Report to the
U.S. Consumer Product Safety Commission
by the

CHRONIC HAZARD ADVISORY PANEL ON ASBESTOS

JULY 1983

U.S. Consumer Product Safety Commission
Directorate for Health Sciences
Washington, D.C. 20207

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UNITED STATES GOVERNMENT

Memorandum

U.S. CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, D.C. 20207

TO: The Commission
THROUGH: Sadye Dunn, Office of the Secretary
THROUGH: Martin H. Hasz, General Counsel
THROUGH: Edgar Morgan, Executive Director

DATE: July 21, 1983

FROM: Peter W. Preuss, Associate Executive Director for Health Sciences

SUBJECT: Report to the Commission by the Chronic Hazard Advisory Panel on Asbestos (July, 1983)

I am pleased to forward to you the final report of the Chronic Hazard Advisory Panel (CHAP) on Asbestos. In response to the Consumer Product Safety Act Amendment of August 1981 and pursuant to a nationwide solicitation, the National Academy of Sciences nominated twenty one candidates for the CHAP. The Commission selected seven Panel members who in turn chose their own Chairman and Vice Chairman.

A Federal Register notice with six questions from the CPSC to the Panel was published on April 22, 1982, and is attached. The Panel convened in January, 1983, to address the concern that the presence of asbestos may, under certain conditions, present a risk of cancer and respiratory disease to consumers. During the following six months the Panel met five times in open meetings. In addition, the Panel advertised and distributed a draft of its report for public comment. A public meeting was held on June 20, 1983 to hear and receive written comments on the draft report. Following the meeting the Panel met to revise its draft report in light of the comments received.

In order to enhance the utility of the report to other federal agencies the Panel considered a number of related asbestos matters of concern to the Environmental Protection Agency, the Occupational Safety and Health Administration and the National Academy of Sciences' Committee preparing a report on asbestiform fibers.

This final report reflects the Panel's response to comments received from the public, industry and other federal agencies which share an interest in the state-of-the-science for the health effects of asbestos.

I would like to express my personal appreciation to the members of the Panel for their efforts in preparing this report. In particular, I thank the Chairman of the Panel, Professor Norton Nelson for his wisdom and tact in guiding the work of the group. Finally, I would thank the CPSC staff who worked with the Panel, Ann Hamann, Paul White, Dodie Kessler and Colin Church.

Attachment

CONSUMER PRODUCT SAFETY COMMISSION

Chronic Hazard Advisory Panel on Asbestos; Invitation to Submit Suggestions for Scientists To Serve as Members

AGENCY: Consumer Product Safety Commission.

ACTION: Invitation to submit suggestions for scientists to serve as members of advisory panel.

SUMMARY: This notice invites suggestions for scientists to serve as members on the Commission's Chronic Hazard Advisory Panel on the Use of Asbestos in Consumer Products. The seven member panel will provide scientific advice to the Commission concerning the potential chronic hazard of cancer associated with this use. This notice also contains information on the function and composition of the panel, general criteria for selection of panel members, and procedures for suggesting candidates for membership. This will be the first Commission advisory panel established under recently-enacted legislation.

The Commission emphasizes that the selection of the panel is only the first step toward a decision on whether to take any action concerning asbestos in consumer products. The Commission has not decided whether to begin any rulemaking.

DATE: Suggestions for membership should be submitted no later than June 7, 1982.

ADDRESS: Membership suggestions should be sent to Susan Guenette, Chemical Hazards Program, Consumer Product Safety Commission, Washington, D.C. 20207.

FOR ADDITIONAL INFORMATION CONTACT: Susan Guenette, Chemical Hazards Program, Consumer Product Safety Commission, Washington, D.C. 20207; telephone (301) 492-6984.

SUPPLEMENTARY INFORMATION:

A. Background

Recent amendments to the Consumer Product Safety Act (CPSA) require the Commission to establish and receive the reports of Chronic Hazard Advisory Panels before beginning rulemaking relating to the risks of cancer, birth defects, and gene mutations associated with consumer products. Section 1206 of the Omnibus Budget Reconciliation Act of 1981 (Pub. L. 97-35); 15 U.S.C. 2077, as amended.

In carrying out its advisory functions, a panel is to review scientific data and other relevant information relating to the potential risks of cancer, birth defects, or gene mutations from a substance in consumer products. The panel is to determine if the substance is a carcinogen, mutagen, or a teratogen and, if feasible, estimate the probable harm to human health that will result from exposure to that substance. The report of the panel must be considered by the Commission and incorporated into any advance notice of proposed rulemaking and final rule.

The Commission therefor emphasizes that establishment of a panel on asbestos, as discussed in section B below, does not mean that the Commission will necessarily regulate any asbestos product. Because the CPSA requires that a panel must meet and advise the Commission before an advance notice of proposed rulemaking can be issued, the Commission is establishing a panel now as a preliminary step. If the panel's advice and other available information are later found to justify regulatory action concerning an asbestos product, the Commission will then decide whether to begin a rulemaking proceeding.

B. Purposes of Panel

The Commission has decided to convene a panel on asbestos as used in consumer products because of concern that the presence of asbestos in consumer products under certain conditions may present a risk of cancer and respiratory disease to consumers. The health hazard may occur when asbestos fibers are released into the air and people inhale them. Inhaled asbestos fibers may become embedded in lung tissue and, once embedded, they may remain there indefinitely. Asbestos fibers that are released from consumer products can remain in the household air for long periods of time and may subject household members to a continuous risk of fiber inhalation.

The Commission's past activities on consumer products containing asbestos include:

1. The Commission banned asbestos-containing patching compounds and artificial emberizing materials in January 1977.

2. In October 1979 the Commission issued, jointly with the Environmental Protection Agency (EPA), an Advance Notice of Proposed Rulemaking (ANPR) on Commercial and Industrial Use of Asbestos Fibers and Consumer Products Containing Asbestos (44 FR 60058, October 17, 1979). The Joint ANPR requested general information concerning the use of asbestos in consumer products and described the Commission's proposed regulatory approach to asbestos in consumer products.

3. In 1979 the Commission negotiated with manufacturers voluntary corrective actions and agreements to cease the use of asbestos in hair dryers.

4. In April 1980 Robert Frye petitioned the Commission and presented data which indicated that consumers were exposed to asbestos fibers when using asbestos paper (CP 80-3). The Commission granted the petition and directed the staff to develop a proposed rule to ban asbestos paper.

5. In June 1980 the Commission voted to issue a general order to require firms to furnish information concerning the use of asbestos in selected categories of consumer products.

From the information obtained through the general order and joint ANPR, the staff has found that many of the remaining uses of asbestos in consumer products do not result in consumer exposure. However, the staff has identified several consumer products (e.g., asbestos paper and millboard, bulk asbestos fibers, dry mix furnace cement, wood and coal burning stove door gaskets, certain laboratory and artists materials and stove pads and iron rests) which may present a risk of consumer exposure to asbestos. The staff believes that the results of investigations of possible exposure and risk from these products could lead them to recommend that the Commission begin one or more regulatory proceedings. Therefore, the Commission has agreed to convene a panel to review the carcinogenicity of asbestos and the risks attendant to exposure to this chemical substance.

The staff has prepared documents which it will ask the panel to review (in addition to other medical and scientific information that the panel may find relevant) relating to the general areas of carcinogenicity and epidemiology and the assessment of the risk to human health from exposure to asbestos. Specifically, the Commission will ask the panel to consider the following questions:

1. Are the available animal and epidemiologic data sufficient to draw a conclusion as to the human carcinogenicity of asbestos?

2. Is there evidence linking low level asbestos exposure, and intermittent or short term exposure, with asbestos related diseases?

3. Are there chronic health effects other than cancer related to low level exposure to asbestos?

4. Can a distinction be drawn by size of the asbestos fiber or fiber type in assessing the potential carcinogenic risk from exposure to asbestos?

5. Is there a basis for numerical evaluation of human risks from a given low level exposure to asbestos? What is the evaluation? How meaningful is it?

6. Is there evidence which indicates a threshold exposure level for asbestos? Is there a biological basis to believe a threshold exists for asbestos?

C. Membership and Selection

The Consumer Product Safety Act specifies that panel members must be scientists who have demonstrated the ability to critically assess chronic hazards and risks to human health presented by the exposure of humans to toxic substances or as demonstrated by the exposure of animals to such substances. 115 U.S.C. 2077, as amended. Members may not be officers or employees of the United States or receive compensation from or have any substantial financial interest in any manufacturer, distributor, or retailer of a consumer product. The Act provides that the President of the National Academy of Sciences (NAS) shall nominate 21 individuals from which the Commission is to appoint a seven member panel.

To provide for the broadest possible consideration of qualified scientists, the Commission, with the concurrence of NAS, is soliciting suggestions for nominees for the asbestos panel. The Commission will forward suggestions to NAS without evaluation. In cases of apparent conflict of interest, the Commission will return the suggestion to the submitting individual with an explanation. However, the NAS, in the preparation of lists of nominees to be submitted to the Commission, will not be limited by the suggestions submitted in response to this public notice.

The panel will meet at least twice for two-day sessions in Washington, D.C. over a 120-day period, beginning approximately in July 1982. Travel expenses are reimbursable in accordance with Federal regulations. Members will receive compensation of $100 for each day (including travel time) during meetings of the panel.

D. Format for Membership Suggestions

Scientists interested in serving on the asbestos panel may suggest themselves for membership, and others may suggest the names of scientists who may be willing to serve on the panel. In either case, the suggestion should include the following information to the extent possible:

(1) Name of scientist suggested for panel membership.

(2) Home address and telephone number, including area code.

(3) Employment affiliation (if any):

a. Current position and description of duties.

b. Employer's name, address, and telephone number (include area code), and type of organization, e.g. health care, manufacturing, educational, testing laboratory, governmental, public interest, retail, etc., including if self-employed.

c. Consulting work (if so, specify kind of consulting work, for whom, and if paid or volunteer).

d. CPSC contract work or grant (if so, specify contract title, number and involvement).

(4) Experience/Expertise: Specify and describe any education, experience, publications related to assessing chronic hazards, particularly from exposure to asbestos. Resumes or curriculum vitae may be submitted.

E. Privacy Act Notice

The information requested in section D may become part of a Privacy Act system of records and will be used to evaluate candidates for the Chronic Hazard Advisory Panel. There are no penalties for not submitting the information except for possibly precluding selection of a candidate. The authority for collecting the information is section 28 of the Consumer Product Safety Act, 15 U.S.C. 2077, as amended by section 1206 of the Consumer Product Safety Amendments of 1981 (Pub. L. 97-35).

Applications should be submitted no later than June 7, 1982, to Susan Guenette, Chemical Hazards Program, Consumer Product Safety Commission, Washington, D.C. 20207. She will also respond to any questions and will provide additional information where possible.

Dated: April 16, 1982.

Sheldon D. Butts,

Acting Secretary.

[FR Doc. 82-10880 Filed 4-21-82; 8:45 am]

BILLING CODE 6355-01-M

DEPARTMENT OF DEFENSE

Department of the Air Force

USAF Scientific Advisory Board; Meeting

April 13, 1982.

The USAF Scientific Advisory Board Aeronautical Systems Division Advisory Group will meet at Wright-Patterson Air Force Base, Ohio in Room 222, Building 14, Area B on May 11 and 12, 1982. The purpose of the meeting will be to review selected programs and projects relating to the missions of the Aeronautical Systems Division and the Air Force Wright Aeronautical Laboratories. The meeting will convene at 8:30 a.m. and adjourn at 5:00 p.m. each day.

The meeting concerns matters listed in Section 552b(c) of Title 5, United States Code, specifically subparagraph (1) thereof, and accordingly, will be closed to the public.

For further information, contact the Scientific Advisory Board Secretariat at (202) 697-8845.

Winnibel F. Holmes,

Air Force Federal Register Liaison Officer.

[FR Doc. 82-10882 Filed 4-21-82; 8:45 am]

BILLING CODE 3910-01-M

Determinations of Active Military Service and Discharge; Civilian or Contractual Personnel

In accordance with Public Law 95-202, Section 401 (The G.I. Bill Improvement Act of 1977) and under the provisions of DODD 1000.20, Determinations of Active Military Service and Discharge: Civilian or Contractual Personnel, the Secretary of the Air Force, acting in accordance with authority delegated to him by the Secretary of Defense, determined on April 7, 1982, that the service of the members of the group knows as the Wake Island Defenders from Guam shall be considered active military service in the Armed Forces of the United States for all laws administered by the Veterans' Administration.

Also, on April 7, 1982, the Secretary of the Air Force determined that the service of the members of the groups known as the U.S. Coast Guard Temporary Reserve and the Guam Local Security Patrol Force shall not be considered active military service in the Armed Forces of the United States for purposes of all laws administered by the Veterans' Administration.

For further information contact: Technical Sergeant Stephen J. Koegie, USAF telephone: 694-3580, Office of the Secretary of the Air Force Personnel Council (SAF/MIPC), The Pentagon, Washington, DC 20330.

Winnibel F. Holmes,

Air Force Federal Register Liaison Officer.

[FR Doc. 82-10883 Filed 4-21-82; 8:45 am]

BILLING CODE 3910-01-M

Department of the Army

Privacy Act of 1974; Amendments to Systems Notices

AGENCY: Department of the Army, DOD.

ACTION: Proposed deletions of and amendments to system notices.

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July 21, 1983

Nancy Harvey Steorts, Chairman
Consumer Product Safety Commission
Washington, D.C. 20207

Dear Chairman Steorts:

I transmit herewith the report of the Chronic Hazard Advisory Panel on Asbestos.

The Panel concluded that on scientific grounds and as a matter of public health prudence, the Commission should regard asbestos at all levels of exposure as a potential human carcinogen.

We recognize that such a conclusion in the absence of means for quantitative risk estimation confronts a regulatory agency with a difficult dilemma. Accordingly we have developed, and include in the report, a suggested approach to quantitative risk estimation (albeit with appropriate caveats as to unavoidable uncertainties).

This report has perhaps been more extensive than originally planned; however, as the analysis proceeded, the Panel became convinced that a thorough examination and presentation was important for the support of the Panel's major conclusion. However, in order to meet the requirements of readers' varying technical backgrounds, the issues are developed at three levels: a brief summary, followed by a somewhat more technical exposition, which in turn is succeeded by a detailed and fully referenced section.

The Panel has extensively discussed and reached agreement on almost all issues; in one case (which is identified) it was unable to reach total agreement. Thus the report as submitted has the complete concurrence of the Panel, and the members have so indicated by affixing their signatures below.

With the hope that our efforts will be helpful to the Commission, we respectfully submit our report.

Sincerely,

Norton Nelson, Chairman
Chronic Hazard Advisory Panel
on Asbestos

Approved:

William J. Nicholson, Vice Chairman

Janet M. Hughes

Nancy K. Kim

Julian Peto

Marvin A. Schneiderman

Carl M. Shy

Report to the
U.S. Consumer Product Safety Commission
by the

CHRONIC HAZARD ADVISORY PANEL ON ASBESTOS

JULY 1983

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PANEL MEMBERS

CHRONIC HAZARD ADVISORY PANEL ON ASBESTOS

Norton Nelson, Ph.D., Chairman
New York University Medical Center

William J. Nicholson, Ph.D., Vice Chairman
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Janet M. Hughes, Ph.D.
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ACKNOWLEDGEMENTS

Many people contributed to the review of the science and expeditious handling of the Panel's work. We extend our thanks to all of them for their aid and advice.

