers were unavoidable because of clumping and fragmentation (e.g., "dimensional measurements on crocidolite are the least representative of all the fibers measured"), and that fine chrysotile fibers could not even be used because they could not be measured with precision. Third, a critical fiber length below which there would be no carcinogenic activity has not been demonstrated. Fibers ≤5 microns in length appear capable of inducing mesothelioma (NRC, 1984). When the data of Stanton et al. were subjected to correspondence analysis, multiple regression on the length and diameter of the fibers, and simple regression on the average fiber aspect ratio, it was reported that carcinogenicity appears to be a continuous, increasing function of the aspect ratio (Bertrand and Pezerat, 1980). Fourth, while clearance of fibers shorter than 5 microns is more efficient than for longer fibers, such clearance is neither instantaneous nor total, permitting shorter fibers to interact for substantial periods of time with pulmonary and pleural cells. Fifth, most asbestos fibers found at the pleura are short (<5 microns), fine chrysotile, as opposed to the mixed fiber populations found in the lung parenchyma (Harington, 1981). Finally, while fiber dimensions clearly affect carcinogenicity, the relationship of physical dimensions to deposition and translocation to the pleura and peritoneum in humans has not been well-characterized (CPSC, 1983).

Because of the foregoing, DHS staff members believe that it is appropriate and reasonable to extrapolate from occupational exposure

measurements (fibers ≥5 microns) to ambient exposures, where most asbestos fibers are less than 5 microns in length. While conversion factors necessarily introduce a large measure of uncertainty, such approximations cannot be avoided in performing a risk assessment.

Risks from ambient exposures may be greater or less than those estimated below if there is a difference in carcinogenic potential between long and short fibers. If the presence of long fibers is a prerequisite for carcinogenesis, the risks would be lower than those presented below.

e. Conversion Factors

In view of the major improvements in fiber measurement techniques that have occurred during the past 25 years, two sets of conversion factors are necessary to develop a risk assessment interpretable by current standards. In order to have consistent units for exposure-response relationships based on cohort mortality studies, midget impinger measurements (in units of millions of particles per cubic foot--mppcf) have typically been converted to PCM fiber counts (i.e. fibers [≥5 μm in length, aspect ratio >3:1]/cc). While there is no consensus about the appropriate conversion factors to use, most reviewers have used numbers within a range of three to nine fibers/cc per one mppcf (Royal Commission, 1984; NRC, 1984). Since DHS staff members have relied on others' derivations of exposure-response relationships, we have not had to designate a value for this conversion factor.

The results of the risk assessment must be expressed in terms consonant with electron microscopic measurement. This requires that PCM fiber counts be converted to total fiber counts. Bearing in mind the variability of the PCM fibers/total fibers ratio (See section 9.a.), DHS staff has concluded that an appropriate conversion factor range by which to multiply PCM fibers is 100 to 1,000. The rationale for this choice is presented in detail in Appendix A.

f. Assumptions Regarding Exposure

There are sparse data regarding nonoccupational exposure to asbestos in California, necessitating the formulation of exposure-related assumptions in this risk assessment. It is assumed that exposure to asbestos occurs at the same average level indoors and outside. While other risk assessments (e.g., NRC, 1984) have partitioned indoor versus outdoor exposures, DHS staff members do not believe this is necessary. Asbestos from indoor sources can undoubtedly result in high exposures. DHS staff members are unaware of good data defining the scope of this potential problem in residences and public buildings in California. Two large studies are currently underway to try to ascertain the contribution of indoor sources to airborne concentrations. Until representative data are available, DHS staff assume that except for indoor sources of asbestos, such as friable asbestos ceilings, there are not significant differences between indoor and outdoor asbestos concentrations measured by TEM (Hayward, 1985). Therefore, models for both lung cancer and mesothelioma have incorporated a factor (168/40 x 52/46 = 4.74) to adjust parameters derived from occupational epidemiologic studies, with

exposures for 40 hr/wk, 46 wk/yr, to be compatible with constant 24 hr/day, year-round exposure (OSHA, 1983).

Although data on average ambient asbestos concentrations in California are nonexistent, the nature of this risk assessment required some assumptions about average exposure levels. To this end, DHS staff members utilized the upper and lower ends of the range of mean TEM values suggested by Air Resources Board staff: 7,700 fibers/m^3 and 45,200 fibers/m^3, rounded to one significant figure (See Part A). Using the conversion factors of PCM fibers = TEM fibers/(100 to 1,000) and multiplying the results by 10^{-6} to convert fibers/m^3 to fibers/cc, the values for F to be used in DHS' model are 0.000008 - 0.00005 and 0.00008 - 0.0005 (PCM-equivalent) fibers/cc. These values are consistent with the results of air sampling in a variety of locations in the U.S. (NRC, 1984). In addition, the tables below include risk estimates for a concentration of 0.002 fibers/cc, chosen by the NRC (1984) as representative of the 90th percentile of ambient asbestos concentrations, usually indicative of a local source of asbestos contamination.

g. Results of Risk Assessment

Using the models described in previous sections, DHS staff members calculated lifetime risks of asbestos-related lung cancer and mesothelioma. These risks are displayed in Tables 9-6 and 9-7 in terms of cases expected per million population. Individual lifetime risks can be estimated by multiplying these results by 10^{-6}.

TABLE 9-6: ESTIMATED LIFETIME EXCESS LUNG CANCER RISK DUE TO CONTINUOUS EXPOSURE TO ASBESTOS (EXPRESSED AS CASES PER MILLION POPULATION)*

Exposure Group	Exposure Level (in Fibers/cc) 0.000008	0.00005	0.00008	0.0005	0.002
Male Smokers	1(0-9)	6(0-55)	9(0-88)	55(0-550)	221(0-2,210)
Female Smokers	<1(0-5)	2(0-25)	5(0-41)	25(0-250)	101(0-1,010)
Male Nonsmokers	<1(0-1)	1(0-8)	1(0-11)	8(0-75)	29(0-290)
Female Nonsmokers	<1(0-1)	<1(0-3)	<1(0-5)	3(0-28)	11(0-110)

*Calculated with $C_\ell = 0.01$. Ranges in parentheses were estimated with a lower limit of zero and an upper limit calculated with $C_\ell = 0.1$. This upper bound is an approximate upper confidence limit (See text for explanation.)

TABLE 9-7: ESTIMATED LIFETIME MESOTHELIOMA RISK DUE TO CONTINUOUS EXPOSURE TO ASBESTOS (EXPRESSED AS CASES PER MILLION POPULATION)*

Exposure Group	Exposure Levels (in fibers/cc) 0.000008	0.00005	0.00008	0.0005	0.002
Male Smokers	2(0-9)	11(0-59)	19(0-95)	120(0-590)	470(0-2,400)
Female Smokers	2(0-12)	16(0-81)	26(0-120)	160(0-810)	640(0-3,300)
Male Nonsmokers	2(0-12)	16(0-79)	25(0-120)	160(0-790)	630(0-3,200)
Female Nonsmokers	3(0-16)	19(0-97)	31(0-160)	190(0-970)	780(0-3,800)

* Calculated with $C_m = 2.4 \times 10^{-8}$, $P = 3.0$, 20-year lag. Ranges in parentheses were estimated with a lower limit of zero and an upper limit calculated with $C_m = 1.2 \times 10^{-7}$, which is the highest estimated value for the proportionality constant C_m (from Finkelstein, 1983).

Under the assumptions of these models, it would appear that ambient asbestos exposure poses a greater risk of mesothelioma than of lung cancer for smokers and nonsmokers alike. The magnitude of the risks for each of these outcomes is consistent with previous estimates, which will be discussed in the following paragraphs.

h. Comparison with Other Risk Assessments

Enterline (1983) estimated lifetime risks from nonoccupational asbestos exposure to be 2 per million for lung cancer and 100 per million for mesothelioma. His lung cancer estimate was based on linear extrapolation from two occupational epidemiologic studies and cannot be considered as reliable as other estimates discussed below (Peto et al., 1980; Henderson and Enterline, 1979). Mesothelioma risk was calculated from current estimates of mesothelioma incidence, using an assumption that about 53% of mesotheliomas in males and 5% in females are due to occupational asbestos exposure (McDonald and McDonald, 1981). Enterline suggested that the predominance of mesothelioma over lung cancer, which is the opposite of what is observed in occupational cohorts, could be explained by the long latency of mesothelioma vis-a-vis lung cancer, combined with the early age at which nonoccupational exposure begins. In other words, exposures starting in childhood permit a full expression of mesothelioma risk, whereas in a working population the shorter latency period for lung cancer would allow the latter to overshadow mesothelioma.

Other recent nonoccupational risk assessments have utilized models similar to those used by DHS staff (Nicholson, 1985; NRC, 1984; CPSC, 1983). The results of these have been adjusted for a continuous exposure of a population of 1,000,000 to a concentration of 0.0001 fibers/cc and are summarized in Tables 9-8 and 9-9.

TABLE 9-8: LIFETIME RISKS OF LUNG CANCER DUE TO CONTINUOUS EXPOSURE TO 0.0001 FIBERS/CC OF ASBESTOS (EXPRESSED AS CASES PER MILLION POPULATION)

Exposure Group	DHS	NRC (1984)	CPSC (1983)	Nicholson (1985)
Male Smokers	11 (0-110)	16 (0-73)	5-49	23.8 (2.38-238)
Female Smokers	5 (0-50)	6 (0-28)	3-30	15 (1.5-150)
Male Nonsmokers	2 (0-15)	2 (0-6)	1-6	1.85 (0.185-18.5)
Female Nonsmokers	1 (0-6)	1 (0-3)	1-50	1.64 (0.164-16.4)

TABLE 9-9: LIFETIME RISKS OF MESOTHELIOMA DUE TO CONTINUOUS EXPOSURE TO 0.0001 FIBERS/CC OF ASBESTOS (EXPRESSED AS CASES PER MILLION POPULATION

Exposure Group	DHS	NRC (1984)	CPSC (1983)	Nicholson (1985)
Male Smokers	24 (0-120)	2.25 (0-87.5)	5.51-55.1	18.1 (1.81-181)
Female Smokers	32 (0-160)	2.25 (0-87.5)	7.80-78.0	25.2 (2.52-252)
Male Nonsmokers	32 (0-160)	2.25 (0-87.5)	6.81-68.1	22 (2.2-220)
Female Nonsmokers	38 (0-190)	2.25 (0-87.5)	8.43-84.3	27.2 (2.72-272)

The Ontario Royal Commission report (1984) does not contain comparable estimates, since its principal focus is on occupational asbestos exposure. DHS' estimates are compatible with those of NRC, CPSC, and Nicholson, though NRC's mesothelioma estimates are an order of magnitude lower. This discrepancy may be due in part to NRC's having calculated a single lifetime risk for a 73-year lifespan, as compared with DHS' summation of five-year interval risks for an 85-year lifespan. Theoretically, NRC's model is equivalent to being at risk only at age 73, while in DHS' model one is at risk for mesothelioma throughout life after 20 years of age. Also, the longer lifespan assumed in DHS' model accounts for part of the discrepancy, since a considerable number of mesotheliomas occur in older age groups. On the other hand, NRC used an exponent for t of 3.2, while DHS used 3.0,

which would tend to counteract the effects of the other differences noted above.