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HEALTH EFFECTS OF ASBESTOS

A. INTRODUCTION, SUMMARY AND CONCLUSIONS

This report was prepared in response to a Consumer Product Safety Amendment of August 1981.* The Panel met five times (January 23-24, March 17-18, April 15-16, May 12-13, and June 20-21) including a public meeting on June 20, 1983.

In approaching its assignment, the Panel examined a series of questions presented by CPSC and after extensive discussion, modified some and added others. These questions or "issues" then became the sections of this report and are briefly introduced and summarized here and more extensively reviewed in the body of our report.

1. Adequacy of Human and Animal Data as to the Carcinogenicity of Asbestos

Industrial and other studies have shown that asbestos exposure is a cause of cancer. Lung cancer is increased in asbestos-exposed persons; mesothelioma is increased in asbestos-exposed persons. Animal studies have fully confirmed these findings. In short, both types of data fully support the conclusion that asbestos is carcinogenic, i.e., leads to cancer. The term carcinogenic is used

*Consumer Product Safety Amendment of 1981, Public Law 97-35, Title 12, Subtitle A, 95 Stat. 703, August 13, 1981 dealing with Chronic Hazard Advisory Panels (Sections 28 and 31).

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here in its most general form, i.e., capable of leading to increased cancer occurrence without any implication as to its mechanism of action. The mechanisms by which exposures to asbestos lead to cancer are not known, and in vitro studies have yet to produce useful hypotheses. Fiber length and diameter have been shown to be major determinants of carcinogenicity in animal implantation studies, but differences in chemical and physical properties among different fiber types may also affect biological activity.

2. Types of Cancer Associated with Asbestos Exposure

Lung cancer and mesothelioma constitute the majority of asbestos produced cancers. The association of these malignancies with asbestos exposure is firmly established. Some other forms of cancer, particularly digestive tract, oral, pharngeal, laryngeal, and kidney, have, in some large studies, been found to be increased; there are disagreements among Panel members as to the strength of the evidence associating this group of cancers with asbestos exposures.

3. Chronic Health Effects other than Cancer Related to Low Level Exposure to Asbestos

Asbestosis, a disabling non-malignant fibrotic lung disease, is clearly associated with industrial exposure to asbestos; there is no evidence that disabling asbestosis is caused by non-occupational exposure. Radiologically detectable "plaques" or pleural thickening and/or parenchymal fibrosis have been associated with non-occupational

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exposures. These can give evidence of asbestos exposure; their health implications are unknown. Studies of the lungs of the U.S. adult population have found asbestos fibers in virtually all instances.

The Panel was able to identify only limited information on teratologic and reproductive effects and asbestos exposure. Therefore, the Panel could reach no conclusions on this issue.

4. Cancer Risk in Relationship to Fiber Type and Size

All major fiber types studied (i.e., chrysotile, amosite, and crocidolite) appear to be capable of causing lung cancer and all except anthophyllite, pleural mesothelioma in humans. Laboratory data are consistent with this conclusion. Epidemiological studies suggest that chrysotile has a lower potential for producing peritoneal mesotheliomas than other fiber types, but there is less evidence of marked differences between fiber types in their potential to produce plural mesothelioma and lung cancer. Among miners, crocidolite appears to cause a much larger risk of plural mesothelioma than chrysotile. However, it is not clear whether this is related to fiber type or to the duration and intensity of exposure, as there are no measures of exposure in crocidolite mining.

Animal studies suggest that longer and finer fibers are more carcinogenic than shorter and coarser fibers. However, short fibers

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are far more numerous in the environment, and no dimensional threshold has been established. It is not yet possible to reconcile different dose-response patterns on the basis of fiber size or type.

5. Age, Time, and Dose Dependence of Cancer Incidence

The effect of asbestos exposure on the production of lung cancer is (at least approximately) to multiply the underlying unexposed population risk by a factor proportional to the total inhaled dose. The multiplicative factor appears to be largely independent of age, and the effect is manifest in about 10 years, and continues for decades thereafter. Thus, the increase in lifetime lung cancer appears to depend largely on total asbestos exposure irrespective of age at first exposure. Because of the lower underlying risk, the absolute increase in non-smokers is about 1/10 of that in smokers.

The risk of mesothelioma rises rapidly with time from the onset of exposure for at least 50 years. Risk is independent of smoking habits and increases with both intensity and duration of exposure. Because of the rapid increase of risk with time, the lifetime effect of exposure in childhood is likely to be much greater than if exposure begins in adulthood.

Accurate quantitative data covering a range of exposure types and patterns are not available; in certain studies where the extent of

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exposure could be approximated, lung cancer appeared to increase linearly with both level and duration of exposure. However, the degree of increase for a fixed unit of exposure has varied widely in different studies. Thus, the reported percent increase in lung cancer risk per unit dose, i.e., percent per fiber-year per ml, even after adjustment for possible biases, varies over an almost 100 fold range. These differences may be a result of the differences in fiber dimensions encountered in different industries and in the inadequacies of exposure assessment.

The Panel concluded that a range of estimates of dose response at low levels may be made (and are illustrated in Section II J), but cautions that the actual risk in a specific circumstance may lie outside this range. Dose extrapolation to low levels of exposure is based on a no threshold linear extrapolation. This no threshold assumption is based on: (1) the inabililty to demonstrate its presence, (2) consistency with accepted theories of cancer induction and (3) prudence. Linearity of dose-response implies that there is neither disproportionally high risk at very low exposures, nor the absence of any risk.

The remainder of Section I of this report expands these brief summaries. This is followed by Section II which sets out in fuller technical detail the background for the Panel's conclusions. Section I is not referenced. Sources are referenced in Section II.

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6. GENERAL CONCLUSION

Asbestos of many fiber types and fiber sizes is clearly linked to the production of cancer, with risk increasing as the amount of asbestos exposure increases; there is no evidence to support the existence of a dose below which there is no effect (threshold). Predictions of risk using responses observed at high exposure levels with varying fiber types to estimate responses to exposure at low levels or with shorter fibers are uncertain. From a public health standpoint, and in the absence of final clarification of the uncertainties, it is prudent to behave as if asbestos fibers may be carcinogenic at low exposure levels and at small particle sizes. However, the estimates of risk at low exposure levels, although uncertain, serve as important guidelines to the magnitude of the potential risk and, as such, are useful in the risk assessment process.

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B. CHEMICAL AND PHYSICAL PROPERTIES OF ASBESTOS

The primary "asbestiform minerals" of health concern can be separated by crystal structure into two general classes: serpentine and amphibole. Serpentine minerals are "layered silicates" and only one of these, chrysotile, is an asbestos mineral. The amphibole asbestiform minerals are "chain silicates" and the five varieties of commercial importance are commonly known as actinolite, amosite, anthophyllite, crocidolite and tremolite. Actinolite, anthophyllite and tremolite also exist as nonasbestiform varieties. For the body of this report, the terms actinolite, anthophyllite and tremolite will refer to the asbestiform varieties only.

Chrysotile fibers are generally longer, softer and more flexible than the amphibole fibers which tend to be more brittle. These differences arise from the differences in crystal structure. The silicate layers in chrysotile are linked to a sheet of magnesium hydroxide-oxide octahedra, by the octahedra sharing oxygen atoms with the silicate tetrahedra. A structural strain is introduced because the dimensions of the two layers do not match. This strain is relieved by curvature, thus producing a hollow, flexible, scroll-like, cylindrical morphology for chrysotile.

Chrysotile, especially long fiber chrysotile, is not expected to penetrate efficiently to the deeper parts of the lungs because of its

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flexibility and curvature (which increases its aerodynamic size). This could reduce the biological activity of long, chrysotile fibers as compared to amphibole fibers of the same length.

Structural properties of the amphiboles which lead to fiber production are a preferred cleavage (splitting) plane with resistance to cleavage in other planes and structural defects (twinning and Wadsley defects). Amphiboles may be more likely to split into thinner fibers of the same length during factory processes because of these properties. The fiber diameters for the amphiboles decrease in the order anthophyllite > amosite > crocidolite. Tremolite fibers are generally short and stubby. The finer fibers are generally more carcinogenic.

The chemical formula for chrysotile is $Mg_3Si_2O_5(OH)_4$; the amphiboles have a general formula of $Me_7Si_8O_{22}(OH)_2$ with Me (metal ion) being a combination of Na^+ (sodium), Mg^{+2} (magnesium), Ca^{+2} (calcium), Fe^{+2} or Fe^{+3} (iron). In amosite and anthophyllite, the metal ion is Fe^{+2} and Mg^{+2}, with Fe^{+2} generally greater than 5 in number in amosite and Mg^{+2} generally greater than 6 in number in anthophyllite. In actinolite and tremolite, Me is $2Ca^{+2}$, Fe^{+2} and Mg^{+2}, with Mg generally greater than 4 in number in tremolite. For crocidolite, Me is Na^+, Fe^{+2} and Fe^{+3}. Weight loss in refluxing 4N

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hydrochloric acid follows the order chrysotile > amosite > crocidolite > anthophyllite which, for the amphiboles, is probably related to the loss of iron. Magnesium loss from amphiboles in the lungs follows the order anthophyllite > amosite > crocidolite. Chemical reactivity of the exposed fibril surfaces follows the order chrysotile > anthophyllite > amosite > crocidolite.

Chrysotile has proportionally more magnesium than the amphiboles. Since magnesium seems to leach more readily than the other metals, and since there is probably more surface area to enable the metal ions to be leached from chrysotile, this form of asbestos would probably "dissolve" more easily than the amphiboles. This would help explain the faster clearance rate for chrysotile.

Chrysotile has a slightly lower specific gravity (2.55) than the amphiboles (2.85 - 3.5); accordingly, the number of fibers of a given size per mass unit would be greater than with amphiboles.

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C. LABORATORY EXPERIMENTS

Inhalation animal studies have shown that amosite, anthophyllite, crocidolite and chrysotile have all produced lung tumors and mesotheliomas in laboratory experiments. Tumors at other sites have not been found at statistically significant levels in animals treated with asbestos.

Injection and implantation studies have shown that mesotheliomas and lung tumors can be caused by all asbestos types and by some other non-asbestos materials such as glass and aluminum oxide. Using implantation studies, it can be concluded that carcinogenic potency is correlated with fiber size for various materials, and that decreasing diameter and increasing length led to greater potency. However, aerodynamic properties (which depend on fiber dimensions) and the size distribution of the asbestos fibers may affect the locus and extent of deposition in the lungs and clearance patterns. The relationship between carcinogenic potency and fiber dimensions may therefore differ between implantation studies and inhalation exposure studies.

The data on the carcinogenic activity of asbestos in animals dosed orally are contradictory. An association between tumor production and asbestos exposure has been suggested in some

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studies. However, recent tests conducted as part of the National Toxicology Program have been negative. If asbestos is primarily a late stage carcinogen (promoter) exposure to an initiator would be required. However, such studies that have been conducted to date have methodoligical deficiencies. Thus, the possibility that asbestos is a carcinogen when ingested cannot be eliminated on the basis of animal studies.

Some in vitro studies have shown that chrysotile, amosite, and crocidolite are mutagenic. These fiber types, as well as anthophyllite, have been shown to be cytotoxic. In vitro studies also have shown that longer fibers have a greater mutagenic potency.

In summary, the laboratory studies show that all asbestos types can cause lung tumors and mesothelioma and perhaps some other types of cancer. Implantation studies indicate that longer, finer fibers have greater carcinogenic potential than shorter, thicker fibers.

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D. ADEQUACY OF HUMAN AND ANIMAL DATA AS TO CARCINOGENICITY

1. Lung Cancer and Mesothelioma

Lung cancer in humans has been associated with exposure to all of the principal commercial asbestos minerals: chrysotile, amosite, crocidolite, and anthophyllite. Excess risks of bronchogenic carcinoma have been documented in mining and milling, manufacturing, and end product uses of asbestos. Cigarette smoking and asbestos have a strong synergistic interaction in the development of lung cancer. Asbestos appears to act principally as a late stage carcinogen (promoting agent) that multiplies the underlying risk of lung cancer that occurs in the absence of asbestos exposure. If the underlying risk is the low one of a non-smoker, the absolute increase in lung cancer mortality will be small (although the relative risk can be high). On the other hand, if the underlying risk is high, as in smokers, the absolute increase in mortality can be very large.

Mesothelioma has been associated with exposure to chrysotile, amosite, and crocidolite in humans, and can be a common cause of death among workers heavily exposed during asbestos products manufacturing, insulation application, and the mining and milling of crocidolite. Lower risks of death from mesothelioma are found among amosite and chrysotile mine and mill employees. Mesothelioma has also been associated with asbestos exposure in other than occupational

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circumstances. The tumor has occurred among family contacts of asbestos workers, in people who lived in the neighborhood of asbestos-using facilities, and in people who were exposed incidentally in other circumstances. There are reported cases of mesothelioma among persons for which no exposure has been identified.

These risks are confirmed and extended in animal studies. All four of the above asbestos varieties have produced lung cancer and mesothelioma in animal inhalation studies, in some cases with exposures as short as one day.

2. Other Cancer

Neither the magnitude of the effect noted nor the quality of the evidence was as great for other cancers as for lung cancer and mesothelioma. Gastrointestinal cancers, however, have been found elevated in many studies in which significant exposure to asbestos occurred.

Elevated occurrences for cancer of the larynx, pharynx, and buccal cavity have been observed in some studies of asbestos exposed workers. As with lung cancer, increases at these sites are also linked to cigarette smoking.

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Asbestos exposure also has been associated with cancers of other sites. However, only cancer of the kidney and of the ovary in females have been shown to be in excess at a 0.05 level of significance. While the excess of malignancy at any other individual site does not achieve statistical significance, the excess at all other sites combined is highly significant in some studies. The magnitude of this excess and its interpretation are uncertain, however, because of the possible misattribution of asbestos-related lung cancers and mesothelioma to other sites.

The asbestos-related risks for cancer other than mesothelioma or lung cancer have not been confirmed in animal studies. As with the epidemiologic data, while some studies have shown excesses at some sites, these have not been consistently seen. If the role of asbestos is that of a promotor, the absence of well done initiation studies in animals could reduce the importance of negative results.

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E. NONMALIGNANT RESPIRATORY EFFECTS OF ASBESTOS EXPOSURE

Three categories of nonmalignant response to asbestos can be identified within the respiratory system: (1) an accumulation of fibers in lung tissue, (2) pleural plaques and thickening, and (3) diffuse pulmonary interstitial fibrosis, which can lead to disabling asbestosis. The first two of these three effects are generally considered to be a markers of asbestos exposure, without associated adverse health effects; however, pleural thickening can lead to disabling lung restriction. Asbestosis is a chronic disease characterized by breathlessness and impaired lung function and is associated with functional disability and early mortality.

1. Asbestos Bodies and Fibers in Lung Tissue

When inhaled asbestos fibers are retained in lung tissue, the larger ones may be identified with the light microscope as fibers or as asbestos bodies, which are asbestos fibers coated with material formed in lung tissue. By means of the electron microscope much smaller fibers can be resolved. These fibers can be found in histological sections of lung tissue, dissolved lung tissue, scrapings of lung tissue from the parenchymal surfaces, and sometimes in sputum. There are far more uncoated asbestos fibers which can be found with electron microscopy than coated fibers seen by light microscopy. The discovery of coated asbestos fibers tends to increase with the vigor of the search. In routine autopsy series, asbestos body prevalences vary from 20 to 60

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percent, with generally higher counts in urban than rural populations; in men than in women and in persons living close to industrial users of asbestos than among persons in other parts of the same city. With electron microscopy asbestos fibers were identified in nearly all lung tissue samples examined from New York City residents. Counts of asbestos fiber or asbestos body counts in lung tissue can be useful in quantifying the accumulation of asbestos in lungs of exposed persons, but its application to dose-response studies is limited by the expense of the procedure and difficulty of access to lung tissue from representative samples of study groups.

2. Pleural Plaques/Thickening

Pleural plaques are raised fibrotic or calcified lesions in the inner surface of the rib cage and diaphragm, and are clinically and epidemiologically important because they can be seen on chest roentgenograms and may occur even after relatively low level exposure to asbestos. As many as 25 percent of household contacts of asbestos factory workers have been found to have pleural abnormalities on their chest films, compared with 2 percent of controls.

Of themselves, pleural plaques do not give rise to clinical symptoms or functional impairment. Pleural plaques may have no long term health consequence. They are, however, markers of asbestos exposure, although there are other causes of pleural plaques such as

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trauma to the chest wall. Their presence on a chest film is useful in alerting the clinician to a possible risk of asbestos-related malignancy in that person. No studies have been done that are capable of resolving the question whether persons with pleural plaques are at increased risk for asbestos-related disease independent of the intensity and duration of their asbestos exposure.

3. Asbestosis

Asbestosis is a chronic fibrosis of lung and pleural tissue. Its diagnosis is made from a constellation of findings which may include: radiographic changes, breathlessness, abnormal pulmonary function, and crepitations heard on auscultation of the lung. Some clinical features of asbestosis are similar to those of other fibrosing lung disease, and a history of occupational exposure to asbestos is a key feature of the clinical diagnosis. Asbestosis can appear and/or progress many years after removal from exposure. Latency and nonspecificity of disease manifestation make it difficult to estimate dose-response relationships for asbestosis.

Much of the early evidence concerning the occurrence of asbestosis in occupationally exposed groups suggest that the disease does not occur from low level exposure to asbestos. However, more recent data on the incidence of asbestosis, among workers for whom cumulative exposure estimates could be obtained from on-site measurements, are

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compatible with a linear exposure-response relationship with no threshold. Based on observations of occupationally exposed workers, different dose-response curves can be derived and will vary depending upon the residence time of fibers in the lung and the induction period for disease manifestation. Whether asbestosis is likely from low doses characteristic of the nonoccupational environment is uncertain. The Panel is not aware of any evidence of reported occurrence of disabling asbestosis in nonoccupationally exposed people. This eventuality can be better addressed now, with personal monitors and epidemiological studies of newly exposed occupational groups followed for more than 10-20 years.

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F. DOSE-RESPONSE RELATIONSHIPS

1. Models for the Dose, Time, and Age Dependence of Lung Cancer and Mesothelioma

a. Linearity of Dose-Response

The dependence of lung cancer and mesothelioma incidence on age, cumulative asbestos exposure, and smoking (in the case of lung cancer) is reasonably well established. Linearity of dose-response is indicated at occupational exposure levels by several large studies of asbestos workers. Linearity will be assumed over the entire range of exposure levels for the purposes of estimating risks from occupational studies and for extrapolations to low dose exposure.

b. Lung Cancer

The relative risk for lung cancer increases with both duration and intensity of asbestos exposure, and a simple model is now widely accepted, at least as a useful approximation, for the resulting cancer incidence in asbestos workers of a given age, history of smoking, and asbestos exposure. The model is given by the equation:

$$I_L(A) = I_U(A)[1+K_L fd],$$

where I_L is the predicted lung cancer incidence rate at age A, f is the average exposure level in fibers/ml, d is duration of exposure, K_L is a constant that probably depends on fiber dimensions and type,

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and L_U is the "normal" lung cancer incidence amoung unexposed individuals of the same age and smoking history. This model can be modified both to accommodate a delay of about 10 years for the manifestation of increased risk and an eventual fall in relative risk observed in certain cohorts. The effects of such adjustments are, however, very much smaller than the uncertainty in the appropriate value of K_L.

As the majority of lung cancers in both smokers and non-smokers occurs in persons over age 60, this model implies that the lifetime risk caused by asbestos exposure before age 50 will be virtually independent of age at first exposure and will be simply proportional to the cumulative dose. Under this model, the age distribution of asbestos-induced lung cancers will be virtually the same as that of lung cancers in unexposed individuals, even if asbestos exposure occurs only in childhood or occurs throughout life due to ambient exposure.

C. Mesothelioma

For both pleural and peritoneal mesothelioma, incidence appears to rise as the third or fourth power of time since first exposure. This rise occurs irrespective of duration of exposure, age, or cigarette smoking. However, the magnitude of the risk is related to both the level and duration of exposure.

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The model for mesothelioma is given by the equations:

$$I_M = fK_M[(t-10)^3 - (t-10-d)^3] \qquad t > 10 + d$$
$$I_M = fK_M(t-10)^3 \qquad 10 + d > t > 10$$
$$I_M = 0 \qquad 10 > t$$

Where the incidence I_M is a function of level of exposure (f), duration of exposure (d), and years after first exposure (t). K_M is a proportionality constant which may depend on fiber dimension and type. The formulae used to model mesothelioma incidence (I) also incorporate a delay of 10 years for the manifestation of an asbestos effect.

2. Risk Estimates for Lung Cancer and Mesothelioma

The estimated slope of the linear dose-response relationship depends on the level of exposure, duration of exposure, the excess of asbestos related disease and (for lung cancer) the smoking habits of the observed group. The level of past asbestos exposure is in many studies the least reliable of these measurements. Two different analytical techiques have been used for measuring intensity of exposure, in earlier studies the total of dust particles per unit volume of air was measured, but, more recently, asbestos fibers per unit volume has been determined.

Two procedures have been used to estimate asbestos exposure levels of industrial workers:

i) measurements of the dust exposure during the earlier years of worker exposure supplemented by parallel measurements relating fiber and dust exposures under similar circumstances; and

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ii) recent fiber measurements for work activities believed similar to those of the group under study.

Unfortunately, in most occupational situations of interest, only recent measurements are available. The factors for converting dust measurements to fiber counts vary greatly between samples at a single job and even more markedly between jobs. The use of current fiber measurements under similar work activities to simulate past occurrences has obvious limitations. Further, all studies are limited by the accuracy of reported employee job assignments and employment activities. Clearly, exposure estimates involve considerable uncertainties.

In addition to errors in the estimates of exposure, errors may also occur in the estimates of risk; these can be a result of incomplete tracing of the cohort, misclassification of causes of death, inappropriate choice of the comparison population, and variability due to small numbers of deaths. Few studies have obtained information concerning the smoking habits of the study group, and the smoking patterns of the general population are therefore usually assumed to hold, which is a further source of possible bias.

In spite of these difficulties, estimates of the slopes (K_L) of dose-response relationships for lung cancer in eleven studies have

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been made assuming a linear association. Because of the multiple sources of possible errors and because the slopes reported in these studies vary widely, each study must be reviewed for possible errors in the estimation of both the dose and the excess risk of the population under study. The observation of a dose-response gradient, with a reasonable level of risk for the lowest exposure levels, provides important additional support for the validity of the study. Greater attention should be given to studies showing a gradient of risk across several doses, to studies having reliable exposure measures and to studies demonstrating high statistical precision.

The limitations discussed above, as well as possible differences in the effects of fibers of different types and dimensions and the use of these fibers in varying processes and with other contaminants, contribute to the wide range of observed slopes.

a. Lung Cancer

The range of values estimated for the dose-response slope (K_L) after attempting to account for possible errors and biases in individual studies, is almost 100 fold. These differences cannot be reconciled on the basis of fiber type; both the lowest and one of the highest values are from exposure to chrysotile, and even estimates from similar processes differ 15 fold. This variability illustrates the effect of some of the uncertainties discussed previously.

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b. Mesothelioma

The values of K_M must be estimated using data on both the time from onset of exposure and exposure level. Such data are present or can be estimated in only four studies. The apparent variability for mesothelioma is less than that for lung cancer, but this is largely because no mesothelioma dose-response data are available from the Canadian miners studies which gave the extreme low value of the dose-response slope for lung cancer (K_L).

The age at first exposure to asbestos is an important determinant of lifetime risk of mesothelioma. The mesothelioma risk may be similar to that for lung cancer for smokers if exposures begin prior to age 20, and in non-smokers the lung cancer risk from asbestos will greatly exceed it.

3. Extrapolations of Risk to Lower Exposure

Using the models of lung cancer and mesothelioma presented above and assuming a linear dose-response relationship, the ranges of lifetime mortality from asbestos cancers are calculated for an assumed exposure to 0.01 f/ml (NIOSH optical method) for different time periods (see Tables J-8A and J-8B). While uncertainties exist in the conversions of fiber/ml measurements to nanogram/m^3 (a common unit of measure of non-occupational exposure), this corresponds approximately to 300

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ng/m^3. In the estimates of risk, current U.S. lung cancer mortality rates were used for males, but female rates were doubled to reflect the more rapid increases seen in lung cancer mortality among U.S. women. A 10 fold range of values of both K_L and K_M was selected to represent the variation of risks observed in occupational studies. If lung cancer rates continue to rise in the United States as they have in the past, then the estimates of lung cancer risk associated with asbestos exposure will be increased in proportion. Currently lung cancer rates are increasing even more rapidly in women than in men. However, the rates for women are not likely to reach the maximum levels observed for men.

It should be emphasized that the range of values for risks represents only a range of estimates of K_L for different occupational studies. Because of qualitative differences between occupational and environmental exposures (particularly in the fiber size distributions), K_L and K_M may lie outside the ranges estimated for a given low level exposure circumstance.

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G. LABORATORY STUDIES INCLUDING DEPOSITION AND CLEARANCE

1. Introduction

Animal studies of asbestos health effects have, for the most part, confirmed previously established human data rather than served as predictors of human disease. This has occurred in part because asbestos usage predated the use of animal studies for ascertainment of risk, in part because the animal models utilized were relatively insensitive to the human diseases of concern, and finally because the principal carcinogenic risk from asbestos, lung cancer, is the result of multifactorial interaction between cigarette smoking and asbestos exposure and is difficult to elicit in a single exposure circumstance. All of the asbestos-related malignancies were first identified in humans. Experimental studies have confirmed the carcinogenicity of asbestos and have provided information on the deposition, clearance and retention of fibers, as well as on cellular changes at short times after exposure. Unfortunately, one of the most important questions raised by human studies, that of the role of fiber type and size, still remains unanswered by animal research. Injection and implantation studies have shown longer and thinner fibers to be more carcinogenic once in place at a potential site of cancer. However, the size dependence of the movement of fibers to mesothelial tissues is not fully elucidated and the questions raised in the human studies

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concerning the relative carcinogenicity of different asbestos varieties still remain.

2. Animal Deposition and Clearance

The deposition and clearance of fibers from the respiratory tract of rats has been studied directly by Morgan and his colleagues (Morgan et al, 1975; Evans et al, 1973) using asbestos samples made radioactive by neutron irradiation. Following 30 minute inhalation exposures in a nose breathing apparatus, the deposition and clearance from the respiratory tract were followed. At the conclusion of the inhalation, the distribution in various organ systems was determined. The results are shown in Table G-1. Rapid clearance, largely from the upper respiratory tract, occurred within 30 minutes with up to two-thirds of the fibers being swallowed and found in the gastrointestinal tract.

Clearance from the lower respiratory tract proceeds more slowly with two distinct components being observed. The first believed to be due to macrophage movement leads to the elimination of a considerable portion of the material deposited in the lower respiratory tract with half of the material removed within six to ten hours. A second phase proceeds much more slowly and involves the clearance from alveolar spaces and takes from 60 to 80 days to remove half the remaining material.

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TABLE G-1

Distribution of Fibers at the Termination of 30 Minute Exposures
(% of Total Deposited)[a]

Fiber	Nasal Passages[b]	Esophagus	GI Tract	Lower Respiratory Tract
Chrysotile A	9 ± 3	2 ± 1	51 ± 9	38 ± 8
Chrysotile B	8 ± 2	2 ± 1	54 ± 5	36 ± 4
Amosite	6 ± 1	2 ± 1	57 ± 4	35 ± 5
Crocidolite	8 ± 3	2 ± 1	51 ± 9	39 ± 5
Anthophyllite	7 ± 2	2 ± 1	61 ± 8	30 ± 8
Fluoramphibole	3 ± 2	1 ± 1	67 ± 5	29 ± 4

[a]Morgan et al, 1975
[b]Mean and SD

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In some cases, it may be necessary to invoke a third intermediate transport phase of approximately eight days but the amount of material involved in that movement is relatively less than in the other two phases. Data for a synthetic fluoramphibole are shown in Figure G-1 which show one short and two long-term (slower) components for fiber clearance. Data for other fibers may show only one long-term component. An anomaly, however, is the observation that the ratio of fibers in the feces to those in the lung at the time of sacrifice is not a constant as would be expected from a single component decay (Morgan et al, 1979).

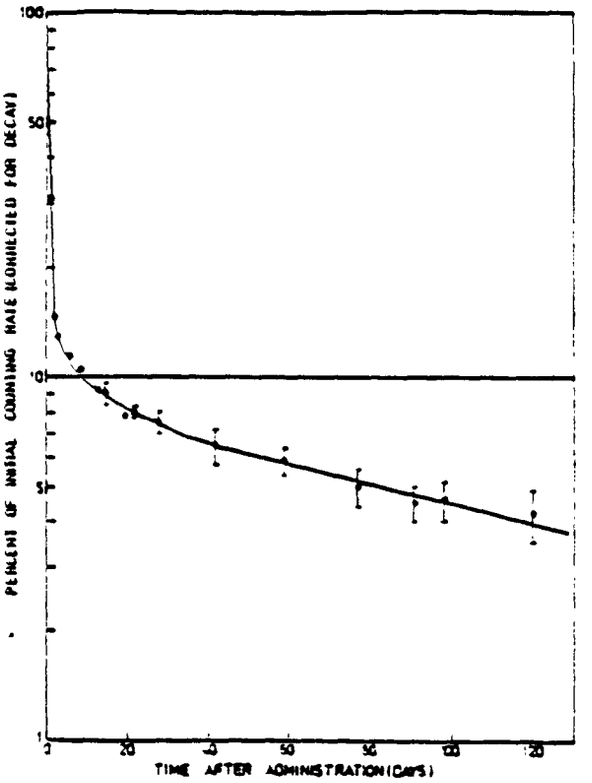
The relative amounts of different fibers deposited in the bronchiolar spaces and the alveoli are shown in Figure G-2. The similarity of the percentage deposited in the lower bronchioles or alveolar spaces for different fiber diameters is a reflection of two competing processes. At smaller fiber diameters, fibers can be inspired and then expired without deposition in the lower respiratory tract. As the fiber diameter increases, impact deposition in the upper respiratory tract becomes important, which leads to a lower percentage being carried to the alveolar spaces.