Another check on the reliability of mesothelioma risk estimates is by comparison with recent incidence rates. Drawing on data from the San Francisco-Oakland SEER for the years 1973-83 (11 years), there were 254 cases of mesothelioma diagnosed among males, with a midpoint population of 1,590,317, and 70 cases among females, with a midpoint population of 1,660,313. Assuming that all mesotheliomas were attributable to asbestos exposure, either occupational or nonoccupational, one can calculate mesothelioma incidence attributable to nonoccupational asbestos exposure among males as:

$$\frac{254}{(1{,}590{,}317)(11)} = 1.45 \times 10^{-5} \text{ cases/person-year;}$$

and among females as:

$$\frac{70}{(1{,}660{,}313)(11)} = 3.83 \times 10^{-6} \text{ cases/person-year.}$$

Assuming further that a human lifespan = 85 years, this would result in 1,233 cases among males and 323 cases among females over the lifetimes of populations of 1,000,000 of each gender.

Extrapolation from recent mesothelioma incidence in the Bay Area yields estimates somewhat higher than those calculated by DHS. When one

considers that the population at risk for mesothelioma was that group of people exposed 20 or more years earlier, then this incidence-based calculation is clearly an underestimate. However, a majority of current cases are probably due to occupational asbestos exposure, in view of the historical presence of large-scale industrial asbestos use in the Bay Area, particlarly during World War II. The clear preponderance of male cases in the SF-Oakland SEER (as contrasted with the more nearly equal male:female ratio in our risk estimates) supports this proposition. To compare our estimates with incidence data, it would be appropriate to limit the comparison to females, since only a small percentage of cases among females are likely to be occupational in origin (McDonald and McDonald, 1981). Using best estimates for female nonsmokers as the comparison group, it can be seen that for concentrations of 0.00008 and 0.0005 fibers/cc (a range representative of concentrations suggested by the Air Resources Board), our estimates would comprise 9.6% (31/323) to 59% (190/323) of cases predicted using recent incidence data (See Table 9-7).

Nevertheless, one would expect recent incidence of mesothelioma to represent a limiting upper bound. The asbestos exposures of recent cases, although unknown, were undoubtedly higher than the levels used in DHS' modelled calculations. The indiscriminate dispersal of asbestos that occurred in the past has diminished during the past 15 to 20 years, so that contemporary environmental asbestos concentrations are probably lower than those to which current cases were exposed. In addition, mesothelioma is often misdiagnosed, and the published literature indicates that recently the trend strongly favors over- rather

than underdiagnosis (Wright et al., 1984). Also, although the ubiquity of asbestos body burdens precludes ruling out this substance as the exclusive cause of all mesotheliomas in California, there may be other agents, including some organic chemicals and man-made fibers, that are also partially responsible (Peterson et al., 1984). Finally, although most cases of mesothelioma in females are considered to be nonoccupational in origin, it is possible that some of the cases in the SF-Oakland SEER had some occupational exposure.

Nonoccupational asbestos exposure is clearly not limited to ambient concentrations of these mineral fibers. Indoor exposures that may be causally related to recent mesothelioma cases could include household contact exposure to contaminated clothes of asbestos workers who were family members and exposure to local indoor sources, such as friable asbestos insulation or surfacing, or consumer products formerly containing asbestos (e.g., hair dryers, spackling compounds). Thus, while DHS risk estimates for ambient asbestos exposures may explain some of the recent mesothelioma incidence, there are alternative explanations.

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APPENDIX A: ASBESTOS CONCENTRATION CONVERSION FACTORS AND THEIR LIMITATIONS

This section will discuss conversion between the standard occupational measure of airborne asbestos concentration (fibers/cm^3 ≥ 5 microns long, aspect ratio ≥ 3/1, as measured by phase contrast light microscopy (PCM)), and three measures of ambient air asbestos concentration, all measured by electron microscopy (EM):

Fiber mass (ng/m^3)

Total fibers (fibers/m^3), and

Large, or "Light-equivalent" fibers (large fibers/m^3), defined as all fibers ≥ 5 μm long, ≥ 0.3 μm in diameter, and aspect ratio ≥ 3/1.

The latter two values are generally determined by analysis after sample preparation by the direct transfer method, whereas the first value can be determined after indirect or direct transfer.

Most estimates of conversion factors between PCM counts and fiber mass have been based on mass measurements by other than EM (Nicholson, 1985), the only exception being a study by Rohl et al. (1976), which reports duplicate analyses of filters used for sampling during automotive brake lining maintenance. There is a wide variation in these conversion factors (geometric mean = 30 $\mu g/m^3$/f/ml, geometric standard deviation = 4). This variation is reasonable, since the measurements included a wide variety of processes, which produce fibers with drastically different size distributions. No published data on ambient air samples can be used to

compute this conversion factor directly because of the limitations of the PCM method vis-a-vis ambient air samples (See Part A).

Conversion factors between PCM and total asbestos fibers can be estimated using samples from a variety of industries as reported in studies by Hwang and Gibbs (1981), Hwang and Wang (1983), and Winer and Cossette (1979). In the first two studies, ratios of 50:1 and 80:1 between total fibers/m^3 and PCM fibers/m^3 were obtained. These ratios are probably low by a factor 2 to 5, since the type of EM sample preparation used, direct clearing of fused cellulose ester filters, has been shown to produce from 50% to as much as 80% fiber loss (Chatfield, 1983). These ratios would also probably be low with respect to results from most laboratories, since the resolution of the optical microscope used was shown to be 0.21 µm, while a more typical value is 0.30 µm. The latter value would render more fibers invisible in the light microscope, thus increasing the ratio.

Winer and Cossette (1979) reported a ratio of approximately 1000:1 total fibers to PCM fibers, but the method of EM sample preparation was not specified. If indirect transfer was used, this ratio would be high. If one takes into account all of the caveats applied to these three studies, a range of ratios between 100:1 and 1000:1 is probably appropriate for this conversion factor.

Conversion between PCM fiber concentrations and large EM fiber concentrations is only discussed by Hwang and Wang (1983). They show that these two measures are highly correlated in samples from many industries, with the large EM fiber concentration either 5 or 7.5 times the PCM value,

depending on the PCM method. Since EM large fiber loss in sample preparation should be negligible, these figures are likely to require no adjustment, although the observation that 80 to 85% of supposed "light visible" fibers are not detected by PCM is not satisfactorily explained. In fact, this result suggests that the PCM resolution limit is actually substantially larger than 0.3 μm, which is the EM size cutoff employed. Table A-1 summarizes the conversion factors and their ranges.

Although ambient air samples are unsuitable for PCM analysis, EM analyses of all three types (total mass, total fibers, large fibers) can be carried out simultaneously. Consistency between these values and the conversion factors determined from industrial samples would suggest that these conversion factors are suitable for ambient air for the purpose of risk assessment.

Data were analyzed from twenty ambient air samples which had been obtained as part of a study of a California community with chrysotile asbestos contamination in its soil. Seventeen of the samples were from sites within the community and three were from a control site in a nearby community. Samples were collected on Nuclepore filters, prepared by direct transfer, and analyzed for total asbestos fibers, total asbestos mass, and large fibers. Geometric means and standard deviations of the results in the community and at the control site are shown in Table A-2, along with two ratios of geometric means: total fibers (f/m^3)/large fibers (large f/m^3) and 1000* mass (ng/m^3)/large fibers (large f/m^3). The latter ratio includes the factor of 1000 to make the units equivalent to $\mu g/m^3/f/ml$.

It can be seen from Table A-2 that, despite the fact that all the geometric means at the control site are an order of magnitude lower than those at the community sites, the two ratios are similar at all sites. If one assumes that the conversion factor between large EM fibers and PCM counts is 1, then the ranges of the other conversion factors in Table A-1 encompass the ratios in Table A-2. If one assumes that the large fiber to PCM conversion factor of 5-7.5 is accurate, than all of the values are either at or above the high end of the range.

TABLE A-1: CONVERSION FACTORS BETWEEN PCM COUNTS AND EM-MEASURABLE VALUES OF AIRBORNE ASBESTOS CONCENTRATIONS

	TYPICAL VALUE	RANGE
1000*M/PCM	30[a]	7 - 120[b]
TF/PCM	320[c]	100 - 1000[d]
LF/PCM		5 - 7.5[e]

PCM: phase contrast light microscopy counts (f/m^3)
EM: electron microscopy
M: total mass (ng/m^3)
TF: total fibers ($fibers/m^3$)
LF: large fibers (large f/m^3)

a. Geometric means of six studies.

b. Range from one geometric standard deviation below to one above the geometric mean.

c. Geometric center of range.

d. Range, including conversion for fiber loss, from three studies.

e. Range of two values from one study.