Morgan et al (1979) has also studied the length distribution of fibers remaining in the lungs of rats in order to determine the significance of fiber length on clearance. He found that the shorter fibers are

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Figure G-1

Measurements of Animal Radioactivity (Corrected for Decay) at Various Times after Inhalation Exposure to Synthetic Flouramphibole.[a,b]

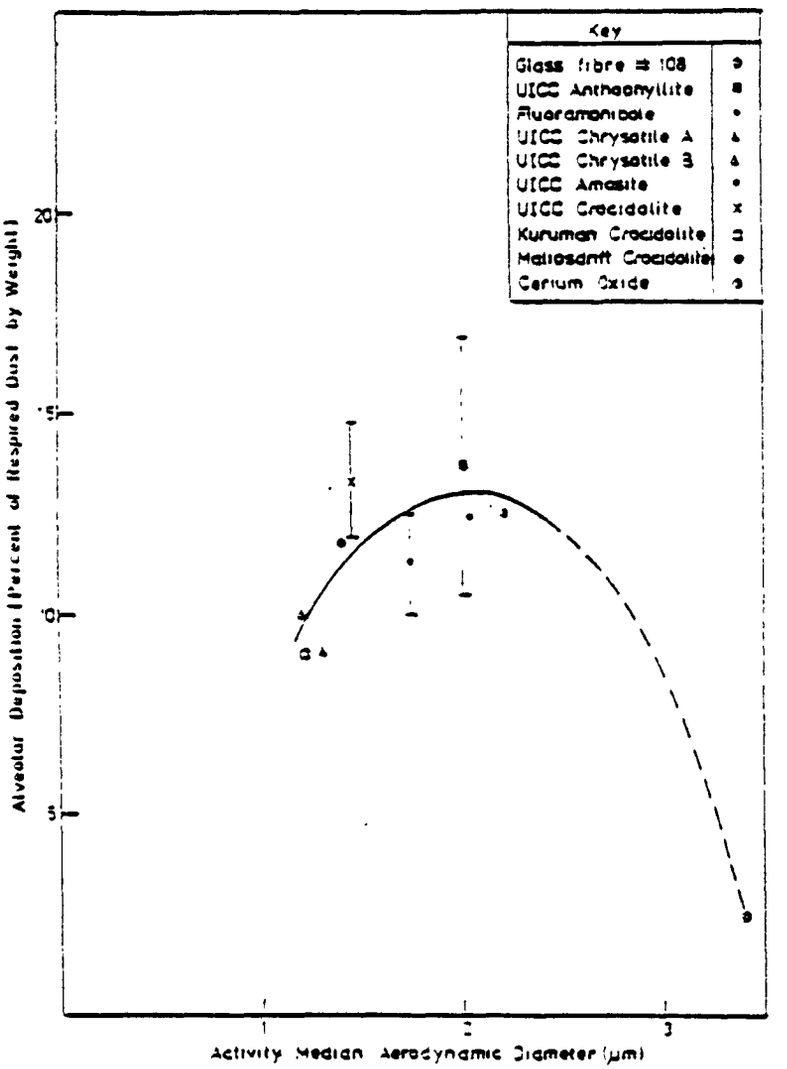


[a]Mean result for three animals expressed as a percentage of the counting rate measured immediately after exposure.
[b]Morgan et al, 1977

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Figure G-2

Alveolar Fiber Deposition as a Function of Aerodynamic Diameter[a]



[a]Morgan et al, 1979

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preferentially removed during the first week after inhalation. The fibers recovered in bronchial washings within this first week show few fibers longer than 15 μm in length and very few exceeding 20 μm, which suggest that fibers of such sizes are inefficiently transported by the alveolar macrophages.

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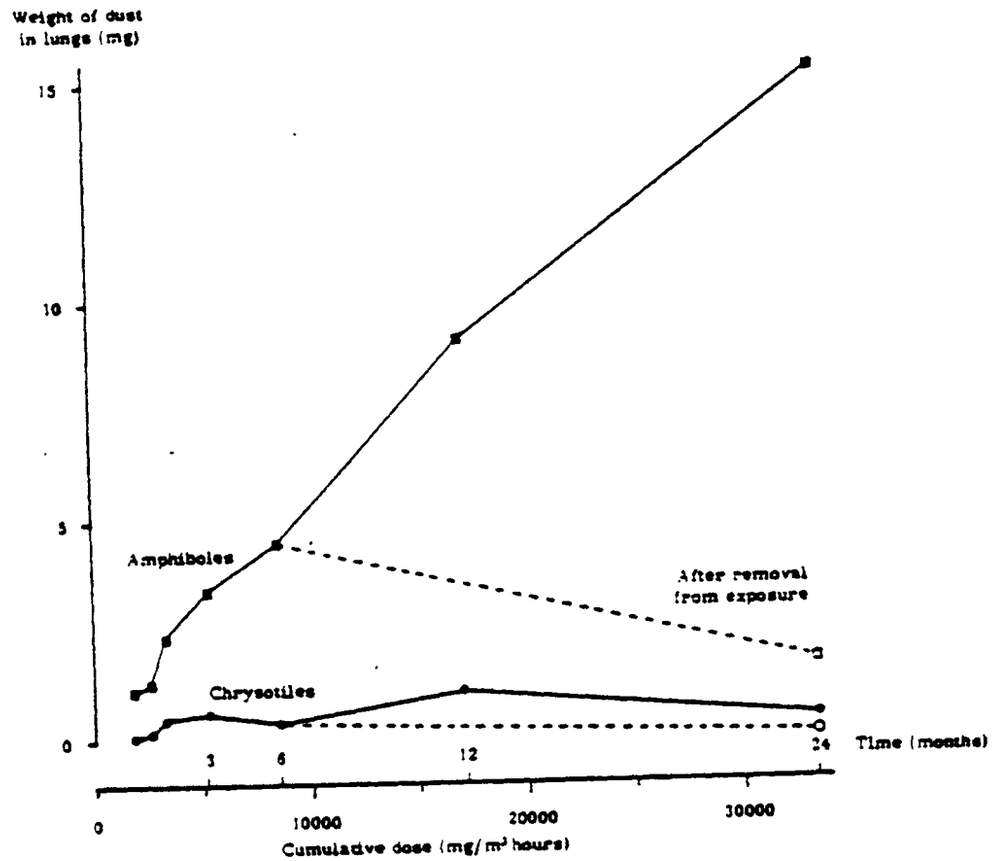
The radioactive chrysotiles used in the clearance experiments allow autoradiography to demonstrate the location of fibers at different times after exposure. At 48 hours after exposure, the distribution of fibers in the lung is relatively uniform. However, at later times, there is a movement of fibers to the periphery of the lung where they accumulate in subpleural foci consisting of alveoli filled with fiber-containing cells.

Other data on the deposition and retention of inhaled asbestos have been reported by Wagner et al (1974). Figure G-3 shows the dust content of rat lungs following exposures to different asbestos varieties. In the case of amphibole exposures, a linear increase in the amount of retained fiber was seen, whereas for chrysotile the content of the lung rapidly reached an equilibrium between removal or dissolution processes and deposition and did not increase thereafter. The long-term build-up of the amphiboles indicates that in addition to the clearance processes observed by Morgan et al (1979), there is permanent retention of some fibers. Using a minute volume for the rat of 100 ml, it would appear that about one percent of the total crocidolite or amosite inhaled is permanently retained in the lung. The slower clearance from the respiratory tract to the gastrointestinal tract demonstrates a route of exposure that may be important for gastrointestinal cancer. The occurrence in humans of peritoneal mesothelioma, and in some studies excess cancer of the

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Figure G-3

Mean Weight of Dust in Lungs of Rats
in Relation to Dose and Time[a]



[a]Wagner et al, 1974

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stomach, colon and rectum, and possibly cancers at other non-respiratory sites, such as the kidneys could be explained by the migration of such fibers to the gastrointestinal mucosa. Additionally, fibers may reach organs in the peritoneal cavity by transdiaphragmatic migration or lymphatic-hematogenous transport.

3. Human Deposition and Clearance

Some limited data are available on the quantity of asbestos fibers in lungs of individuals with and without known exposures to asbestos (Sebastien et al, 1979; Jones et al, 1980a; McDonald, 1980; Wagner et al, 1982). Most of the cases analyzed have been selected because of death from mesothelioma, often coupled with an investigation of a specific work group (Wagner et al, 1982; Berry and Newhouse, 1983). Generally, amphibole burdens of individuals heavily exposed range from 10^7 to 10^8 fibers/gram dry weight; general population controls (in Great Britain) usually have less than 10^6 fibers/gram dry weight (Jones et al, 1980a). Similar concentrations of chrysotile were seen in exposed workers (Wagner et al, 1982) and unexposed controls (Jones et al, 1980a).

Very few data are available that provide a basis for establishing a model for the deposition and clearance of fibers in humans. It would be expected that both short and long term clearance mechanisms

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would exist in humans as they do in animals. If only long-term processes are considered (characterized by months or years), the simplest model is one in which the change in lung burden (N) is proportional to the rate of deposition of fibers (A) (assuming constant, continuous exposure) diminished by a clearance that is proportional (by factor B) to the number of fibers present.

$$\frac{dN}{dt} = A - BN$$

This yields for the number of fibers present after a constant exposure of duration, t_1,

$$N = \frac{A}{B} \quad (1 - e^{-Bt_1})$$

and at a time, t_2 after cessation of a constant exposure of duration t_1,

$$N = \frac{A}{B} \quad (1 - e^{-Bt_1})e^{-Bt_2}$$

Such a model would be applicable at times t_1 and t_2 which are long compared to any short-term clearance mechanisms. This is clearly a very simplistic model in that it considers only one characteristic time for long-term removal processes. Nevertheless, it illustrates the difficulty of applying even the simplest model. In order to characterize lung burdens, one needs information on the duration and intensity of the exposure and the time from last exposure in order to obtain a measure of the characteristic removal time for a given fiber type. Such information has not been available for the individuals whose lungs have been analyzed.

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Data have been presented by Bignon et al (1978) on the number of amphibole fibers detected in lung washings of seven asbestos insulation workers. All were exposed between 10 and 16 years. Table G-2 shows the number of fibers found in the lung washings according to time since last employment. While individual exposures were unknown, fewer fibers were found in the washings of those longest removed from exposure. The data are consistent with a decrease of 50% in the number of washable fibers at five to seven years after cessation of exposure. The fibers found in the lung washings were largely amphibole; no corresponding data are available for chrysotile fibers.

Bignon et al (1978) also presented data on the relative numbers of fibers of different types (amphibole or chrysotile) and their dimensions in different thoracic tissues. Figure G-4 shows the percentage of chrysotile fibers (of total) found in lung parenchyma and pleural tissue. Amphiboles predominated in lung parenchyma and were not commonly found in pleural tissue. (Amphiboles were virtually the only fiber found in the lymph nodes, but only 3 cases were studied.) Data on the fiber dimensionality from these studies (Table G-3) show a decrease in the average length and diameter of fibers found in the pleura compared with those found in the parenchyma. However, no distinction was made between amphiboles and chrysotile in this analysis and the different length-width data could simply be a

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Table G-2

Amphibole Fibers Obtained in Lung Washings of Asbestos Insulators[a]

Case	Years of exposure	Years since last exposure	Millions of fibers per washing
1	16	2	21
2	10	4	5
3	11	3	6
4	10	11	2.4
5	15	4	3.8
6	11	0	10.3
7	14	3	7

Table G-3

Parameters of the Size Distribution for Asbestos Fibers Encountered in Lung Parenchyma and Parietal Pleura[a]

	Lung Parenchyma	Parietal Pleura
Mean Length μm	4.9	2.3
Mean Diameter μm	.13	.06
Longer than 4μm (%)	42	16
Longer than 8μm (%)	15	2

[a]Bignon et al (1978)

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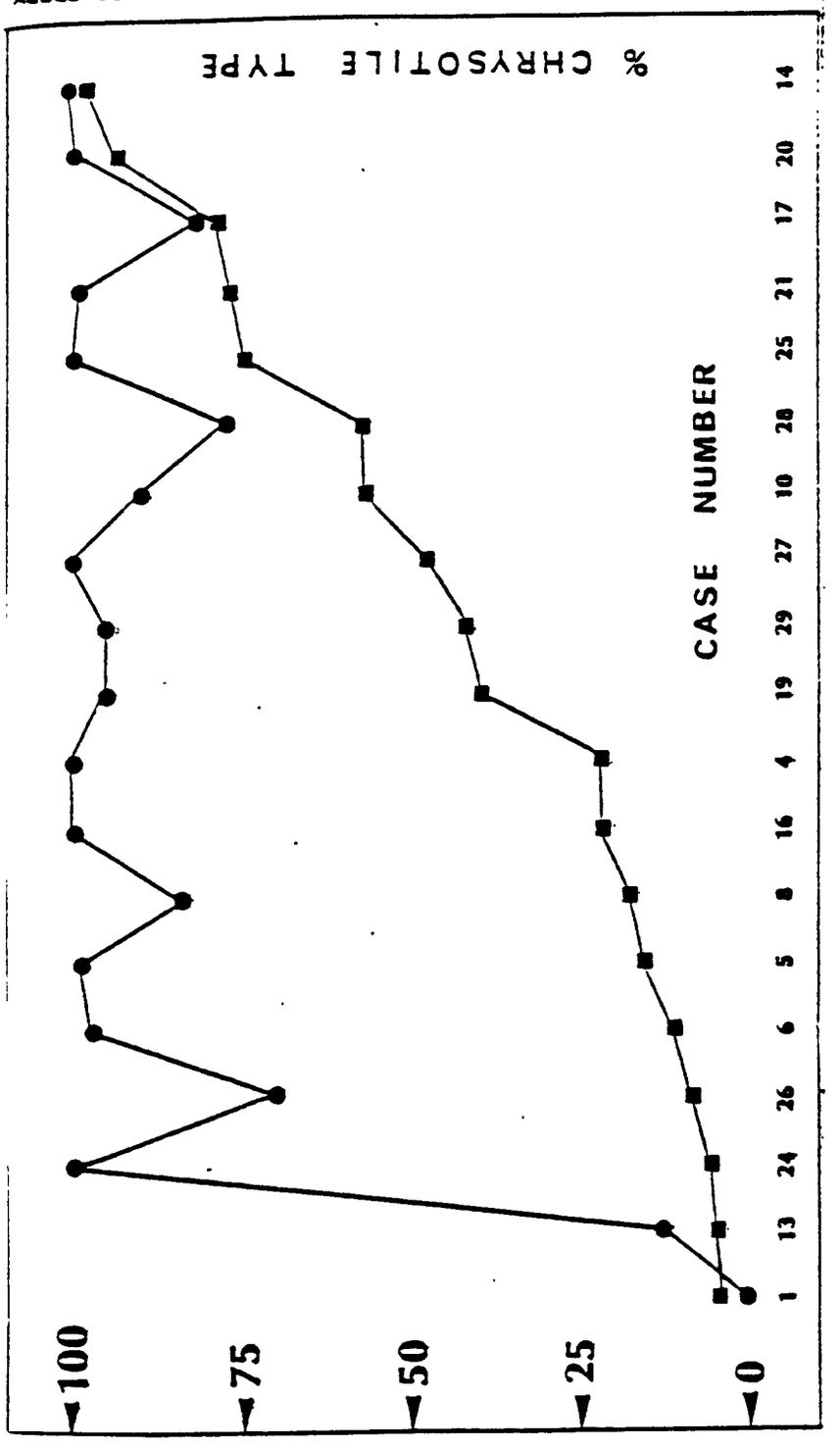


Figure G-4

Mineralogical Type of Asbestos Fibers in Lung Parenchyma (■) and Parietal Pleura (●)[a]

[a]Bignon et al, 1978

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reflection of the predominance of the different fiber types in the lung as compared to the pleura.

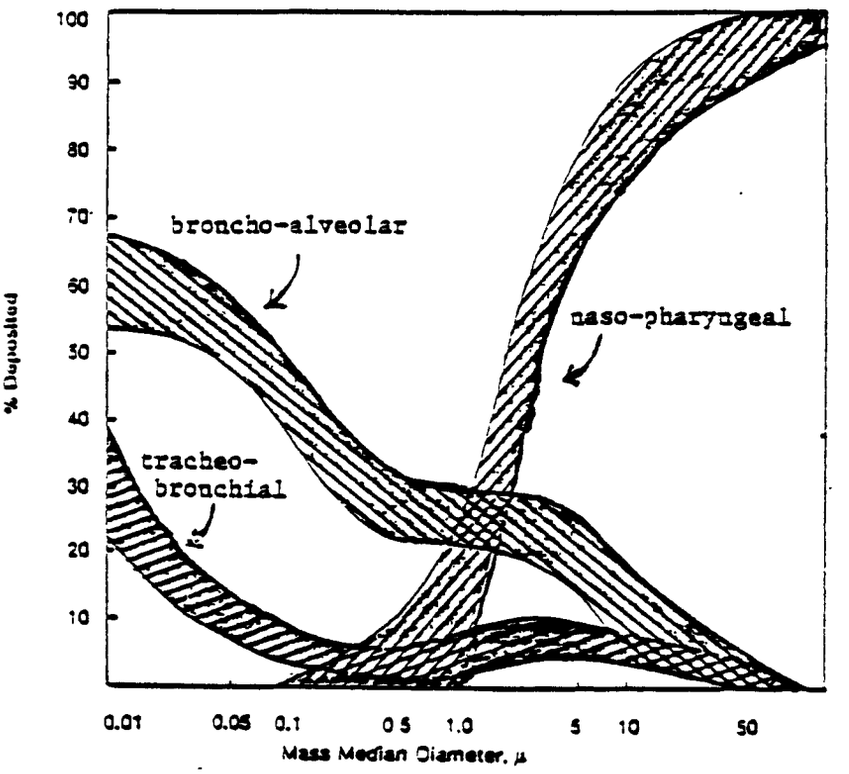
4. Models of Deposition and Clearance

The Task Group on Lung Dynamics of the International Commission on Radiological Protection has proposed a model for the deposition and retention of particles (ICRP, 1966). Figure G-5 depicts the percentages of particles of different sizes deposited in the various compartments of the respiratory tract. As can be seen, alveolar deposition is dominant for particles with a mass medium diameter of less than 0.1 μm. As the particle size increases, deposition in this area decreases falling to 25% at 1 μm and to 0 at 10 μm or above. Nasal and pharyngeal surface deposition becomes important above 1 μm and rises rapidly to be the dominant deposition site for particles 10 μm in diameter or greater. The above models were developed for spherical particles. Timbrell (1965) has shown that the settling velocities of particles and their aerodynamics are such that a fiber behaves like a particle with a diameter three times as great, independent of the length of the fiber (for fibers having an aspect ratio of at least 3). This has been corroborated by calculations of Harris and Fraser, 1976. Thus, few fibers with a diameter as large as 2 μm are likely to penetrate into the alveolar spaces, although finer fibers, even as long as 200 μm, may do so.

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Figure G-5

Aerosol Deposition in Respiratory Tract[a,b]



[a]Tidal volume is 1,430 ml; frequency, 15 breaths per minute. Variability introduced by change of sigma, geometric standard deviation, from 1.2 to 4.5. Particle size equals diameter of mass median size.

[b]Brain and Valberg, 1974, adapted from ICRP, 1966.

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5. Inhalation Experiments

Reports on inhalation experiments published after about the mid 1970's generally contain information on both the source of asbestos [e.g., UICC (International Union Against Cancer) samples] and the methods used to produce the asbestos cloud. This information is important because both the source and the cloud production can affect the size distribution (length and width) of the fibers. In turn, the potency of a given asbestos sample may be related to fiber dimensions. Later experiments recognize the importance of fiber source and cloud production to potency.

Chrysotile, amosite, anthophyllite and crocidolite have all produced fibrosis in experimental animals. (Davis et al, 1979; Wagner et al, 1974; Wagner, 1963; Reeves et al, 1974; Davis et al, 1978.) Davis found that rats exposed to UICC chrysotile exhibited more fibrosis than those exposed to UICC amosite although factory samples of the two minerals produced similar amounts of fibrosis (Davis et al, 1979). Wagner concluded that no important differences existed in the amount of fibrosis in rats exposed to UICC samples (generated with a Timbrell machine) of anthophyllite, crocidolite and chrysotile (Canadian and Rhodesian) although amosite was slightly less potent (Wagner et al, 1974). (In earlier experiments, Wagner had

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concluded that amosite caused more asbestosis in guinea pigs, rats and monkeys than chrysotile (Wagner, 1963). Rats, rabbits, guinea pigs, gerbils and mice were exposed to chrysotile, amosite and crocidolite using a procedure involving hammer milling which reduced the particle size and fibrous structure of the asbestos materials, especially chrysotile. However, all species developed fibrosis with crocidolite producing the greatest response and chrysotile the least (Reeves et al, 1974). In rats exposed to fiber clouds produced with a Timbrell dust generator, chrysotile produced a significantly greater amount of fibrosis than either crocidolite or amosite (Davis et al, 1978). These experimental results at first appear contradictory. However, the methods of generating the dust clouds offer an explanation.

All asbestos materials can produce fibrosis, and chrysotile would appear to be the most potent if the clouds were produced with a Timbrell generator. Under these circumstances chrysotile has more fibers in a given mass/volume and a greater number of longer fibers. Chrysotile is less potent than the amphiboles when clouds are generated by a milling process. This process destroys the fibrous structure of chrysotile to a greater extent than the amphiboles. This would appear to support the hypothesis that longer fibers have a greater fibrogenic potency. However, a threshold length cannot be established.

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Mesotheliomas have been found in animals exposed to amosite, anthophyllite, crocidolite, and chrysotile (Wagner et al, 1974; Reeves et al, 1974, Davis et al, 1978). In two experiments with rats in which the clouds were produced with a Timbrell generator, Canadian chrysotile produced mesotheliomas in 5/219 (2.3%); crocidolite in 5/225 (2.2%); amosite in 1/189 (0.5%) and anthophyllite in 2/145 (1.4%). The mesothelioma produced by amosite occurred after only a 1 day (7 hours) exposure to 14.1 mg/m^3. Both crocidolite and Canadian chrysotile produced peritoneal mesotheliomas.

Amosite, anthophyllite, crocidolite and Canadian and Rhodesian chrysotile have all produced lung tumors. In the rat (Timbrell generator experiments) chrysotile, both Canadian (27/219, 12.3%) and Rhodesian (30/144, 20.8%), produced more malignant lung tumors than anthophyllite (16/145, 11.0%) or crocidolite (16/224, 7.1%); amosite (11/189, 5.8%) was the least potent. Adenoma (and adenomatosis) incidence did not vary with asbestos type although it was increased over the control animals.

Tumors, other than lung tumors, have not been found at statistically significant levels at other sites in rats treated with asbestos. However, increased incidences have been seen in ovaries, male genito-urinary organs and peritoneal connective tissue.

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No carcinogenic response was found in rabbits, guinea pigs or gerbils in the inhalation experiments with chrysotile, amosite and crocidolite conducted by Reeves et al (Reeves et al, 1974). Two mice exposed to crocidolite developed lung carcinomas as did six rats exposed to chrysotile and crocidolite. Chrysotile and amosite caused mesotheliomas in rats only. These experiments could indicate a species difference although the survival of rats was better than that of rabbits and guinea pigs.

6. Injection and Implantation Experiments

Mesotheliomas have been caused by amosite, Canadian chrysotile, crocidolite, and extracted crocidolite following intra-pleural injection (Wagner and Berry, 1969). Using specific pathogen-free (SPF) rats and standard rats, amosite (38/96-SPF; 26/84) produced fewer mesotheliomas than chrysotile (61/96-SPF; 62/90), crocidolite (55/94-SPF; 62/91) or extracted crocidolite (56/95-SPF; 57/89). (Repeated reflex extraction in cyclohexane to remove oils did not affect the potency of crocidolite.) Chrysotile and crocidolite had a higher percentage of fibers with lengths greater than 10 microns than amosite. In addition to asbestos minerals, silica was also injected intrapleurally; no mesotheliomas were observed, but about half the animals developed intrathoracic tumors diagnosed as histocytic reticulum cell sarcomas.

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Mesotheliomas have been found in hamsters following the intrapleural injection of amosite, crocidolite and chrysotile (Smith and Hubert, 1974). Dose-response relationships held for 25 mg (9/50), 10 mg (4/50) and 1 mg (0/50) doses of chrysotile and 10 mg (4/50) and 1 mg (0/50) doses of amosite; no mesotheliomas were caused by 25 mg of talc containing 50% fibrous tremolite. The mesothelioma response decreased when the fiber diameter and length of chrysotile were reduced. Three preparations with mean fiber lengths of 5.3μm to 6.9μm and diameters of 0.18μm to 0.2μm produced mesotheliomas in 8, 9 and 10 animals while three preparations with lengths of 0.37μm to 0.86μm and diameters 0.03μm to 0.07μm did not produce any.

Stanton summarized the results from experiments in which test materials were applied to glass pledgets and applied to the pleural surface of rats (Stanton, 1973). The dimensional distributions of the experimental fibers were measured. Fibrosis and mesothelioma incidence were measured and the responses generally paralleled each other. Stanton concluded that carcinogenic potential increased as the percentage of fibers less than 2.5μm in diameter increased and that tumor incidence is greater when the fiber lengths are 10 to 80μm. In later studies, Stanton et al concluded that carcinogenic potency correlated with fibers of various materials and those less than 0.25μm in diameter and greater than 8μm in length had the greatest potency (Stanton et al, 1977; Stanton and Layard, 1978; Stanton et al, 1981).

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Bertrand and Pezerat, 1980, analyzed Stanton's data. They concluded that the effects are well described by modeling carcinogenic potency as a continuous, increasing function of the aspect ratio (length to diameter) of the fibers, with no threshold related to diameter or length.

Pott has also analyzed Stanton's work and plotted this information in three dimensions (Pott, 1978). This analysis indicates that long, thin fibers have an increased carcinogenic potency.

Injection and implantation studies have shown that mesotheliomas and fibrosis can be caused by all asbestos types and by other non-asbestos materials such as glass and aluminum oxide. Amosite generally produced fewer mesotheliomas than other asbestos materials but also had a lower percentage of fibers greater than 10μm. These results agree with Stanton's suggestions that a long, thin fiber morphology has greater carcinogenic potential.

Injection and implantation experiments have been used to study the relation of potency to fiber dimensions. The major disadvantage of these experiments is that the asbestos materials are not inhaled into the respiratory tract. The inhalation process can affect the size distribution of the asbestos fibers which reach the lungs and therefore the potency of the same fiber distribution may differ between implantation studies and inhalation exposure. Using these studies to measure potency may not be valid.

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Factory processes can change the fiber length and width distribution and the fibrous structure of asbestos materials. Chrysotile is more likely to have its fibrous structure destroyed during factory processes which resemble hammer or ball milling techniques. Amphiboles, are more likely to be "split" to thinner fibers of the same length during factory processes. As such, the amphibole versus chrysotile fiber distribution could change following industrial treatment so that the amphiboles in factories are likely to have a relative increase of long, thin crystals. Davis et al (1979) has measured fiber distributions for amosite and chrysotile in both UICC and factory samples and determined their fibrogenic and carcinogenic potency in animals. The factory chrysotile produced the same fibrogenic response and a lower carcinogenic response than the UICC sample. He concluded that "... while fibrogenicity and carcinogenicity both depend on the presence of relatively long fibers in dust clouds, different lengths are involved in each process and tumour production requires the longest fibres."

The greatest unknown as far as the importance of fiber dimensions from these animal experiments is how fiber dimensions influence the deposition of asbestiform minerals in human lungs. Timbrell (1973) has discussed the importance of the aerodynamic properties of asbestos minerals. Chrysotile, especially long fibers, is not expected to penetrate efficiently to the deeper parts of the lungs because of its

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flexibility and curvature. However, short fibers of the different asbestos varieties are expected to have similar deposition characteristics. The aerodynamic properties of the amphibole fibers favor a greater fiber deposition in the deeper areas of the lung and therefore may be more likely to produce disease. In contrast, the animal inhalation experiments show chrysotile to be just as potent as the other asbestos forms but the fibers are airborne using a process that produces a larger proportion of long, thin fibers for chrysotile than that found in factory environments. In summary, animal experiments may not be directly comparable to the human experience because of differences which are caused by the methods of administering the asbestos.

7. Ingestion Experiments

Hamsters exposed via drinking water to UICC samples of amosite, amosite tailings and milled ores related to amosite did not show a significant increase in tumors although one peritoneal mesothelioma, one pulmonary carcinoma and 2 squamous cell carcinomas of the forestomach were found. The authors concluded that these tumors were not associated with asbestos (Smith et al, 1980).

Rats injected with azoxymethane and orally dosed with chrysotile and amosite had similar incidence rates of intestinal tumors than those dosed with azoxymethane alone. A slightly higher, but not

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statistically significant, incidence of metastatic intestinal carcinomas was seen in the two asbestos groups. Rats exposed to amosite alone had a 32% incidence rate of colon tumors. The authors concluded that this suggested but did not prove that amosite may have increased the incidence of these tumors. It should be noted that a control group was not used in this experiment (Ward et al, 1980).

Rats given chrysotile in the diet did not show a statistically significant increase in tumors. The authors concluded that there was "evidence of increased probability of asbestos-fed animals to develop colon lesions in general"; in addition, one mesothelioma was found (Donham et al, 1980). Gibel et al (IARC 1977) found a significant increase in malignant tumors in rats given asbestos filter material; the sites of increase were other than gastro-intestinal and the composition of the filter material was not completely defined.

Recent, well designed lifetime studies have not reported increased tumor production following the ingestion of asbestos materials. Chrysotile and amosite at levels of one percent in the diet of Syrian golden hamsters did not produce a carcinogenic response (National Toxicology Program, 1981a and 1981b). Crocidolite, at a 1%

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concentration in a pelleted diet was administered to Fischer 344/N rats. The preliminary conclusions were that under these conditions, crocidolite was neither overtly toxic nor carcinogenic (National Toxicology Program, 1983). The nonfibrous form of tremolite was administered to Fischer 344 rats at a 1% concentration in the diet; preliminary results were negative (National Toxicology Program, 1982a).

Amosite was administered to Fischer 344/N rats over their lifetime at a concentration of 1% in the diet. The animals were dosed alone and in combination with 1,2-dimethylhydrazine dichloride (DMH), an intestinal carcinogen. Preliminary results indicate amosite is neither toxic nor carcinogenic under the conditions of the study. The cocarcinogenic studies were considered inadequate because DMH induced a high incidence of intestinal neoplasia in both the amosite and nonamosite exposed groups (National Toxicology Program, 1982b).

In summary, the data on the carcinogenic activity of asbestos in animals dosed via an oral route are inconsistent. An association between tumor production and asbestos exposure has been suggested in some studies. However, recent tests conducted as part of the National Toxicoloty Program have given consistently negative results. If asbestos is primarily a late stage carcinogen (promoter), exposure to

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an initiator would be required. Thus the possibility that asbestos is a carcinogen when ingested is not excluded by these animal studies.