TABLE A-2: MEASURES OF AMBIENT AIR ASBESTOS CONCENTRATION

	COMMUNITY SITES	CONTROL SITES
No. OF SAMPLES	17	3
$\overline{TF}g$	7.0×10^5	6.0×10^4
$\overline{S.D.}g(TF)$	2.8	2.5
$\overline{M}g$	55	2.8
$\overline{S.D.}g(M)$	9.4	1.8
$\overline{LF}g$	1.7×10^3	1.3×10^2
S.D.g(LF)	3.1	1.1
$\overline{TF}g/\overline{LF}g$	410	460
$1000*\overline{M}g/\overline{LF}g$	32	22

$\overline{TF}g$= Geometric mean of total asbestos fibers (f/m^3)

$\overline{LF}g$= Geometric mean of large asbestos fibers ($f \geq 5$ µm long, ≥ 3 µm wide, $l/w \geq 3/1$)/m^3)

$\overline{M}g$= Geometric mean of asbestos mass (ng/m^3)

S.D.g= Geometric standard deviation of total fibers, large fibers or mass

APPENDIX B: LIFETABLES USED IN RISK ESTIMATES

FEMALE NONSMOKERS

AGE	DEATH RATE	PROB DEATH	PROB SURVIVAL	CUM PROB SURVIVAL
0	0.00270137	0.01338860	0.98661143	1.00000000
5	0.00024176	0.00120796	0.99879205	0.98661143
10	0.00023843	0.00119147	0.99880856	0.98541963
15	0.00055835	0.00278854	0.99721152	0.98424554
20	0.00061598	0.00307506	0.99692500	0.98150098
25	0.00072081	0.00359769	0.99640232	0.97848284
30	0.00083280	0.00415568	0.99584436	0.97496253
35	0.00106739	0.00532361	0.99467641	0.97091091
40	0.00146183	0.00728464	0.99271542	0.96574217
45	0.00195652	0.00973783	0.99026221	0.95870709
50	0.00354839	0.01759522	0.98240483	0.94937140
55	0.00566653	0.02795250	0.97204751	0.93266702
60	0.00895199	0.04381854	0.95618147	0.90659660
65	0.01420102	0.06861770	0.93138230	0.86687082
70	0.02423740	0.11452508	0.88547492	0.80738813
75	0.03883206	0.17729288	0.82270712	0.71492189
80	0.06132982	0.26588279	0.73411721	0.58817130

MALE NONSMOKERS

AGE	DEATH RATE	PROB DEATH	PROB SURVIVAL	CUM PROB SURVIVAL
0	0.00345681	0.01709085	0.98290920	1.00000000
5	0.00033185	0.00165772	0.99834234	0.98290920
10	0.00036056	0.00180131	0.99819869	0.98127985
15	0.00153433	0.00764758	0.99235243	0.97951221
20	0.00204935	0.01019348	0.98980653	0.97202128
25	0.00202064	0.01005341	0.98994660	0.96211296
30	0.00203747	0.01013776	0.98986226	0.95244044
35	0.00203842	0.01014354	0.98985648	0.94278485
40	0.00249807	0.01241902	0.98758101	0.93322164
45	0.00388088	0.01922904	0.98077101	0.92163193
50	0.00667165	0.03284334	0.96715671	0.90390986
55	0.01008949	0.04925474	0.95074528	0.87422246
60	0.01574687	0.07586706	0.92413294	0.83116287
65	0.02579340	0.12130153	0.87869847	0.76810497
70	0.04256139	0.19308394	0.80691606	0.67493266
75	0.06699324	0.28773868	0.71226132	0.54461396
80	0.05032698	0.22351301	0.77648699	0.38790745

FEMALE SMOKERS

AGE	DEATH RATE	PROB DEATH	PROB SURVIVAL	CUM PROB SURVIVAL
0	0.00270137	0.01338860	0.98661143	1.00000000
5	0.00024176	0.00120796	0.99879205	0.98661143
10	0.00023843	0.00119147	0.99880856	0.98541963
15	0.00055835	0.00278854	0.99721152	0.98424554
20	0.00061598	0.00307506	0.99692500	0.98150098
25	0.00072081	0.00359769	0.99640232	0.97848284
30	0.00083280	0.00415568	0.99584436	0.97496253
35	0.00159041	0.00792246	0.99207759	0.97091091
40	0.00315754	0.01567387	0.98432618	0.96321893
45	0.00508695	0.02513429	0.97486573	0.94812161
50	0.00716774	0.03524503	0.96475500	0.92429125
55	0.01127639	0.05489634	0.94510370	0.89171457
60	0.01727735	0.08294731	0.91705269	0.84276271
65	0.03124223	0.14510441	0.85489559	0.77285779
70	0.03805271	0.17434162	0.82565838	0.66071266
75	0.04970503	0.22154599	0.77845401	0.54552293
80	0.12020642	0.46214920	0.53785080	0.42466450

MALE SMOKERS

AGE	DEATH RATE	PROB DEATH	PROB SURVIVAL	CUM PROB SURVIVAL
0	0.00345681	0.01709085	0.98290920	1.00000000
5	0.00033185	0.00165772	0.99834234	0.98290920
10	0.00036056	0.00180131	0.99819869	0.98127985
15	0.00153433	0.00764758	0.99235243	0.97951221
20	0.00204935	0.01019348	0.98980653	0.97202128
25	0.00202064	0.01005341	0.98994660	0.96212296
30	0.00203747	0.01013776	0.98986226	0.95244044
35	0.00303725	0.01507863	0.98492140	0.94278485
40	0.00539584	0.02664847	0.97335154	0.92856896
45	0.01009029	0.04928283	0.95071721	0.90382397
50	0.01347673	0.06531513	0.93468487	0.85928100
55	0.02007807	0.09577513	0.90422487	0.80315691
60	0.03039145	0.14162713	0.85837287	0.72623444
65	0.05674545	0.24909639	0.75090361	0.62337989
70	0.06682128	0.28793067	0.71206933	0.46809816
75	0.08575130	0.35431761	0.64568239	0.33331829
80	0.09864080	0.39563894	0.60436106	0.21521771

APPENDIX C: EVALUATION OF A NEGATIVE EPIDEMIOLOGIC INVESTIGATION

Recently Neuberger et al. (1984) reported that there was no increased incidence of lung cancer, stomach cancer or mesothelioma in two Austrian towns with documented environmental asbestos contamination. The sources of contamination were, in one case ("Town A"), naturally occurring tremolite deposits mined until 1945, with dispersal of asbestos into air, soil, and water, and in the other ("Town B"), the oldest asbestos cement factory in the world, which processes about 90% of Austria's imported asbestos (presumably the latter consists mainly of chrysotile, although this is not specified). Results of air sampling in both towns were reported in an Austrian government publication, which has been requested but not yet received by DHS.

Neuberger et al. analyzed mortality data from official death certificates for each town from 1970 through 1980, and calculated standardized mortality ratios (SMRs) using 5 reference populations: the national, provincial, and district populations and national subpopulations consisting of persons living in towns of similar size and "agricultural index." Relevant demographic data are shown in Table C-1. Lung cancer deaths and SMRs during the period of observation are shown in Table C-2.

TABLE C-1: POPULATIONS UNDER STUDY AND DETECTABLE RELATIVE RISKS

	Population 1971	Population 1981	Migration 1971-1981	Minimum Relative Risk to be Detected in 1970-1980 Lung Cancer
Town A	3,412	3,425		2.04
District	53,471	54,172	+195 (+0.4%)	1.21
Province	272,119	272,274	-1,855 (-0.7%)	
Town B	10,627	11,039		1.45
District	109,663	114,378	+553 (+0.5%)	1.16
Province	1,223,444	1,270,426	+7,091 (+0.7%)	
Austria	7,456,403	7,555,338	+73,710 (+1.0%)	

TABLE C-2: LUNG CANCER MORTALITY (1970-1980) TWO AUSTRIAN TOWNS

	Austria			Province		District	
	OBS	EXP	SMR	EXP	SMR	EXP	SMR
Town A							
Male	9	11.8	76	12.0	75	10.7	84
Female	3	2.9	105	2.0	147	1.5	200
Total	12	14.6	82	14.1	78	12.2	98
Town B							
Male	30	56.2	53+	53.8	56+	51.8	58+
Female	11	8.6	128	7.0	158	5.2	211*
Total	41	64.8	63+	60.8	67*	57.0	72*

NOTES: Observed deaths (OBS), Expected Values (EXP), and standard mortality ratio (SMR) calculated from different reference populations.

* $p < .05$.
+ $p < .01$.
(Statistical significance test methodology not reported by Neuberger et al.)

SMRs for lung cancer for males were well below 100 in both towns, regardless of the reference population used to calculate expected numbers of deaths, suggesting that there was no increased risk from exposure to asbestos. SMRs for females, based on expected values generated from national, provincial, and district populations, varied inversely with the size of the reference population, ranging from 105 to 200 in Town A and from 128 to 211 in Town B, suggesting that there may have been an increased risk of lung cancer for females. On the other hand, because of the small numbers of deaths, in only one instance did the increased SMR attain statistical significance.

There were no deaths from mesothelioma in Town A, although an increased prevalence of pleural plaques (a marker of asbestos exposure) had been reported earlier. In Town B there were two mesotheliomas, both of which were reportedly attributable to occupational exposure. For the purposes of the following exercise it will be assumed that there was a zero incidence of mesothelioma attributable to environmental asbestos exposure.

Table C-1 shows the minimum statistically significant SMRs detectable for Towns A and B. To achieve these levels, there would have had to have been a minimum of 24 total cases of lung cancer (12 excess) in Town A and 83 (26 excess) in Town B over the 11 years of observation (using the district population as the reference population for purposes of calculating minimum number of cases). However, if DHS' risk projections are applied to each of these towns, the expected numbers of excess cases are below the minimum detectable in the study by Neuberger et al.

Although the extent of airborne asbestos contamination in these towns is currently unavailable (see above), we assume that the exposure level has been roughly comparable to 0.002 fibers/cc, the highest level of average airborne asbestos for which estimates were made in our risk assessment. This value is consistent with a high level of asbestos contaimination , such as would be found in buildings with asbestos surfaces, and may be higher than the levels found in these Austrian towns.

In the absence of actual data, we assume a M:F sex ratio of 1:1 and a 50% prevalence of smoking for both sexes in this towns during the 1940s to 1970s, when the relevant exposures would have occurred. Using the risk estimates in the last column of Table 9-6, one finds a mean lifetime risk of

$$\frac{221+101+29+11}{4} = 91 \text{ cases per million population.}$$

Multiplying this result by $\frac{11}{75}$ (representing the years of observation in this study divided by the assumed average length of a human lifetime) and by fractions scaling down the population at risk to the sizes of Towns A and B, one arrives at the following:

$$\text{Town A:} \quad \frac{91 \text{ excess cases}}{} \times \frac{11 \text{ years of observation}}{75 \text{ years/lifetime}} \times \frac{3,419}{1,000,000} = 0.05 \text{ cases;}$$

$$\text{Town B:} \quad \frac{91 \text{ excess cases}}{} \times \frac{11}{75} \times \frac{10,833}{1,000,000} = 0.1 \text{ cases.}$$

where 3,419 = midpoint population of Town A and 10,833 = midpoint population of Town B. As can be seen, the study by Neuberger et al. would not have

been capable of detecting the slight excess of lung cancer predicted for either of these towns.

A similar calculation for DHS' mesothelioma estimates gives a mean lifetime expected excess of 630 cases per million population (See Table 9-7, last column). Similar assumptions and scaling factors as above yield the following results:

$$\text{Town A: } 630 \text{ excess cases} \times \frac{11}{75} \times \frac{3,419}{1,000,000} = 0.2 \text{ cases;}$$

$$\text{Town B: } 630 \text{ excess cases} \times \frac{11}{75} \times \frac{10,833}{1,000,000} = 1.0 \text{ case.}$$

Even assuming high-level airborne asbestos contamination, one would not have expected to detect any excess of mesothelioma in town A using DHS' risk model. In town B one case would have been expected. However, the predicted numbers of cases shown here are, in fact, overestimates since the real populations at risk were those exposed long ago enough for the relevant latency periods to have passed. Thus, the numerators in the scaling factors should probably be substantially smaller. Therefore, even the results of this negative epidemiologic study are not incompatible with the risks predicted in the main body of this document.

3.9.1 Textile Products Manufacturing, United States (Chrysotile): Dement et al. (1982, 1983a, 1983b)

Mortality data from a chrysotile textile plant studied by Dement et al. (1982, 1983a, 1983b) allow a direct estimate of lung cancer risk per fiber exposure. Here, data from impinger measurements of total dust in terms of mppcf were available, characterizing dust concentrations since 1930. Further, 1106 paired and concurrent impinger-membrane filter measurements allow conversion of earlier dust measurements to fiber concentrations, suggesting that 3 f/ml is equivalent to 1 mppcf for all operations except fiber preparation. (The 95 percent confidence interval is 2-3.5 f/ml/mppcf.) A value of 8 f/ml/mppcf characterizes fiber preparation work (confidence interval, 5-9). Subsequent to 1940, average fiber concentrations in most operations are estimated to range from 5 to 10 f/ml, with the exception of fiber preparation and waste recovery where mean concentrations are 10-80 f/ml.

The study cohort consisted of all 1261 white males employed one or more months between January 1, 1940 and December 31, 1965. Vital status was determined for all but 26 individuals who were considered alive for purposes of analysis. SMRs for lung cancer were presented for five exposure categories in terms of cumulative fiber exposure (Table 3-11). A weighted regression line yields SMR = 150 + 4.19 x f-y/ml, for a K_L of 0.042. The standard error of the estimate of the slope is ± 0.84.

Dement et al. (1983b) uses U.S. rates for calculating expected deaths. Age-adjusted county rates are 75 percent higher ($66.5/10^5$ versus $38.0/10^5$) (Mason et al., 1975). Dement et al. presents arguments for using national rates. Local rates are probably influenced by nearby shipyard employment (and perhaps by the study plant) and the smoking habits of the study population reflect those of the U.S. general population. Blot et al. (1979) found that World War II shipyard employment leads to a 60 percent increased risk of lung cancer. This increase, however, would be substantially diluted in county rates. Across the United States these rates are 11 percent higher in shipyard counties compared with control counties. Further, Acheson and Gardner (1983) point out that the rates for women in the county are equally high and they suggested an exposure to some unknown carcinogen in the population. The age-adjusted rates of contiguous counties are only 16 percent greater than those of the United States; those of the State of South Carolina are virtually identical to the United States rates.

TABLE 3-11. LUNG CANCER RISKS, BY DOSE, AMONG SOUTH CAROLINA ASBESTOS TEXTILE WORKERS
(Dement et al., 1983b)

Exposure in f-y/ml	SMR
1.4 (<2.74)	140 (5)[a]
15.1 (2.74-27.4)	279 (9)
68.5 (27.4-109.6)	352 (7)
191.8 (109.6-274.0)	1099 (10)
411.0 (>274.0)	1818 (2)

Complete cohort: 336 (33)

Estimated average cumulative exposure: 43.9 f-y/ml

[a]( ) = number of deaths.

Regression equations

SMR = 150 + 4.19(±0.84) x f-y/ml weighted
SMR = 169 + 4.13(±0.32) x f-y/ml unweighted

Weighted regression equation forced through an SMR of 100
SMR = 100 + 4.48(±0.56) x f-y/ml

It is unlikely that the origin of the high local rates will ever be resolved. As seen above, the SMR at zero exposure is calculated to be 150 from the weighted regression analysis. We will use this value as a measure of possible overestimates of the SMRs at all exposures, and we will divide the value of K_L above by 1.5. This brings the SMR at zero exposure to 100 and allows virtually full consideration that higher local rates are the appropriate comparison. (The remainder would be accounted for by shipyard employment.) The adjusted K_L is 0.028.

3.9.2 Textile Products Manufacturing, United States (Chrysotile): McDonald et al. (1983a)

Exposure-related mortality data at this same plant have recently been published by McDonald et al. (1983a). Their cohort consisted of all individuals employed for one or more months prior to January 1, 1959 and for whom a Social Security Administration (SSA) record existed. This eliminated from consideration individuals who began and ended their employment prior to mid-1937, when

SSA numbers were first assigned. The same data on past exposures were utilized to assign cumulative dust exposures, in mppcf-y, to each study participant. Male deaths, by cause, 20 years after first employment, are related to dust exposure accumulated to 10 years prior to death. Data for lung cancer are shown in Table 3-12. A weighted regression analysis yields the relation SMR = 110 + 6.22 mppcf-y. No data are given by McDonald et al. on cumulative fiber exposures. If we use the average relationship found by Dement et al., 1 mppcf = 3 f/ml, we obtain a K_L of 0.021. Adjusting by the value 1.5, as above, to account for the higher local rates, yields a K_L of 0.014. (McDonald et al. used South Carolina rates rather than local rates).

TABLE 3-12. LUNG CANCER RISKS, BY DOSE, AMONG SOUTH CAROLINA ASBESTOS TEXTILE WORKERS (McDonald et al., 1983a)

Exposure in mppcf-y[a]	SMR	RR[b]
5 (<10)	143.1 (31)[c]	1.00 (25)
15 (10-19)	182.7 (5)	0.98 (3)
30 (20-39)	304.2 (8)	2.95 (8)
60 (40-79)	419.5 (7)	4.32 (7)
120 (≥80)	1031.9 (8)	15.00 (6)
Complete cohort:	199.5 (53)	

Estimated average cumulative exposure: 10.3 mppcf-y.

[a] Exposure accumulated to 10 years before death.
[b] Relative risk from an internal case-control analysis.
[c] ( ) = number of deaths.

Regression equations

SMR = 110 + 6.22(±0.76) x mppcf-y weighted
SMR = 63 + 7.68(±0.76) x mppcf-y unweighted

RR = 0.61 + 0.068(±0.019) x mppcf-y weighted
RR = -0.80 + 0.123(±0.017) x mppcf-y unweighted

Weighted regression equation forced through an SMR of 100:
SMR = 100 + 6.63 (±0.61) x mppcf-y

McDonald et al. also made estimates of risk using a Mantel-Haenszel (1959) case-control analysis, as in Table 3-12. A weighted regression line yields a slope of 0.068. Because the RR regression was obtained using internal controls, no adjustment for local rates is necessary. However, since the controls were exposed, the zero dose intercept should be used as the measure of risk in an unexposed group. This requires dividing the slope by the intercept to obtain an adjusted regression line. Dividing by the zero exposure intercept, 0.61, and by 3 to convert to fiber exposures, gives a value of K_L = 0.037. We will use 0.025, the average of 0.014 and 0.037, to represent this study. The agreement with Dement's result is very good.

3.9.3 Textile Products Manufacturing, Rochdale, England (Chrysotile); Peto (1980)

Table 3-13 shows the lung cancer and mesothelioma mortality experience from an often-studied British textile plant (Doll, 1955; BOHS, 1968; Berry et al., 1979; Knox et al., 1968; Peto, 1980; BOHS, 1983). The data are difficult to interpret because dust concentrations have changed fairly dramatically over the past five decades of plant operations, and so have subsequent estimates of those concentrations. No measurements of dust concentrations were made prior to 1951. Between 1951 and 1964, thermal precipitators were used to evaluate total dust levels; thereafter, filter techniques similar, but not identical, to those in the United States were used. Average fiber concentrations are published for earlier years based on a comparison of fiber counting with thermal precipitator techniques (Berry, 1973). Later these estimates were stated to be inaccurate; Berry et al. (1979) reported that a re-evaluation of the work histories indicated that some men had spent more time in less dusty jobs than previously believed and that previous average cumulative doses to 1966 had been overestimated by 50 percent.

Recently, as part of the British Government's review of its asbestos standard, the hygiene officers of the plant re-evaluated previously reported exposure data. It is now suggested that earlier static sampling methods underestimated personal exposures by a factor of about 2, and that whole field, rather than graticule field, microscopic counting understated fiber concentrations by another factor of 2 to 2.5 (Steel, 1979). In 1983, the British Occupational Hygiene Society (BOHS, 1983) reported information on the differences between personal and static sampling. Data were presented for

TABLE 3-13. MORTALITY EXPERIENCE OF 679 MALE ASBESTOS TEXTILE WORKERS (Peto, 1980)

Year first exposed	Period since first exposure (yrs)	Man-years	Lung cancer		Mesothelioma	
			O	E	O	rate per 10^3 p-y
1933-1950	10-14	1633	2	1.80	0	0.0
	15-19	1860	4	2.98	0	0.0
N = 424	20-24	1760	3	3.97	1	0.6
	25-29	1496	10	4.54	2	1.3
	30-34	837	8	3.14	2	2.4
	35-39	507	1	2.20	2	3.9
	Total	8093	28	18.63	7	-
1951 or later	10-14	1123	1	1.30	0	0.0
	15-19	1022	3	1.74	0	0.0
N = 255	20-24	556	7	1.31	0	0.0
	25-29	96	1	0.31	0	0.0
	Total	2797	12	4.65	0	-

thirty-one simultaneous samples comparing the two techniques, the personal samplers indicating a greater fiber concentration in 22 cases. Using these data, the BOHS committee evaluated the cumulative fiber exposure (as of approximately 1976) for 284 individuals employed for 10 or more years subsequent to 1951. The overall average of the entire group was 182 f-y/ml. This is slightly less than the estimate of Peto (1983), who suggested that the exposure of 10+ years employees was 200-300 f-y/ml. However, Peto's estimate was based on preliminary data on only 126 men first employed between 1951 and 1955 (see Table 3-14).

These most recent estimates are clouded by questions concerning the appropriateness of multiplying static sampler concentrations by a factor approaching two. The BOHS data are directly contradicted by published data (See Table 3-15) from the factory on other comparisons of static and personal sampling results by job (Smither and Lewinsohn, 1973). Dr. Lewinsohn (personal communication) confirmed these results. He stated that the static sampler concentrations were generally higher than those of the personal samplers of

TABLE 3-14. PREVIOUS AND REVISED ESTIMATES OF MEAN DUST LEVELS IN f/ml (WEIGHTED BY THE NUMBER OF WORKERS AT EACH LEVEL IN SELECTED YEARS)

	1936	1941	1946	1951	1956	1961	1966	1977	1974
Previous estimates corresponding to early fiber counts	13.3	14.5	13.2	10.8	5.3	5.2	5.4	3.4	-
Revised estimates corresponding to modern counting of static samples[a]	No measurements prior to 1951			32.4	23.9	12.2	12.7	4.7	1.1

[a]These estimates are based on preliminary data on 126 workers first employed between 1951 and 1955, and should be regarded as provisional.