Very little information on the potential for asbestos to cause reproductive or teratogenic effects was found in the literature. Schneider and Maures (1977) administered chrysotile in drinking water to pregnant mice; neither the survival nor the development of the embryo were affected. Blastocysts from pregnant mice were exposed to chrysotile in vitro and then transferred into pseudopregnant females. A decrease in post implantation survival was noted although some of the embryos developed into viable fetuses. The authors speculated that the survival of the embryos was affected by heavy metals leaching from asbestos rather than by the physical properties of asbestos. In another experiment pregnant rats were injected with chrysotile on the 10th to 14th days of pregnancy (Cunningham and Pontefract, 1974); the lungs and livers of the fetuses were saved for analyses. The amounts of asbestos found in these organs were highly variable, but the authors concluded that this experiment "... added evidence to the theory that asbestos fibers can cross the placenta." Based on these limited results, no firm conclusions can be reached as to the potential for asbestos to cause reproductive or teratogenic effects.

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8. In Vitro Studies

Amosite, chrysotile and crocidolite have not been shown mutagenic in E. coli or S. typhimurium (Chamberlain and Tarmy, 1977) or rat liver cells (Reiss et al, 1982). However, chrysotile and crocidolite have induced chromosomal changes in Chinese hamster cells (Sincock and Seabright, 1975). Amosite, chrysotile and crocidolite are reported to be weakly mutagenic in tests using Chinese hamster lung cells (Huang, 1979). Chrysotile has induced chromosomal aberrations in cultures of Syrian hamster embryo cells (Lavappa et al, 1975) and human lymphocytes (Valerio et al, 1979).

Barrett et al (in press) have studied the effects of asbestos on Syrian hamster embryo fibroblasts (SHE) in culture. They have shown that asbestos did not induce detectable gene mutations under conditions producing morphological transformatons of SHE cells. The fibers were taken up by SHE cells and were found in the perinuclear region of the cytoplasm. They have concluded that asbestos "... causes transformation by binding to microtubules or other cytoskeletal proteins that are important in the disjunction of chromosomes during mitosis, thereby resulting in aneuploidy and polyploidy."

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Asbestos has been reported to be cytotoxic in culture systems. Using tumor cells with phagocytic ability, the cytotoxicity of amosite, chrysotile and crocidolite were found to increase with increasing fiber length (Tilkes and Beck, 1979). Amosite and crocidolite were generally less cytotoxic and hemolytic than chrysotile to P388D cells and sheep erythrocytes. Heating chrysotile decreased its cytotoxicity (Gormley et al, 1979). Crocidolite, amosite and anthophyllite were cytotoxic to mouse peritoneal macrophages. Ball-milling decreased the cytotoxicity of crocidolite and amosite to a greater extent than anthophyllite (Davies, 1979). Brown and Chamberlain studied the effects of chrysotile and crocidolite on the plating efficiency of V79-4 cells and concluded that "some cellular effect dependent only on fibre size must be the major contributor to the pathogenesis of mineral fibres." (Brown and Chamberlain, 1979).

Crocidolite, amosite and chrysotile have increased the sister chromatid exchange (SCE) rate in mammalian cells in in vitro studies (Livingston et al, 1980; Babu et al, 1980; and Babu et al, 1981). The SCE rates in circulating peripheral lymphocytes of asbestos insulation workers, both smokers and non-smokers, has been compared to a control population (Rom et al, 1983). Smoking caused a greater increase in SCE than asbestos exposure. The increased rate between asbestos

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workers who did not smoke and their controls was greater than that found between asbestos workers who did smoke and their controls.

The amphiboles and chrysotile have been found to be cytotoxic and mutagenic. Brown and Chamberlain (1979) concluded that "Chemical and physicochemical properties of the fibre may affect the rate of interaction between fibres and cells in vitro, but this does not alter their overall effect. Failure to detect activity in vitro may result from choosing conditions that inhibit or prevent the initial fibre-cell interaction rather than from the absence of appropriate fibres."

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H. CANCERS OF CONCERN

1. Lung Cancer and Mesothelioma

Lung cancer and mesothelioma are the principal cancers associated with exposure to asbestos. Dozens of studies have demonstrated an excess risk of death from these malignancies among groups exposed occupationally to asbestos (See Table H-1). Lung cancer has been unambiguously associated with human exposure to chrysotile, amosite, crocidolite and anthophyllite. Mesothelioma has been associated with exposure to all of the above except anthophyllite. Those studies which provide dose-response information are described in detail in Section J.

2. Other Cancers

Increased risks of malignancies, other than mesothelioma, at extrapulmonary sites have been found in a number of asbestos mortality studies. The Panel members were unable to agree on the interpretation of these excesses. Some members thought it possible that these excesses could conceivably be due to a combination of misdiagnosis of peritoneal mesothelioma and the use of inappropriate expected numbers. Other members thought that after allowance is made for these possible

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TABLE II-1[f]

Respiratory and Digestive System Cancers in Asbestos Exposed Workers

	Reference	Country[a]	Cohort traced	Deaths	Mesothelioma	Respiratory (162-4) O	Respiratory (162-4) E	Respiratory (162-4) O/E	Digestive (150-9) O	Digestive (150-9) E	Digestive (150-9) O/E	Power (β) to detect O/E = 1.5 at E = 0.05
Males												
Mining and Milling												
Chrysotile	1. McDonald et al (1980)	A	9,850	3,291	10	230	184.0	1.25	276	272.4	1.01	100.0
	2. Nicholson et al (1979)	A	544	178	1	28	11.0	2.55	10	9.5	1.05	35.6
	3. Rubino et al (1979)	I	933	332	0	10	10.4	0.96	19	19.3	0.98	59.5
Anthophyllite	4. Newman et al (1974)	F	1,041	248	0	21	12.6	1.67	7	8	0.88	31.8
Talc	5. Kleinfeld et al (1965b)	A	220	91	2	9	2.3[c]	3.91	6	1.5[c]	4.00[e]	7.8
	6. Brown et al (1979)	A	382	74	1	8	2.8	2.86	3	3.0	1.00	16.9
Manufacture												
Chrysotile	7. Weiss (1977)	A	264	66	0	0	0.6	0.93	2	2.0	1.00	8.4
	8. Dement et al (1982)	A	746	191	1	26	7.5	3.47	9	7.1	1.27	27.4
Crocidolite	9. McDonald and McDonald (1978)	A	93	43	8	8	4.0[c]	2.00	1	2.0[c]	0.50	8.4
Amosite	10. Seidman et al (1979)	A	820	528	14	83	22.8	3.64	28	22.7	1.23	66.0
Mixed	11. Hoshouse and Berry (1979)	B	2,887	545	46	103	43.2	2.38	40	34.0	1.17	81.8
	12. Hoshouse et al (1982)	B	8,804	1,640	8	143	139.5	1.03	103	107.2	0.96	99.9
	13. Peto et al (1977)[b]	B	1,080	317	10	51	23.8	2.14	16	15.7	1.02	57.3
	14. Henderson & Enterline (1979)	A	1,075	781	4	63	23.3	2.72	55	39.9	1.38[e]	86.1
	15. Robinson et al (1979)	A	2,666	912	13	49	36.1	1.36	50	41.4	1.21	89.1
	16. Hughes and Weill (1980)	A	5,645	601	0[d]	49	49.1	1.00	25	50.1	0.50	91.1
Insulation	17. Mancuso and Coulter (1963)	A	1,266	135	4	15	5.5	2.73	12	7.0	1.71[e]	25.8
Mixed	18. Kleinfeld et al (1967a)	A	152	46	4	10	1.4[c]	7.14	7	2.7[c]	2.59[e]	11.6
	19. Selikoff et al (1979)	A	632	478	38	93	13.3	6.99	43	15.0	2.87[e]	48.6
	20. Selikoff et al (1979)	A	17,800	2,271	175	429	105.6	4.06	122	84.1	1.45[e]	99.3
	21. Elmes and Simpson (1977)	B	162	122	13	35	5.0	7.00	13	2.2[c]	5.90[e]	11.7
	22. Hoshouse and Berry (1979)	B	1,368	85	10	21	5.6	3.75	3	4.3	0.70	20.3
Shipyards												
Mixed	23. Hosstiter and Coles (1980)	B	6,076	1,042	28	88	100.7	0.87	73	83.3	0.88	99.3
Females												
Manufacture												
Crocidolite	24. Jones et al (1980b)	B	578	166	17	12	3.8	3.16	10	20.3	0.49	62.8
Mixed	25. Hoshouse and Berry (1979)	B	783	200	21	27	3.2	8.34	20	10.2	1.96[e]	36.5
	26. Hoshouse et al (1982)	B	4,219	346	2	6	11.3	0.53	29	27.4	1.06	16.0
	27. Robinson et al (1979)	A	544	128	4	14	1.7	8.24	8	6.0	1.33	29.4
	28. Mancuso and Coulter (1963)	A	229	20	1	1	0.2	8.00	2	1.0	2.00	6.6

[a]A = America, B = U States, F = Finland, I = Italy.
[b]One possible case (Rubino et al, 1979); 2 cases not meeting criteria (Hughes and Weill, 1980).
[c]Estimated from proportional mortality data.
[d]Males and females.
[e]Statistically significant increase (P = .05)
[f]Table modified from: McDonald and McDonald, 1981.

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errors that some of the observed excess must be attributable to asbestos. These cancers fall into four groups:

1. Upper respiratory tract, including the pharynx, buccal cavity and larynx.
2. Gastrointestinal, including esophagus, stomach, colon and rectum.
3. Kidney.
4. All other cancers, excluding the above three categories, lung cancer and mesothelioma.

a. Larynx, Buccal Cavity and Pharynx

Cancers of these sites are relatively uncommon. A statistically significant excess has only been shown in large cohort or case control studies. The study of Selikoff et al (1979) of 17,800 insulation workers shows each of these sites to be elevated in comparison with the general population using death information as recorded by death certificates (O/E = 1.91 for the larynx and 1.59 for the buccal cavity and pharynx combined) at an 0.05 level of significance (Table H-2). Laryngeal cancer has also been shown to be significantly elevated in a study of shipyard workers in Genoa (Puntoni et al, 1979). Two case control studies have also shown an elevated risk for laryngeal cancer. (Stell and McGill, 1975; Morgan and Shettigara, 1976). However, the study of Stell and McGill, showing a very high relative risk, may be affected by some unknown bias. Tumors at these sites are also related to cigarette smoking, and the possibility of a

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TABLE H-2

Deaths Among 17,800 Asbestos Insulation Workers
in the United States and Canada, 1/1/67 - 12/31/76[a]

Underlying Cause of Death	Expected	Observed (BE)	Observed (DC)	Ratio o/e (BE)	Ratio o/e (DC)
Total deaths, all causes	1,658.9	2,271	2,271	1.37	1.37
Total cancer, all sites	319.7	995	922	3.11	2.88
Cancer of lung	105.6	486	429	4.60	4.06
Pleural mesothelioma	**	63	25	...	...
Peritoneal mesothelioma	**	112	24	...	...
Mesothelioma, n.o.s.	**	0	55	...	...
Cancer of esophagus	7.1	18	18	2.53	2.53
Cancer of stomach	14.2	22	18	1.54	1.26
Cancer of colon-rectum	38.1	59	58	1.55	1.52
Cancer of larynx	4.7	11	9	2.34	1.91
Cancer of pharynx, buccal cavity	10.1	21	16	2.08	1.59
Cancer of kidney	8.1	19	18	2.36	2.23
All other cancer	131.8	184	252	1.40	1.91
Non-infectious pulmonary diseases, total	59.0	212	188	3.59	3.19
Asbestosis	**	168	78	...	...
Cor pulmonale due to asbestosis	**	16	14	...	...
All other causes	1,280.2	1,064	1,161	0.83	0.91

* Expected deaths are based upon white male age-specific U.S. death rates of the U.S. National Center for Health Statistics, 1967-1976.

** Rates are not available, but these have been rare causes of death in the general population.

(BE) Best evidence. Number of deaths categorized after review of best available information (autopsy, surgical, clinical).

(DC) Number of deaths as recorded from death certificate information only.

[a]Selikoff et al, 1979

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synergistic interaction between asbestos and smoking may exist. Other studies did not report an excess of laryngeal cancer (e.g., Newhouse et al, 1980).

b. Gastrointestinal

Table H-1 lists data from 28 studies that reported the incidence of GI cancer (esophagus, stomach, colon and rectum). Five of 8 studies with satifactory power (80% or more) to detect a 50% increase in relative risk found increases in deaths from digestive system malignancies. Two of these increases were statistically significant. Among 20 studies with less power, 13 showed increases, 6 of which were stastistically significant. Thus, in total, 8 out of 28 studies showed statistically significant increases. In general, studies that showed high observed-to-expected ratios for respiratory cancer were also likely to show high O/E ratios for digestive system cancers. The converse is also true.

The possibility exists that some gastrointestinal cancers in some studies were misclassified peritoneal mesotheliomas. In the study of Selikoff et al (1979, 1982), however, a diligent search was made for such misattribution and only four peritoneal mesotheliomas were so misclassified (see Table H-3 "Other asbestos associated cancers"). When clinical and pathological evidence was reviewed several (at least 5 of Table H-2) cancers that were classified as malignancies at other sites were found to be primarily gastrointestinal cancers.

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TABLE H-3

Cause of Death (BE) and Cause of Death (DC)[a]

	Cause of Death (BE)						
Cause of Death (DC)	Lung Cancer	Pleural Mesothelioma	Peritoneal Mesothelioma	Asbestosis	Other Asbestos Associated Cancers[b]	Cor Pulmonale	Total
Lung Cancer	415	7	1	3	3	0	429
Pleural Mesothelioma	2	23	0	0	0	0	25
Peritoneal mesothelioma	0	0	24	0	0	0	24
Mesothelioma, n.o.s.	1	26	28	0	0	0	55
Asbestosis	1	0	1	76	0	0	78
Other asbestos - associated cancers[b]	1	0	4	0	132	0	137
Cor Pulmonale	0	0	0	6	0	8	14
Other Cancer	28	2	52	0	11	0	93
Other	38	5	2	83	4	8	140
Total	486	63	112	168	150	16	995

[a]Selikoff, I.J., 1982.
[b]Cancer of the esophagus, stomach, colon-rectum, larynx, oropharynx or kidney.