Source: Peto (1980).

TABLE 3-15. DUST LEVELS: ROCHDALE ASBESTOS TEXTILE FACTORY, 1971

Department	Process	Static	Personal
Fiberizing	Bag slitting	3	1
	Mechanical bagging	4	1
Carding	Fine cards	3.5	2
	Medium cards	4.5	3.5
	Coarse cards	8	6
	Electrical sliver cards	1.5	1
Spinning	Fine spinning	2.5	3
	Roving frames	6	3
	Intermediate frames	5.5	3
Weaving	Beaming	0.5	0.5
	Pirn weaving	1.5	1
	Cloth weaving	2	1
	Listing weaving	0.5	0.5
Plaiting	Medium plaiting	4	2

Source: Smither and Lewinsohn (1973).

men working at the monitored job. The company placed the static samplers to best reflect the breathing zone dust concentrations of machine operators while tending machines. Dr. Lewinsohn stated that if a machine were running smoothly, a worker would often leave the site (to talk with fellow workers, go to the rest room, etc.) and experience a lower dust concentration. The difference between static and personal sampling data is therefore greater in the dustier jobs (compare weaving vs. carding) because workers would tend to leave a dusty area more often. In the Rochdale factory, the average of the ratios of static to personal sample concentrations at the same work station is 1.8 (1.5 if the fiberizing operation is not considered). The recent comparison may not reflect the movement of a worker from his machine.

We will use a value of 200 f-y/ml to represent cumulative exposure of the post-1951 group fifteen or more years from onset of exposure, which probably overestimates the effective exposure of the group. While 200 f-y/ml, the average dose of all men employed 10 or more years, underestimates the average total dose of men employed 15 or more years, it overestimates the effective dose that accumulates to about 10 years prior to end of follow-up or death. As was shown above, this yields a K_L of 0.011. To reflect some of these uncertainties in exposure, the upper exposure-related uncertainty in risk was increased from 2 to 4 in Figure 3-7.

A second difficulty of the British textile factory study is that the dose-response data calculated from groups exposed before and after 1950 differ considerably. While no cumulative exposure data are published for the pre-1951 group, it is surprising that more disease is seen in the later group, as the average intensity of exposure was certainly greater for the earlier group, perhaps by a factor of three. It is difficult to reconcile the differences between the two subcohorts employed in this facility. The data are severely limited by the relatively small size of the cohort and the few deaths available for analysis. Nevertheless, what would appear to be a nearly tenfold difference in the estimated risk of death from lung cancer suggests the possible existence of some unidentified bias in the pre-1951 group. The post-1950 group's mortality experience is more in accord with U.S. textile plants. The finding of only a 50 percent increase in lung cancer in exposure circumstances leading to 5.3 percent of deaths being from asbestosis is certainly unusual, as is the finding that there are as many mesotheliomas as excess lung cancers.

3.9.4 Textile and Friction Products Manufacturing, United States (Chrysotile, Amosite, and Crocidolite); McDonald et al. (1983b); Robinson et al. (1979)

A plant located near Lancaster, Pennsylvania, which produced mainly textiles but also friction products and packings, was studied by Robinson et al. (1979), McDonald et al. (1982), and earlier by Mancuso et al. (1963, 1967). The plant, which began operations in the early 1900s, used between 3000 and 6000 tons of chrysotile over most of the period of its operation. Amosite constituted less than 1 percent of the fiber used, except for a three-year period, 1942 - 1944, when 375-600 tons of amosite were used in insulation blankets and mattresses. Crocidolite usage was approximately 3-5 tons per year (Robinson et al., 1970). Neither the report of Robinson et al. nor Mancuso et al. provides any information on the exposure of the cohort members to asbestos, so they cannot be used in establishing exposure-response relationships. In the study of McDonald et al., dust concentrations, measured in mppcf, are available from the 1930s through 1970. However, no attempt was made to relate particle exposures to fiber exposures. The study cohort of McDonald comprised all individuals employed for one or more months prior to January 1, 1959 with their Social Security file identifiable in the Social Security Administration offices. These individuals were traced through December 31, 1977, and cause-specific mortality ratios, based on state rates, were related to cumulative dust exposure.

The results for lung cancer are shown in Table 3-16. The regression of SMR on dose has an unusually low intercept of 53. The overall SMR for lung cancer is also low. The low local rates (30.1 versus 37.7 for the state) (Mason et al., 1975) do not fully account for these deficits. Smoking histories are reported for only 36 individuals and indicate no unusual pattern. Because the full deficit cannot be explained, we have adjusted the slope by the ratio of the local to state lung cancer rates (0.81) rather than by 0.53, resulting in a slope of 0.032. The adjusted slope of the RR regression is 0.051. If these two values are averaged and a factor of 3 is used to convert from mppcf to f/ml, the exposure-response relationships give average $K_L = 0.014$. The factor of 3 was previously measured in textile manufacturing, the predominant activity in this plant. Calculating K_L using the overall SMR of the study suggests that the lower confidence limit of K_L is 0, but the SMR and RR regression lines strongly contradict this. Thus, for the lower confidence limit we will use a value calculated from the highest exposure relationship, where the uncertainty in comparison rates has less of an effect.

TABLE 3-16. LUNG CANCER RISKS, BY DOSE, AMONG PENNSYLVANIA ASBESTOS TEXTILE AND FRICTION PRODUCTS WORKERS
(McDonald et al., 1983b)

Exposure in mppcf-y[a]	SMR	RR[b]
5 (<10)	66.9 (21)[c]	1.00 (20)
15 (10-19)	83.6 (5)	0.83 (4)
30 (20-39)	156.0 (10)	1.54 (10)
60 (40-79)	160.0 (6)	2.90 (6)
120 (>80)	416.1 (11)	6.82 (11)
Complete cohort:	105.0 (53)	

Estimated average cumulative exposure: 16.9 mppcf-y.

[a]Exposure accumulated to 10 years before death.

[b]Relative risk from an internal case-control analysis.

[c]( ) = number of deaths.

Regression equations

SMR = 53 + 2.58(±0.45) x mppcf-y weighted
SMR = 41 + 2.94(±0.42) x mppcf-y unweighted

RR = 0.70 + 0.036(±0.010) x mppcf-y weighted
RR = 0.24 + 0.050(±0.005) x mppcf-y unweighted

Weighted regression equation forced through an SMR of 100:
SMR = 100 + 1.22 (±1.07) x mppcf-y

3.9.5 Friction Products Manufacturing, Great Britain (Chrysotile and Crocidolite); Berry and Newhouse (1983)

Berry and Newhouse analyzed the mortality of a large workforce manufacturing friction products. All individuals employed in 1941 or later were included in the study, and the mortality experience through 1979 was determined. Exposure estimates were made by reconstructing the work and ventilation conditions of earlier years. Fiber measurements from these reconstructed conditions suggested that exposures prior to 1931 exceeded 20 f/ml but those afterwards seldom exceeded 5 f/ml. From 1970, exposures were less than 1 f/ml. These relatively low intensities of exposure kept the average cumulative exposure for the group to less than 40 f-y/ml.

The overall mortality of all study participants, 10 years and more after onset of exposure, was no greater than expected for all causes. Data for lung cancer are shown in Table 3-17. Cancer of the lung and pleura was slightly elevated in men (151 observed versus 139.5), but the excess was largely accounted for by eight mesothelioma deaths. No unusual mortality was found in those employed 10 or more years. Using a case-control analysis according to cumulative exposure, Berry and Newhouse estimated that the lung cancer increased risk was 0.06 percent per f-y/ml (K_L = 0.00058), with an upper 90 percent confidence limit of 0.8 percent per f-y/ml. Table 3-17 lists the results of the case control analysis. The weighted regression of RR on dose has a negative slope. The ratio of excess lung cancer to average group exposure yields a value of K_L = 0.00068 = [(143/139.5)-1]/37.1. We will use the value published by Berry and Newhouse, 0.00058, and their confidence limits for K_L.

TABLE 3-17. LUNG CANCER RISKS, BY DOSE, AMONG BRITISH ASBESTOS FRICTION PRODUCTS WORKERS
(Berry and Newhouse, 1983)

Exposure in mppcf-y	RR[a]
5 (0-9)	1.00 (50)[b]
30 (10-49)	0.79 (37)
75 (50-99)	0.86 (13)
200 (100-356)	0.88 (5)

Estimated average cumulative exposure: 31.7 f-y/ml.

[a]Relative risk from an internal case-control analysis.

[b]( ) = number of deaths.

Regression equations

RR = 0.91 - 0.00076(±0.0016) x f-y/ml weighted
RR = 0.90 - 0.00019(±0.00070) x f-y/ml unweighted

3.9.6 Friction Products Manufacturing, United States (Chrysotile): McDonald et al. (1984)

McDonald et al. (1984) analyzed the mortality of the workforce employed in friction products production in the United States and attempted to relate it to cumulative dust exposure. However, a highly unusual mortality experience is observed. The overall mortality shows an elevated risk of death in the

complete cohort for virtually all causes, largely confined to individuals employed for less than one year. The correlation of respiratory cancer SMR with cumulative dust exposure of those employed for more than one year shows little, if any, trend with increasing dust exposure, even though the overall SMR for lung cancer (see Table 3-18) is 137 for these individuals. The slopes of the regression equations of SMR on dose are slightly negative and those of relative risk are slightly positive. As with the McDonald et al. Pennsylvania textile study, we will use the dose-response regression relationship for the measure of risk and set K_L = 0.0001 for this group. In Figure 3-7, this

TABLE 3-18. LUNG CANCER RISKS, BY DOSE, AMONG ASBESTOS FRICTION PRODUCTS PRODUCTION WORKERS (McDonald et al., 1984)

Exposure in mppcf-y	SMR	RR[a]
5 (<10)	167.4 (55)[b]	1.00 (54)
15 (10-19)	101.7 (6)	0.40 (4)
30 (20-39)	105.4 (5)	0.91 (5)
60 (40-79)	162.8 (6)	1.40 (16)
120 (>80)	55.2 (1)	1.13 (1)

Complete cohort: 148.7 (73).

1+ yrs employment: 136.8 (49).

Estimated average cumulative exposure: 10.3 mppcf-y.

Estimated average exposure for those employed more than 1 year: 15.5 mppcf-y.

[a]Relative risk from an internal case-control analysis.

[b]( ) = number of deaths.

Regression equations

SMR = 160 - 0.85(±0.52) x mppcf-y weighted
SMR = 147 - 0.62(±0.46) x mppcf-y unweighted

RR = 0.69 + 0.00006(±0.01) x mppcf-y weighted
RR = 0.78 + 0.0041(±0.0039) x mppcf-y unweighted

Weighted regression equation forced through an SMR of 100:
SMR = 100 + 0.13 (±0.83) x mppcf-y

represents "zero" for the purpose of calculating geometric means. The low value, however, is qualified by the overall high lung cancer mortality. As the origin of this higher lung cancer mortality is workers employed for more than one year (where total mortality is close to that expected) is unknown, the upper limit of uncertainty will be given by the upper confidence limit on the ratio of lung cancer excess risk to average exposure in the 10-19 mppcf-y exposure groups. This procedure is similar to that used to estimate the lower confidence limit in the Pennsylvania textile cohort.

3.9.7 Mining and Milling, Quebec, Canada (Chrysotile): Liddell et al. (1977); McDonald et al. (1980)

The results reported by Liddell et al. (1977) and McDonald et al. (1980) on mortality (Table 3-19) according to total dust exposure in Canadian mines and mills can be converted to relationships expressed in terms of fiber exposures. SMR values are provided by McDonald et al. for various exposure categories in four different duration-of-employment categories. A weighted regression analysis of these data yields a relationship, SMR = 92 + 0.13 x mppcf-y. Using a value of 3 f/ml/mppcf for the particle fiber conversion factor yields a K_L of 0.00043. The factor of 3 f/ml/mppcf is the midpoint of the range of 1-5 f/ml/mppcf suggested by McDonald et al. as being applicable to most jobs in mining and milling. However, since McDonald et al. used the rates of the Province of Quebec for his comparison data, K_L is likely to be underestimated. In an earlier paper, McDonald et al. (1971) suggested that the lung cancer rates in the counties adjacent to the asbestos mining counties were about two thirds those of the Province. This is substantiated by lung cancer incidence rates, in the Province of Quebec, published by Graham et al. (1977). These data for the years 1969-1973 are shown in Table 3-20 and confirm the earlier statement of McDonald et al. Thus, the above K_L will be multiplied by a factor of 1.5. Liddell et al. (1977) performed a case control analysis of the relative risk of lung cancer in this same period. Their regression equation suggests a K_L of 0.00057. We will use the average of these two estimates, 0.00060, for K_L.

The overall SMR of 125 for lung cancer mortality among all miners is surprising, based upon Quebec rates. In studies of the mortality of male residents of Thetford, in the midst of the Canadian asbestos mining area (Toft et al., 1981; Wigle, 1977), an SMR of 184 was seen for lung cancer and 230 for

TABLE 3-19. LUNG CANCER RISKS, BY DOSE, AMONG CANADIAN CHRYSOTILE ASBESTOS MINERS

McDonald et al., 1980 in mppcf-y	SMR	Liddell et al., 1977 Exposure in mppcf-y	RR[a]
< 1 year of employment			
.5	117 (19)[b]	3 (<6)	1.00 (43)
1.7	91 (12)	8 (6-10)	1.07 (10)
5.8	88 (9)	20 (10-30)	0.96 (24)
39.0	80 (7)	65 (30-100)	1.16 (37)
		200 (100-300)	1.22 (31)
1 to 4.9 years of employment		450 (300-600)	1.88 (27)
		800 (600-1000)	2.39 (18)
3.3	66 (5)	1250 (1000-1500)	3.49 (10)
13.6	95 (13)	1750 (1500-2000)	4.97 (6)
59.0	82 (6)	3000 (2000+)	5.42 (9)
231.3	78 (5)		
5 to 19.9 years of employment			
16.0	141 (13)		
58.2	122 (14)		
178.5	83 (7)		
704.0	217 (16)		
20+ years of employment			
104.6	121 (28)		
261.3	108 (20)		
549.1	220 (24)		
1141.4	265 (32)		

Complete cohort: 125 (230).

Estimated average cumulative exposure: 185 mppcf-y.

[a]Relative risk from an internal case-control analysis.

[b]( ) = number of deaths.

Regression equations

SMR = 92 + 0.13(±0.024) x mppcf-y weighted
SMR = 93 + 0.13(±0.024) x mppcf-y unweighted

RR = 0.99 + 0.0017(±0.00013) x mppcf-y weighted
RR = 1.10 + 0.0017(±0.00013) x mppcf-y unweighted

Weighted regression equation forced through an SMR of 100:
SMR = 100 + 0.12 (±0.02) x mppcf-y

TABLE 3-20. LUNG CANCER INCIDENCE RATES IN URBAN AND RURAL AREAS OF QUEBEC PROVINCE, 1969-1973

Region	MALES		FEMALES	
	Rate	Population	Rate	Population
Asbestos counties	33.59	57,685	4.39	57,630
Peripheral counties	23.71	209,320	4.64	210,180
Other rural	27.29	1,295,895	3.87	1,264,795
Montreal	48.67	1,222,245	8.70	1,281,865
Quebec City	50.53	204,435	6.96	218,745
Province	37.47	2,989,580	6.20	3,033,215
Ratio: Rural/Province	.728		.624	
Ratio: Peripheral/Province	.633		.748	

From: Graham et al. (1977).

cancer of the stomach. Because no corresponding increases were seen in female cancer rates, Toft et al. (1981) and Wigle (1977) attributed the excesses to occupational exposure in the mines. Siemiatycki (1982) presented data on the mortality of Asbestos and Thetford Mines, Quebec, that indicated an SMR for lung cancer of 148 compared to Quebec rates. The origin of a lower SMR for those employed in mining and milling compared to all male residents has not been explained. While the risk appears low compared to town mortality, the agreement between the SMR and RR analyses is very good.

3.9.8 Mining and Milling, Thetford Mines, Canada (Chrysotile); Nicholson et al. (1976b, 1979)

Somewhat higher risks in the mining industry were obtained by Nicholson et al. (1976b, 1979) from the mortality experience of a smaller group of miners and millers employed 20 or more years at Thetford Mines, Quebec. In this study, 178 deaths occurred among 544 men who were employed during 1961 in 1 of 4 mining companies. In the ensuing 16 years of follow-up, 26 deaths occurred from asbestosis, 28 (25 on DC) from lung cancer (11.1 expected), and 1 from mesothelioma.

Fiber measurements were made during 1974 in five mines and mills, and data on particle counts from 1948 were supplied by the Canadian Government. From these data, exposure estimates were made for each of the 544 individuals

according to their job history. Fiber exposures for earlier years were estimated by adjusting current measurements by changes in particle counts observed since 1950. The 20-year cumulative exposure for the entire group was estimated to be 1080 f-y/ml.

The mortality experience of the whole group from an earlier follow-up was reported by two exposure categories (Nicholson, 1976b) (see Table 3-21). The difference in lung cancer SMRs in these two exposure groups suggests that K_L = 0.0023 (333-55)/(1760-560)/100. However, Quebec rates were used to estimate expected deaths and these overestimated mortality. As with the McDonald study, K_L will be multiplied by a factor of 1.5 to 0.0034 and then reduced to 0.0030 to convert to DC lung cancer diagnosis. An analysis, adjusted to local rates, using the overall SMR and average group exposure, yields a value of K_L = 0.0017. Because there is likely to be greater uncertainty associated with the regression analysis than with the use of average values, we will use the estimate of K_L = 0.0017 for this study.

TABLE 3-21. EXPECTED AND OBSERVED MORTALITY AMONG 544 QUEBEC ASBESTOS MINE AND MILL EMPLOYEES, 1961-1973

	Average Exposure 560 f-y/ml			Cumulative Exposure 1760 f-y/ml		
Causes of death	Exp.	Obs.[a]	Ratio	Exp.	Obs.[a]	Ratio
All causes of death	68.29	65	0.95	44.56	67	1.50
All cancers	15.45	15	0.97	10.11	18	1.78
Lung	4.52	7	1.55	3.00	13	4.33
Mesothelioma	--	1	--	--	0	--
Gastrointestinal	4.18	3	0.72	2.71	3	1.11
Other cancers	6.75	4	0.59	4.40	2	0.45
Respiratory diseases	4.79	10	2.09	3.02	15	4.24
Pneumonia	2.01	1	0.50	1.27	1	0.78
Asbestosis	--	7	--	--	11	--
Other respiratory	2.79	2	0.72	1.76	3	1.70
All other causes	48.05	40	0.83	31.43	34	1.08

[a]Best estimate cause of death.

3.9.9 Mining and Milling, Italy (Chrysotile): Rubino et al. (1979)

A final study of chrysotile mining and milling is that of Rubino et al. (1979) of the Balangero Mine and Mill, northwest of Turin. A cohort was established of 952 workers, each with at least 30 calendar days of employment between January 1, 1930 and December 31, 1965, who were alive on January 1, 1946. Ninety-eight percent of the cohort was traced and their mortality experience through 1975 was ascertained. Overall, an exceptionally high mortality was seen compared to that expected; 332 deaths were observed versus 214.4 expected. The excess mortality, however, was largely confined to non-malignant respiratory diseases, cardiovascular diseases, and accidents. The overall SMR for all malignant neoplasms was 106, with only cancer of the larynx found to be significantly in excess in the whole group. While the overall data were relatively unremarkable, the age standardized rates of lung cancer according to cumulative dust exposure showed a relative risk of 2.29 (2.54 based upon cancer of the lung and pleura) for a high exposure group (376 f-y/ml) compared to a low exposure group (75 f-y/ml) [K_L = 1.29/(376-75) = 0.0043)]. A case-control analysis of lung cancer according to cumulative dust exposure showed a relative risk of 2.61. Adjusting to a relative risk of 1 at zero exposure gives a K_L of 0.089. However, the characterization of the exposures in the study may have created an artificially steeper dose-response relationship then actually exists. Rubino et al. calculated the person-years at risk in two exposure categories (±100 f-y/ml). A person contributed to the lower category until his exposure exceeded 100 f-y/ml. However, in Section 3.6 it is shown that there is a 5-10 year lag before the risk is manifest from a given exposure. Thus, the transition should be delayed by 5-10 years after achievement of 100 f-y/ml. Deaths and person-years at risk occurring in this delay period should be attributed to the lower exposure category. If lung cancer deaths occurred in the delay period, the dose-response relationship is probably artificially steeper than it should be; if no lung cancer deaths occurred, it is artificially shallower. The overall SMR of those 20 years from onset yields a K_L of 0.00013 [(103.4 - 100)/100/273 f-y/ml]. The uncertainty in the estimate of K_L is enormous. We will use the geometric mean of 0.0043 and 0.00013, 0.00075, to represent K_L.