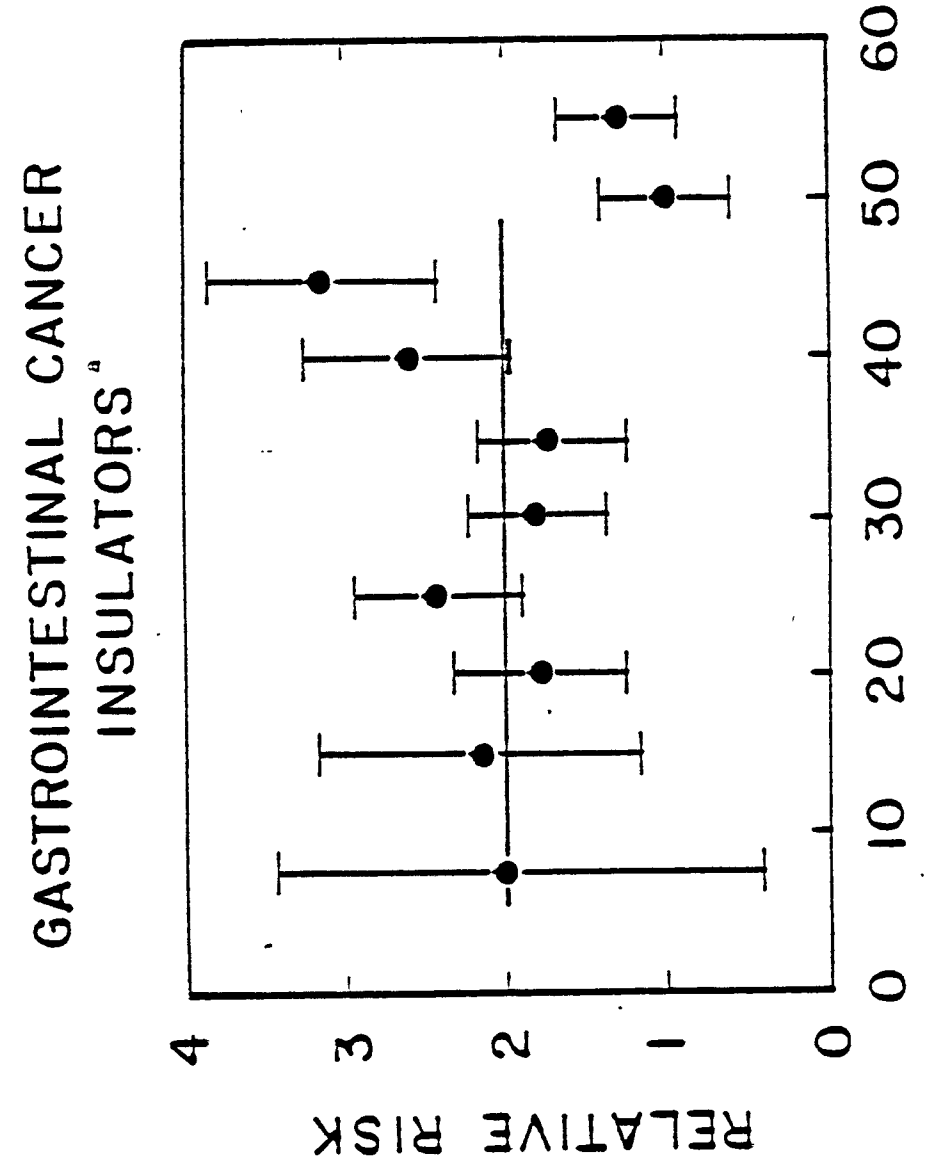
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Thus, gastrointestinal cancer may be understated rather than overstated on death certificates in groups exposed to asbestos. Some regional and ethnic differences exist in the incidence of these cancers which can account for some of the variation in observed/expected ratios reported in different studies. In particular the high incidence of gastrointestinal cancers among New York and New Jersey insulation workers (O/E = 2.99) may be the result of a larger proportion of individuals of Slavic origin in the group under observation than in the United States general population. However, this is unlikely to explain the even higher ratio among Belfast insulators. Further, because of the consistency between elevated risk of lung cancer and gastrointestinal cancer in a wide variety of asbestos exposed groups in different countries, it would be difficult to ascribe the excesses to a general underestimate of expected rates.

An unusual aspect of gastrointestinal cancer is that the relative risk in insulators was relatively independent of the time from first exposure to asbestos (Figure H-1). This may be the result of removal processes in the gastrointestinal tract reaching an equilibrium with deposition fairly quickly, with the effect of asbestos being to increase the relative risk in proportion to the tissue burden. If so, one would expect a diminution of risk with reduction in exposure. A

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FIGURE II-1



[a]The relative risk of deaths (observed to expected) from gastrointestinal cancers among insulation workers according to time from onset of exposure (Selikoff and Seidman, personal communications).

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marked secular decline occurred among Belfast insulators (Elmes and Simpson, 1977), but some of this may be due to improved diagnosis for peritoneal mesothelioma. This is coincident with declines in stomach cancer seen in most industrialized countries.

While there is evidence of an association of asbestos exposure and GI cancer, the consistency of the findings, the number of cases and the relative risk is much less than for lung cancer. Overall, when an excess of gastro-intestinal cancers has been observed the ratio of excess GI cancer to lung cancer is about 0.1. To date, there has been no direct evidence of a dose response relationship with asbestos exposure. Further, in earlier years, peritoneal mesotheliomas may have been misclassified as gastro-intestinal cancers. For these reasons, some members of the Panel believe the causal relationship of gastro-intestinal cancer with asbestos exposure has yet to be resolved.

c. Kidney

Two studies have presented data on the risk of kidney cancer. In that of Selikoff et al (1979), the excess mortality (18 observed vs. 8.1 expected $p<.05$) suggested an association with asbestos exposure. Puntoni et al in 1979 also found elevated kidney cancer (29 observed 14.65 expected). An etiological relationship with asbestos exposure is plausible with the finding of excretion of fibers in the urine of individuals known to have ingested asbestos-like material (Cook and Olsen, 1979).

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d. Other Sites

The observed and expected mortality for cancers of the other sites has been found to be elevated in some studies where the risk of respiratory cancer is high (Goldsmith, 1982). However, many studies have reported no such excess. When present, the excess relative risks at all other sites are usually small.

Some of the excesses listed in some studies for these other cancers may be due to misdiagnosis of lung cancer or mesothelioma. This possibility is compatible with the greater risk for these other cancers in the heavily exposed groups. In the large study by Selikoff (1979), 252 deaths among insulation workers were certified as "other cancer" (Table H-2) of which 54 were reclassified on review as mesothelioma and 28 as lung cancer (Table H-3). Approximately 80% of these 28 lung cancers (about 22 deaths) were probably caused by asbestos, so roughly 76 deaths (54 + 22) coded as other cancers were actually caused by asbestos and were sufficiently well investigated to be reliably reclassified as lung cancer or mesothelioma. This accounts for 63% (76/120) of the excess deaths coded on death certificates as other cancers. Some additional misclassification may have occurred, but several Panel members thought it unlikely that misclassification could explain the entire excess mortality. Two sites, particularly liable to be certified incorrectly are pancreas

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and liver; 16 of the 49 deaths certified as pancreatic cancer were in fact peritoneal mesothelioma (Selikoff and Seidman, 1981). While the magnitude of any excess at these other sites is uncertain, it is no more than the excess gastrointestinal cancer and much less than the excess lung cancer.

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I. HEALTH EFFECTS OTHER THAN CANCER

Extensive information is available for three categories of nonmalignant respiratory effects: asbestos bodies and/or asbestos fibers in lung tissue, pleural plaques or thickening, and diffuse pulmonary interstitial fibrosis. The first two of these three effects are generally considered to be markers of asbestos exposure rather than diseases although pleural thickening can lead to disabling lung restriction. Classical asbestosis is characterized by radiographic changes, breathlessness, impaired lung function, and crepitations heard on auscultation of the lung. However asbestos bodies/fibers and pleural plaques are epidemiologically important markers of environmental exposure, even in the absence of occupational exposure to asbestos and, as such, their identification and measurement may be useful in evaluating the risk of subsequent malignant or nonmalignant asbestos related respiratory disease associated with low dose exposures.

1. Asbestos Bodies

Asbestos bodies are coated asbestos fibers visible under light microscopy; the coating is formed in lung tissue to different degrees following inhalation of any type of asbestos fiber. They are elongated, golden brown structures 20-100 μm long and 3-5 μm wide, usually having a beaded appearance and a rounded end. They can be demonstrated in sputum, histological sections of lung tissue, fluid extracted from cut lung tissue, dissolved lung tissue, or scrapings

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from the parenchymal surface of the lung. Not all coated fibers seen in the lung have an asbestos core, for the process of coating appears to be a tissue response in the lung to a variety of fibers including glass, cotton, talc, graphite and diatomaceous earth. Accurate identification of an asbestos core in a presumed asbestos body is possible, using electron beam, laser microprobes, mass spectroscopy and other techniques. The use of electron microscopy has revealed the presence of many more asbestos fibers and fibrils in the lungs of asbestos exposed persons than was estimated when lung fiber counts were evaluated by light microscopy alone. The reported prevalence of coated asbestos fibers (asbestos bodies) tends to increase with the vigor of search and the amount of lung tissue examined, and although some asbestos bodies do not necessarily contain an asbestos core, it is probable that most of those found in human lungs, particularly of urban residents, do. Thus the prevalence of asbestos bodies in nonoccupationally affected persons may reasonably be regarded as a reflection of community exposure. Routine autopsy series show prevalences varying from 20 to 60 percent, with generally higher counts in urban vs. rural populations, in men than in women, in persons living close to industrial sources and users of asbestos than in other parts of the same city. Highest counts are found in asbestos workers. With electron microscopy, asbestos fibers were identified in nearly all lung tissue examined from a sample of New York City residents (Langer et al, 1971). The utility of quantifying low dose asbestos exposure in epidemiologic studies by electron microscopic

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examinations has not been assessed and is limited by the expense of the procedure and access to lung tissue for representative samples of study groups.

2. Pleural Plaques

Pleural plaques occur as discrete, fibrotic or calcified lesions on the parietal pleura and on the diaphragm. The plaques are often multiple and bilateral and are visible on roentgenograms of the lungs. The association between pleural plaques and asbestos exposure, both environmental and occupational, has been repeatedly demonstrated in population studies. Pleural plaques are sometimes found in chest films of persons environmentally exposed to asbestos and are thus more likely to be observed than are parenchymal changes in persons exposed to low levels of asbestos. Whereas parenchymal changes on chest films are more related to asbestos dust concentrations, the prevalence of pleural plaques appears to be more related to time since first exposure. Of themselves, pleural plaques do not give rise to clinical symptoms or functional impairment.

In a study of household contacts of asbestos factory workers (Anderson et al, 1979), pleural abnormalities (including plaques and thickening of pleura) were found among 26 percent of persons resident in the same household during the employment period of an occupationally

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exposed worker but in only 2 percent of controls. None of the household contacts had known occupational exposure to asbestos.

The disease significance of pleural plaques has not been fully evaluated. Compared with controls, a group of construction workers exposed to asbestos and having pleural plaques without parenchymal involvement on chest films had significantly reduced lung function (Hedenstierna et al, 1982). On stratification by smoking habits, the difference was found only among non-smokers. However, since this study was cross sectional, it was not possible to determine whether pleural plaques preceded the development of reduced lung function and whether asbestos dose rather than the presence of a pleural plaque was the true determinant of impaired lung fuction. McMillan and Rossiter (1982) compared shipyard workers with and without pleural abnormalities; both groups were free of parenchymal lesions at the start of the study. Over a 10-year period, the incidence of parenchymal fibrosis in the group with pleural abnormalities was 4.5 percent vs. 0.6 percent in the other group. The type of pleural lesion at start of study, time since first exposure, occupation, age and smoking habit did not predict which workers subsequently were affected with parenchymal fibrosis. The authors suggest that pleural lesions in asbestos exposed workers may not be mere markers of exposure but may identify those at greatest risk of parenchymal fibrosis. However,

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the intensity of asbestos exposure may have been the determinant of parenchymal fibrosis in this study. The applicability of these findings to low dose environmental exposures is unknown. In another study of persons with asbestos-related pleural plaques and otherwise normal chest films (Fredriksson et al, 1981), lung function tests revealed decreased lung volumes and decreased elastic recoil of the lungs compared with standard predicted values. Significant correlations of these changes were found with measures of asbestos exposure and extent of pleural changes. This study was lacking in population controls for major determinants of lung function and also suffered from the limitations of a cross sectional study.

The long term significance of pleural plaques is difficult to assess. No studies have been reported that are capable of resolving the question whether persons with pleural plaques are thereby at increased risk of asbestos related disease independent of the intensity and duration of asbestos exposure. Pleural plaques, if they are associated with subsequent disease outcomes, are likely to represent an independent reaction rather than an intermediate event in the causal chain between asbestos exposure and disease. The primary epidemiologic and clinical importance of pleural plaques is their value as a marker of asbestos exposure, apparently even for low doses, and as a stimulus to look carefully for more important asbestos related disease outcomes.

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3. Asbestosis

The clinical diagnosis of asbestosis depends on a constellation of findings, which may include radiographic signs of pulmonary fibrosis, breathlessness, abnormal pulmonary function, and crepitations heard on auscultation of the lung. The essential feature of the diagnosis is a history of asbestos exposure but this is often not elicited unless asbestosis is specifically considered in the differential diagnosis. Asbestosis can both appear and/or progress many years after removal from exposure. This latency and nonspecificity of disease manifestation makes it difficult to estimate dose-response relationships for asbestosis.

Peto (1978) argues that it is reasonable to postulate a safe threshold for mortality from asbestosis. If this is true, asbestosis mortality would not be expected from low dose asbestos exposure, and risk of mesothelioma and/or lung cancer should be determinants of the public health limits to low level asbestos exposure, since these outcomes appear to be linearly related to dose without a threshold. Still, current occupational standards are based on the risk of asbestosis, and efforts have been made to estimate the risk of certain signs of asbestosis. As for most similar chemical or physical exposures, accurate dose-response data at the low end of the curve (below 1 fiber/ml for asbestos) are unlikely to be obtained by direct

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observation and must usually be derived by extrapolating from higher doses. Thus the form of the curve at the low end cannot be determined empirically.

Dose-response data on "certified" asbestosis and cumulative exposure to asbestos are available from two studies, one from an asbestos textile factory in England (Berry and Lewinsohn, 1979) and the other from an asbestos cement factory in Ontario, Canada (Finkelstein, 1982). The study end-point, "certified" asbestosis, is generally comparable in the two studies in that the diagnosis of asbestosis was reviewed and confirmed by a panel of medical advisors to the respective official government compensation board, and the same clinical findings were considered by both groups, although a formal comparison of the criteria for certification has not been made.

In the study by Berry et al (1979), dose-response calculations were restricted to 197 workers employed only after 1950 and followed to 1975. The average interval from first exposure to end of follow-up was 16 years. Fiber counts were not available for 1951-60 but were estimated from thermal precipitator particle counts available for 1952 and 1960. All estimates were based on area samplers. Finkelstein's dose response calculations were based on 157 production workers exposed to asbestos dust for at least one year prior to 1961, employed for at least 15 years, and followed to 1980. Cumulative probabilities of having developed asbestosis were calculated from first exposure

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through the thirty-second year of follow-up, and the measure of exposure was the cumulative exposure in the first 18 years from initial exposure. Although dose estimates were based on personal sampling for asbestos fibers by the membrane filter method, this sampling procedure was not introduced until 1969, and prior doses were estimated from impinger samples collected between 1949 and 1968 and related to the 1969-1970 baseline personal samples for the various jobs held by production workers. Both reports obtained dose response estimates with life table methods and assumed that the logit of the incidence of asbestosis was proportional to the log of the dose.

Table I-1 tabulates results from the two studies as given in the discussion section of Finkelstein's paper. Differences in the two studies may be attributable to differences in the length of follow-up, differences in measurements and estimates of fiber concentrations (particularly for the years preceding use of the membrane filter method), and differences (probably slight) in the criteria for certifying asbestosis. As shown in Table I-1, mean fiber concentrations were similar between 1951 and 1972 in both studies and estimates of the average annual incidence rates at the same ranges of asbestos exposure were also similar. Reported differences in prevalence rates at the same asbestos exposure in the two studies may be explained by differences in survival. In each study, the probability of developing "certified" asbestosis falls to zero or near

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TABLE I-1

Comparison of Dose-Response Estimates[a]

		Berry et al (1979)	Finkelstein (1982)
Number of workers		197	157
Length of follow-up		16 years average 23 years maximum	18 years minimum 32 years maximum
	Years		
Mean fiber Concentration (f/ml)	1951	10.8	11.5
	1956	5.3	7.6
	1966	5.3	4.3
	1972	2.4	2.1
	f-y/ml		
Average/annual Incidence Rate	0-49	0.4%	0.7%
	50-99	1%	1.6%
	100-149	2%	2.4%
	f-y/ml		
Prevalence of Certified Asbestosis	50-99	2.5%	4%
	100-149	8.5%	6%

[a]Berry et al, 1979 and Finkelstein, 1982.
[b]End point is "possible" rather than certified asbestosis under the assumption that these cases would become certified if the study population was followed-up beyond the average of 16 years.