3.9.10 Insulation Manufacturing, Paterson, NJ (Amosite): Seidman et al. (1979)

The study by Seidman et al. (1979) also can be used for quantitative risk estimates. The study was recently updated and the new mortality results were

The uncertainty in the value extends from 0.0084 to 0.074 to account for the statistical variability on the number of deaths and different values of K_L obtained from different analysis procedures.

3.9.11 Insulation Application, United States (Chrysotile and Amosite)

The previously discussed mortality study of Selikoff et al. (1979) can be combined with published information on asbestos exposures measured for members of this cohort to obtain an exposure-risk estimate. The data on insulation workers' exposure were reviewed by Nicholson (1976a) and are summarized in Table 3-23. Using the standard membrane filter technique of the U.S. Public Health Service for counting asbestos fibers (NIOSH, 1979), three different laboratories in the United States found that the average fiber concentration of asbestos dust in insulation work, between 1968 and 1971, ranged from about 3 to 6 f/ml. A similar study in the Devonport Naval Dockyard in Great Britain, with the same techniques, obtained 8.9 f/ml for the average of long-term sampling of asbestos concentrations measured during application of insulating materials aboard ship (Harries, 1971). In the research that led to these data, it was reported that peak exposures could be extremely high. It was not uncommon, for example, to get 2- to 5-minute concentrations of asbestos exceeding 100 f/ml during the mixing of cement. This mixing, however, would only be done perhaps once an hour, so that exposures measured during that hour, including the mixing, would seldom average more than 10 f/ml. Similar experiences were subsequently reported by Cooper and Miedema (1973), who stated, "Peak concentrations may be high for brief periods, while time-weighted averages are often deceptively low."

Direct information on asbestos fiber concentration, measured by the currently prescribed analysis procedures, has been available only since 1966. Although insulation materials have changed from earlier years (fiber glass has found extensive use, and work with cork is seldom done today) and changes in the asbestos composition of insulating products have taken place (pipe coverings and insulation blocks may have had twice the asbestos content in earlier years), work practices are virtually identical and few controls of consequence were in use. Therefore, dust concentrations measured under these conditions have relevance for estimating the levels of past years. Considering the possible doubling of the asbestos content of older insulation materials, the

TABLE 3-23. SUMMARY OF AVERAGE ASBESTOS AIR CONCENTRATION DURING INSULATION WORK[a] (Selikoff et al., 1979)

Research group	Average fiber concentration, f/ml: Light and heavy construction	Average fiber concentration, f/ml: Marine work
Nicholson (1975)	6.3	
Cooper and Balzer (1968)	2.7	6.6
Ferris et al. (1971)		2.9
Harries (1971)		8.9
Average concentrations of all visible fibers counted with a konimeter and bright-field microscope.		
Murphy et al. (1971)		8.0
Fleisher et al. (1946)		30-40
Estimates of past exposure based on current membrane-filter data.		
Nicholson (1976a)	10-15	

[a]Average concentrations of fibers longer than 5 μm evaluated by membrane filter techniques and phase-contrast microscopy.

Source: Nicholson (1976a).

data from the studies listed in Table 3-23 suggest that the average exposures of insulation workers in the United States during past years could have ranged from 10-15 f/ml for commercial and industrial construction. In marine construction, it may have been between 15 and 20 f/ml. We will use a value of 15 f/ml as an overall average. Because of the great variability in work activities of this group, the range of uncertainty in the exposure is estimated to be from 7.5 to 45 f/ml, and this range is indicated in Figure 3-7.

This information and the data in Figure 3-4 allow one to calculate a lung cancer risk per unit of asbestos exposure (in f-y/ml) from the linearly rising portion of the curve, the slope of which is 0.16 per year or 0.07 per f-yr/ml (for an exposure intensity of 15 f/ml). However, the data of Figure 3-4 utilized BE (best estimates) in establishing lung cancer mortality. Adjusting to DC (death certificate) diagnosis reduces the value of K_L from 0.011 to 0.0094 (0.011 x 3.06/3.60). The statistical uncertainty on the estimate of risk is very low. However, there is no independent indication that the use of

submitted for the OSHA hearings record on a revised standard for asbestos (Seidman, 1984). In this update, dose-response data, based upon estimates of individual exposures for each cohort number, are available. Data for lung cancer are listed in Table 3-22.

Because no data exist on air concentrations for the Paterson factory, the data in terms of fiber counts were estimated from air concentrations in two other plants manufacturing the same products with the same fiber and machinery. One of these plants, in Tyler, Texas, opened in 1954 and operated until 1971; the other, in Port Allegany, Pennsylvania, opened in 1964 and closed in 1972. As in the Paterson factory, efforts to control dust in these newer plants were limited. One, in fact, was housed in a low Quonset-type building where the confined space exacerbated dust conditions. During 1967, 1970, and 1971, asbestos fiber concentrations in these plants were measured by the U.S. Public Health Service and the results published in the Asbestos Criteria Document of the National Institute for Occupational Safety and Health (NIOSH, 1972). These data were supplemented by company data in one plant (M. Corn, personal communication) and individual worker estimates of dustiness (which were used for some jobs not sampled).

The zero dose SMR intercept of 325 is highly anomalous and difficult to understand. The use of New Jersey rates for calculating expected deaths is appropriate for the Paterson area (the age standardized county rates are 46.8 versus 46.3 for the state). The high intercept is largely the result of a disproportionately high risk observed in individuals employed for less then 6 months, whose SMR is 295 (32 observed, 10.86 exposed). Certainly, new employees usually get the dustiest jobs and if there are effects of intensity of exposure separate from those of dose, very dusty environments may have contributed a disproportionately greater risk. However, longer term employees also would have had such jobs at one time and intensity effects are not seen in other asbestos-exposed groups. Another possibility is that the short-term group includes many men exposed to carcinogens at work elsewhere or they are unusually heavy smokers. Abnormally high risks were also seen in the short-term employees of a friction products plant studied by McDonald et al. (1984). A third possibility is that there could have been misestimates of exposure for the short-term employees who would have the extremely dusty jobs. However, the dose-response relationship for death from asbestos is a reasonable one and there is no unusual mesothelioma risk among those employed less than 6 months.

TABLE 3-22. CUMULATIVE OBSERVED AND EXPECTED DEATHS FROM LUNG CANCER 5 TO 40 ELAPSED YEARS SINCE ONSET OF WORK IN AN AMOSITE ASBESTOS FACTORY, 1941-1945, BY ESTIMATED FIBER EXPOSURE
(Seidman, 1984)

Cumulative exposure (f-y/ml)	Number of men	Number of deaths (BE)	(DC)	Expected deaths[a]	SMR (BE)	(DC)
<6.0	177	15	14	5.31	282	264
6.0 - 11.9	109	12	12	2.89	415	415
12.0 - 24.9	139	15	15	3.39	442	442
25.0 - 49.9	123	13	12	2.78	468	432
50.0 - 99.9	104	17	17	2.38	714	714
100.0 - 149.9	57	9	9	1.49	604	604
150.0 - 249.9	58	15	12	1.32	1136	909
250+	53	15	11	0.94	1596	1170
Total	820	111	102	20.51	541	497

Estimated average cumulative exposure: 67.1 f-y/ml.

BE = best estimate of cause of death based on all medical evidence.

DC = Death certificate cause of death.

[a]Expected deaths based on New Jersey white male quinquennial age and calendar year period specific death rates.

Regression equations

SMR = 325 + 2.72(±0.54) x f-y/ml weighted
SMR = 330 + 2.45(±0.37) x f-y/ml unweighted

Weighted regression equation forced through an SMR of 100:
SMR = 100 + 4.28 (±1.17) x f-y/ml

Finally, part of the excess may simply be the result of statistical fluctuations.

The values of K_L estimated by different treatments of the data range from 0.0084, obtained by adjusting the slope of the weighted regression line by the intercept (2.72/325), to 0.059, obtained by dividing the excess overall lung cancer SMR by the average group exposure [(495-100)/67.1/100]. If inappropriate underlying rates (because of other exposures) apply only to the short-term group, an adjustment can be made by forcing the dose-response line through the origin. This yields a value of K_L = 0.043. Because this is most likely to be the case, this value will be used for K_L.

U.S. mortality rates is appropriate. Hammond et al. (1979a) reported that 53.5 percent of insulation workers were current cigarette smokers, 27.3 percent were past smokers, and 17.2 percent never smoked cigarettes. The corresponding data for the 1967 U.S. population were 49.1 percent current smokers, 23.6 percent past smokers, and 27.3 percent non-cigarette smokers (USPHS, 1979). This difference would only affect the underlying rates by about 10 percent. However, because insulation workers may have smoked more cigarettes, we will reduce the value of K_L by 20 percent to 0.0075.

3.9.12 Asbestos Products Manufacturing, United States (Chrysotile and Crocidolite); Henderson and Enterline (1979)

The data of Henderson and Enterline (1979) (Figure 3-1 and Table 3-24) can also be used to establish fiber dose-response data even though their data were presented in terms of total dust concentrations measured in millions of particles per cubic foot (mppcf). No data exist on the conversion between mppcf and f/ml for most of the plants studied. However, there are data on the relationship between fiber and total dust concentrations in textile operations and asbestos cement production. Dement et al. (1982) found that conversion of 3 f/ml/mppcf was appropriate to most textile operations, although Ayer et al. (1965) had earlier suggested a value of 6 f/ml/mppcf. In a plant making asbestos cement pipe and sheets, Hammad et al. (1979) determined the conversion value to be 1.4. It would be expected that the cement products value would be most applicable to the Henderson and Enterline circumstance because of the extensive use of cement and other mineral particles (e.g., calcium silicate, talc, SiO_2, MgO) in asbestos products manufacturing. The least squares weighted regression line of SMR on dose is SMR = 143 + 0.51 x mppcf-y (see Table 3-24). Using a value of 1.5 f/ml/mppcf to represent the conversion relationship, the estimate of K_L is 0.0034 (0.51/100/1.5).

As described previously, observing a cohort beginning at age 65 may seriously understate the full impact of asbestos exposure. Most of the workers in this cohort began employment prior to age 25. To partially account for selection effects among retirees, we will multiply the above value by 1.45. [This adjustment is the ratio of the lifetime mortality from age 25 to lifetime mortality at age 65 (see Table 3-8)]. Thus, K_L is adjusted to a value of 0.0049.

TABLE 3-24. LUNG CANCER RISKS, BY DOSE, AMONG RETIREES OF U.S. ASBESTOS PRODUCTS MANUFACTURERS (Henderson and Enterline, 1979)

Exposure in mppcf-y	SMR
62 (<10)	197.9 (19)[a]
182 (10-19)	180.0 (9)
352 (20-39)	327.6 (19)
606 (40-79)	450.0 (9)
976 (>80)	777.8 (7)

Complete cohort: 270.4 (63)

Estimated average cumulative exposure: 249 mppcf-y.

[a]() = number of deaths.

Regression equations

SMR = 143 + 0.51(±0.13) x mppcf-y weighted
SMR = 100 + 0.66(±0.07) x mppcf-y unweighted

Weighted regression equation forced through an SMR of 100:
SMR = 100 + 0.64 (±0.097) x mppcf-y

3.9.13 Asbestos Cement Products, United States (Chrysotile and Crocidolite): Weill et al. (1979); Hughes and Weill (1980)

A study of an asbestos cement production facility also provides exposure-response information (Weill et al., 1979; Hughes and Weill, 1980), as shown in Table 3-25. Although the experience of 5645 individuals was reported, 1791 of whom had been employed for longer than two years, the dose-response information is uncertain because of limitations in the mortality data. Of even greater significance, tracing was accomplished through information supplied on vital status by the Social Security Administration, and this information only allowed the vital status of 75 percent of the group to be determined. Those individuals untraced were considered alive in the analyses, which assumption may have led to serious misestimates of mortality because prior to 1970, many deaths, particularly of blacks, were not reported to the Social Security Administration. The percentage of unreported deaths of both sexes ranged from nearly 80 percent in 1950 to 15 percent in 1967 (Aziz and Buckler, 1980). Thus, many

TABLE 3-25. LUNG CANCER RISKS, BY DOSE, AMONG ASBESTOS CEMENT PRODUCTION WORKERS (Weill et al., 1979)

Exposure in mppcf-y[a]	SMR	RR[b]
5 (<10)	77 (19)[c]	1.00
25 (11-50)	70 (8)	1.14
75 (51-100)	26 (1)	0.52
150 (101-200)	290 (9)	2.85
400 (>200)	226 (14)	2.75
	104 (51)	

Estimated average cumulative exposure: 63.6 mppcf-y

[a]Accumulated during first 20 years from initial employment.

[b]Relative risk from an internal case-control analysis.

[c]( ) = number of deaths.

Regression equations

SMR = 70 + 0.43(±0.22) x mppcf-y weighted
SMR = 77 + 0.46(±0.31) x mppcf-y unweighted

RR = .96 + 0.47(±0.18) x mppcf-y weighted
RR = .99 + 0.50(±0.26) x mppcf-y unweighted

Weighted regression equation forced through an SMR of 100:
SMR = 100 + 0.31(±0.22) x mppcf-y

cohort members could be deceased, a fact unknown to the researchers. This could likely be the source of the extraordinarily low overall reported mortality of the cohort, which allowed deficits of about 40 percent in several exposure categories. (The overall SMR is 68.)

Two methods of adjustment for incomplete trace can be made. In one, the overall SMR for lung cancer is divided by the SMR for causes other than lung and gastrointestinal cancer (66). This yields a value of K_L = 0.0064, using a value of 64 mppcf for the group exposure and a fiber-particle conversion factor of 1.4 (Hammad et al., 1979) [((104/66)-1)/64/1.4]. Alternatively, a regression of SMR on dose yields SMR = 70 + 0.43 x mppcf-y. The low value of SMR is probably the result of missing deaths. If the percent missing is similar in each category then K_L = 0.0042 (0.43/100/1.4/0.70). We will use

the average of these values, 0.0053, for the point estimate of K_L. The assumption that there is an equal percentage of missing deaths in each category is uncertain. There are more untraced in the lowest category (J. Hughes, personal communication) but a greater percentage of those untraced in the most exposed group may be deceased. If one considers all of the untraced deaths to be in the lowest exposure categories and forces a regression line through the origin, its slope is 0.0040. These uncertainties in possible methods of adjusting for untraced deaths are indicated in Figure 3-7.

3.9.14 Asbestos Cement Products, Ontario, Canada (Chrysotile and Crocidolite); Finkelstein (1983)

A recent study by Finkelstein (1983) also relates mortality in an asbestos cement products facility to measured exposures. He established a cohort of 241 production and maintenance employees from records of an Ontario asbestos cement factory, consisting of all individuals who had nine or more years of employment beginning prior to 1960. Their mortality experience was followed through October 1980. Impinger particle counts of varying degress of comprehensiveness were available from various sources (government, insurance company, employer) from 1949 until the 1970s. After 1973, membrane fiber counts were taken. Individual exposure estimates were constructed based on recent fiber concentrations at a particular job. They were modified for earlier years due to changes in dustiness of the job, as determined by the impinger particle counts. These counts were thought to be accurate to within a factor of 3-5. Examples of exposure estimates for the years 1948-1954 for willow operators, forming machine operators, and lathe operators were 40 f/ml, 16 f/ml, and 8 f/ml, respectively.

The lung cancer mortality data are shown in Table 3-26. The dose-response relationship is anomolous. The first two exposure categories show the risk increasing steeply with exposure, but in the last category it falls significantly. Both GI cancer and mesothelioma show a strong positive trend with exposure, suggesting that the exposure rankings are correct. The only regression line that makes sense is one forced through an RR of 1 at zero exposure. This yields a K_L of 0.048, which is close to that calculated from the overall mortality excess and average group exposure. The average cumulative 18-year exposure for the production group in the asbestos cement work was 112.5 f-y/ml. Lung cancer deaths observed in this group were 17 versus 2.0 expected from

TABLE 3-26. LUNG CANCER RISKS, BY DOSE, AMONG ONTARIO ASBESTOS CEMENT WORKERS (Finkelstein, 1983)

Exposure in f-y/ml	Standardized mortality deaths/1000 p-y Lung Cancer
Ontario	1.6
44	13.6 (5)[a]
92	92.1 (7)
180	11.9 (6)

Complete cohort: 850 (17).

Estimated average cumulative exposure: 112 f-y/ml.

[a]() = number of deaths.

Regression equations
(Forced through the value 1.6 at zero exposure)

Lung cancer RR = 1.60 + 0.077 x f-y/ml weighted
Lung cancer RR = 1.60 + 0.108 x f-y/ml unweighted

Ontario rates for an SMR of 850. This yields a value of K_L = 0.067 [(850-100)/112.5/100] which will be used as the estimate from this study.

We do not know the reasons for the very significant difference in risk seen in two plants (of the same company) producing the same product. The point estimate of risk from Finkelstein et al. (1983) (K_L = 0.067) is 13 times that of Weill et al. (1979) (K_L = 0.0053) even after attempting to correct for the incomplete trace of the latter study. Data on the duration of exposure are not given by Finkelstein, but it would appear that the estimated average fiber exposure of his cohort was between 7 f/ml and 12 f/ml. (The average cumulative exposure over 18 years was 112 f-y/ml; all cohort members were employed for at least 9 years, one of which must have been in an asbestos work area.) This average concentration is about half of that estimated by Weill et al., using the particle-to-fiber conversion of Hammad et al. (1979). It is not possible to evaluate the accuracy of either set of exposure estimates. The exposure estimates of Finkelstein were submitted to company officials who thought they were reasonable, but worker descriptions of plant conditions

suggest that very high exposures occurred periodically (Ontario Royal Commission, 1984). In a study of asbestosis in the Ontario plant (Finkelstein, 1982a), data comparable to that of Berry et al. (1979) were obtained. Finkelstein observed prevalence rates of asbestosis of 4 percent and 6 percent at 50-99 f-y/ml and 100-149 f-y/ml versus 2.5 percent and 8.5 percent by Berry et al. Henderson and Enterline (1979) observed SMRs of 231 and 522 among retirees of cement sheet and shingle workers and cement pipe workers, respectively. These values are more consistent with the higher risk of Finkelstein then the lower one of Weill. In Figure 3-7, a fivefold downward uncertainty is indicated in K_L to reflect the maximum stated uncertainty in the exposure estimates of Finkelstein.

3.9.15 Lung Cancer Risks Estimated in Other Reviews

A number of other individuals or groups have also estimated unit exposure risks for lung cancer from these same epidemiological studies. These are shown in Table 3-27. Because of general agreement on the appropriate model for lung cancer, the unit exposure risks estimated in this document are very similar to those estimated by others. The differences in the values lie in the choice of the method to obtain a dose-response relationship and the treatment of potential biases in a study.

TABLE 3-27. COMPARISON OF ESTIMATED LUNG CANCER RISKS BY VARIOUS GROUPS OR INDIVIDUALS IN STUDIES OF ASBESTOS-EXPOSED WORKERS

Study	Percent increase in lung cancer per f-y/ml of exposure ($100 \times K_L$)					
	This Document	CPSC[a]	NAS[b]	Ontario Royal Commission[c]	Liddell and Hanley (1985) mppcf-y	Liddell and Hanley (1985) f-y/ml
Dement et al. (1983b)	2.8	2.3	5.3	4.2	6.9	2.4
McDonald et al. (1983a)	2.5				5.9	2.0
Peto (1980) after 1950	1.1	1.0	0.8	1.0		
before 1951			0.07			
McDonald et al. (1983b)	1.4				5.1	1.7
Berry and Newhouse (1983)	0.058	0.06		0.058	0.00	0.00
McDonald et al. (1984)	0.010				0.00	0.00
McDonald et al. (1980)	0.06	0.06	0.06	0.020-0.046	0.16	0.05
Nicholson et al. (1979)	0.17	0.12	0.15			
Rubino et al. (1979)	0.075	0.17				
Seidman (1984)	4.3	6.8[d]	9.1[d]		3.3[d]	1.1
Selikoff et al. (1979)	0.75	1.0	1.7	1.0	3.7	1.2
Henderson and Enterline (1979)	0.49	0.50	0.3	0.069	0.35	0.23
Weill et al. (1979)	0.53	0.31			0.66	0.47
Finkelstein (1983)	6.7	4.8		4.2[e]		
Newhouse and Berry (1979) Males			1.3			
Females			8.4			
Values used for risk extrapolation		0.3-3.0	2.0	0.02-4.2		
Geometric mean of all studies	0.65					
Geometric mean excluding mining and milling	1.0					

[a]Consumer Products Safety Commission (1983).

[b]National Research Council, National Academy of Sciences (1984).

[c]Ontario Royal Commission on Matters of Health and Safety Arising from the Use of Asbestos (1984).

[d]Data from Seidman et al. (1979).

[e]Unpublished data supplied to the Commission.