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zero for cumulative exposures of 10f-yr/ml or less. However, Berry and Lewinsohn (1979) in plotting incidence of "possible asbestosis" per person year of observation for cases (among workers in a textile factory in England) occurring since 1966 as related to the cumulative exposures up to 1966, observed a linear relationship compatible with a no-threshold interpretation. An incidence of 0.5% per person year (based on two cases) was found in association with a cumulative dose of approximately 35 fiber years/ml, the lowest dose at which cases were identified. This dose estimate has since been revised upwards (Peto, 1980).

Weill et al (1973) in a cross-sectional study of 908 American asbestos-cement factory workers, found the prevalence of diffuse radiographic opacities to be related to the magnitude of cumulative dust exposure. However, the study end-point, diffuse radiographic opacities, is not comparable to that of Berry et al and Finkelstein and hence was not incorporated into this evaluation of asbestosis risk.

Whether there is a threshold dose for the probability of developing asbestosis cannot be decided from these or other empirical data. Even if many more observations were available for workers exposed to very low asbestos concentrations (0.1-1.0 fibers/ml) and followed for 30-50 years, the dose-response relationship would vary as a function of a number of arbitrary assumptions such as half-life for

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asbestos fibers in the lung, the appropriate lag period for the development of asbestosis from a delivered dose, the appropriate weighting for earlier versus more recent asbestos exposures, and the contribution of modifying factors such as cigarette smoking and other respiratory system insults. The Panel knows of no reports of disabling asbestosis occurring among persons whose maximum exposure to asbestos was of the order of 1 f/ml or less. Hence, it is likely that, as Finkelstein (1982) concludes, "the major risk at lower exposures will be due to cancer rather than to asbestosis".

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J. DOSE-RESPONSE RELATIONSHIPS

1. Age, Time and Dose-Dependence of Lung Cancer and Mesothelioma

a. Introduction

The risks that may be caused by the levels of asbestos exposure in most modern factories, or the even lower levels in schools, other buildings, or urban air, are possibly too low to produce an easily detectable increase in mortality for any disease with the possible exception of mesothelioma. To predict these risks, it is therefore necessary to extrapolate from observations of more heavily exposed industrial cohorts. For this purpose, the effects of intensity and duration of asbestos exposure, age, cigarette smoking and fiber type must be known for each asbestos-related disease, since bronchial carcinoma, mesothelioma and asbestosis rates exhibit quite different relationships with these factors.

b. Linearity of dose-response

Available data are consistent with the assumption that excess mortality from lung cancer and mesothelioma following a fixed duration of exposure is proportional to the airborne concentration of asbestos and increases with increasing duration of exposure, but severe limitations on the quality of past exposure measurements limit the quantification of this observation. The most direct evidence for

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linearity of response comes from three studies that compared lung cancer mortality to the total dose of asbestos inhaled (Henderson and Enterline, 1979; Liddell et al, 1977; Dement et al, 1982). Figure J-1 shows the dose-response data in these studies in which the ratio of observed to expected lung cancer mortality is plotted against the estimated cumulative exposure dust count. While different dose-response relationships exist for the three circumstances, each suggests a linear relationship over the entire range of observation.

While all three studies suggest a linear dose-response with cumulative exposure, there are too few cases in these studies to specify accurately the shape of the exposure intensity-response curve after adjustment for duration of exposure. Separate analyses by duration and intensity show a less impressive relationship with intensity than with cumulative dose (cf. Fig. J-1 and Table J-1A). In one study of chrysotile miners employed for over 20 years, for example, an increase in mean estimated dust level from 19.2 to 46.8 mppcf produced a small and non-significant increase in relative risk (Table J-1B).

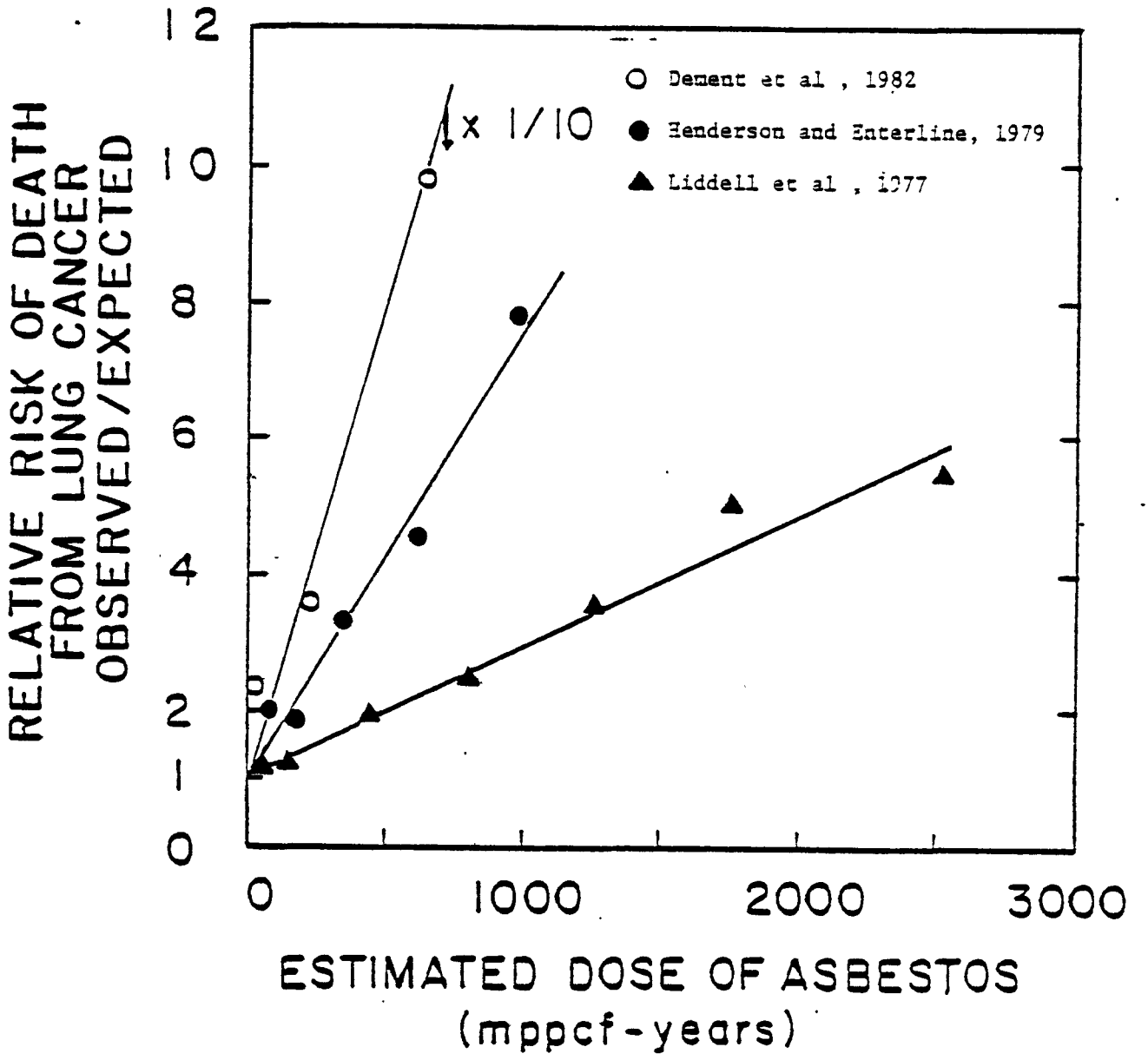
The difference in the slopes found in the three studies may relate to differences in the quantity of the other dust present, the fiber size distribution, and the representativeness of the dust sample program. These factors will be discussed later when the dose-response relationships of all available studies are compared.

Less extensive data are available on the dose-response relationship for mesothelioma (Seidman et al, 1979; Hobbs et al, 1980; and Jones et

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Figure J - 1

The Ratio of Observed to Expected Deaths from Lung Cancers Observed in Three Studies of Asbestos Workers According to Cumulative Exposure in Millions of Particles per Cubic Foot - Years (MPPCF-YR) [a,b]



[a] Note that the dose values for the study of Dement et al, are to be divided by by 10, i.e., a relative risk of 10 is achieved at a cumulative exposure of 65 mppcf-yr.

[b] Dement et al, 1982; Henderson and Enterline 1979; Liddell et al, 1977

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Table J - 1A

Lung Cancer Incidence in Quebec Miners and Millers by Duration and Level of Exposure[a]

GROSS SERVICE		EXPOSURE LEVEL LOW-MED.	HIGH-VERY HIGH
<5 YEARS	OBS.	49	27
	EXP.	50.7	32.7
	O/E	0.97	0.83
>5 YEARS	OBS.	75	79
	EXP.	62.4	38.8
	O/E	1.20	2.04

[a] McDonald et al, 1980

TABLE J - 1B

Analysis of the Most Heavily Exposed Men (Subdivision of lower right-hand cell of Table J-1A)[a,b,]

GROSS SERVICE		HIGH	VERY HIGH
5-20 YEARS	OBS.	7	16
	EXP.	8.4	7.4
	O/E	0.83	2.16
	LEVEL[c]	17.0	62.3
OVER 20 YEARS	OBS.	24	32
	EXP.	10.9	12.1
	O/E	2.20	2.64
	LEVEL[c]	19.2	46.8

[a] McDonald et al, 1980
[b] The lung cancer rates on other cells in Table J-1A are not significantly raised.
[c] Mean million particles per cu. ft. years.

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al, 1980b). Table J-2 lists mesothelioma mortality (in terms of cases per 1,000 person-years of observation beginning 10 years after first exposure). While few deaths are available for analysis, the data for exposure periods longer than 3 to 5 months are consistent with a linear relationship. There were no deaths from mesothelioma observed in any of the lowest exposure categories, whereas 1 to 2 would have been expected in each study on the basis of a linear dose-response relationship. It thus appears that the assumption of a roughly linear relationship is unlikely to greatly underestimate the risks from brief exposures.

c. Lung cancer

The most extensive information on time course of lung cancer is from the large study of insulation workers by Selikoff et al (1979). Figure J-2 shows the relative risk (here taken to be the ratio of observed-to-expected deaths) of death from lung cancer according to age for individuals first employed between ages 15 and 24 and for those first employed between ages 25 and 34. As can be seen, the two curves rise with the same slope and are separated by approximately ten years. This suggests that the relative risk of developing asbestos-related lung cancer is independent of age and of the pre-existing risk at the time of exposure. In contrast, both the slope and the value of the added risk (attributable risk) are two to four times greater for those exposed at older ages compared to the younger exposure group. Figure J-3 combines these data and plots them according to time from onset of exposure. A

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Table J - 2

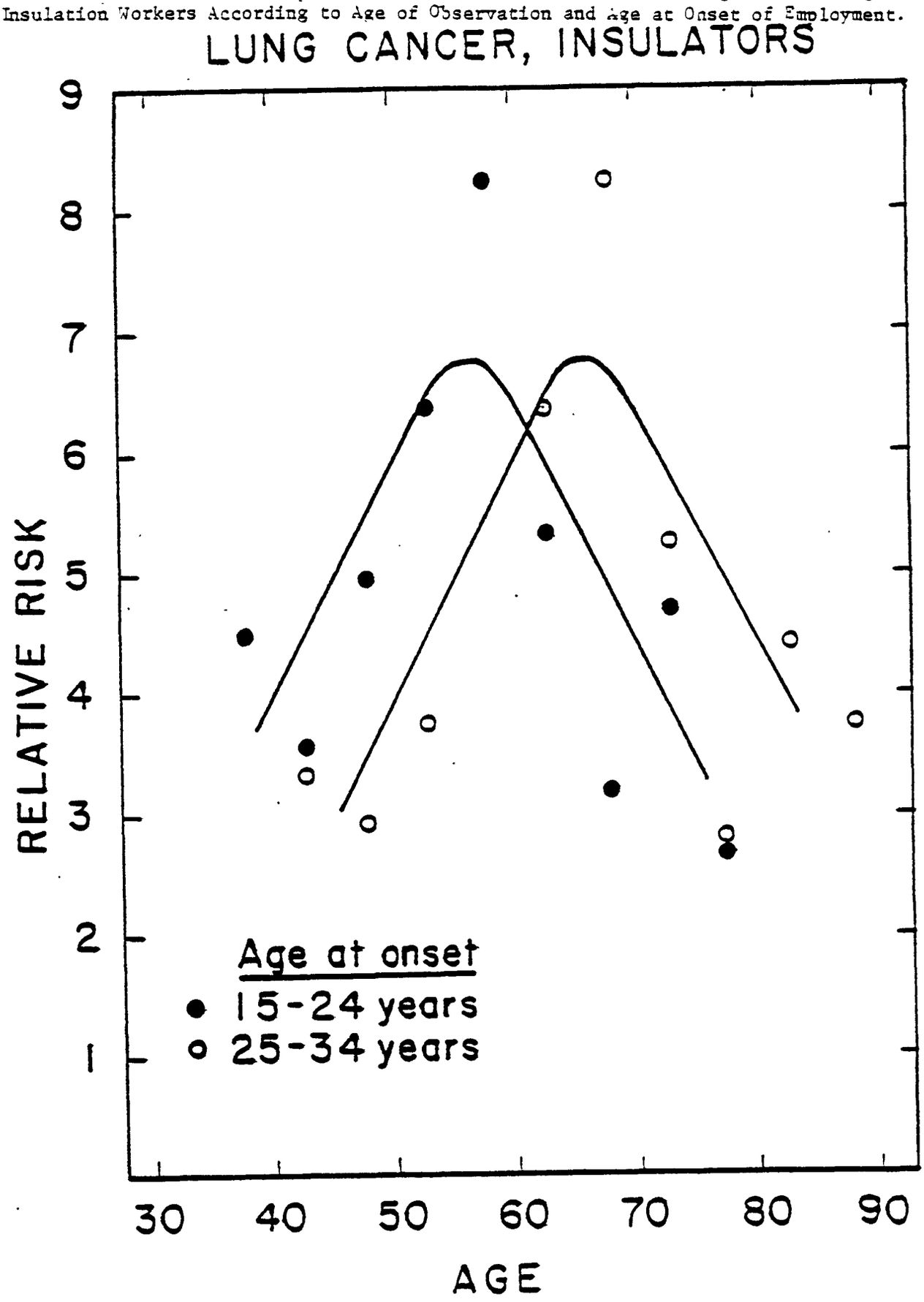
The Risk of Death from Mesothelioma According to Time of Asbestos Exposure in Three Studies

Exposure (range in months)	Mean	Number of deaths	Estimated person years 10+years from first exposure	Deaths/1000 person years
			Hobbs et al (1980)	
< 3		0	21,213	0
3 - 11		10	19,548	0.5
12+		16	14,833	1.1
			Seidman et al (1979)	
6	2.2	0	6,640	0
6-11	7.1	3	2,000	1.5
12-23	15.4	4	2,290	1.7
24+	57	7	2,480	2.8
			Jones et al (1980b)	
			# Exposed	% of all deaths
< 5		0	314	0
5 - 9		3	116	2.6
10 - 19		4	145	2.8
20 - 29		4	101	4.0
30+		5	51	9.8

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Figure J - 2

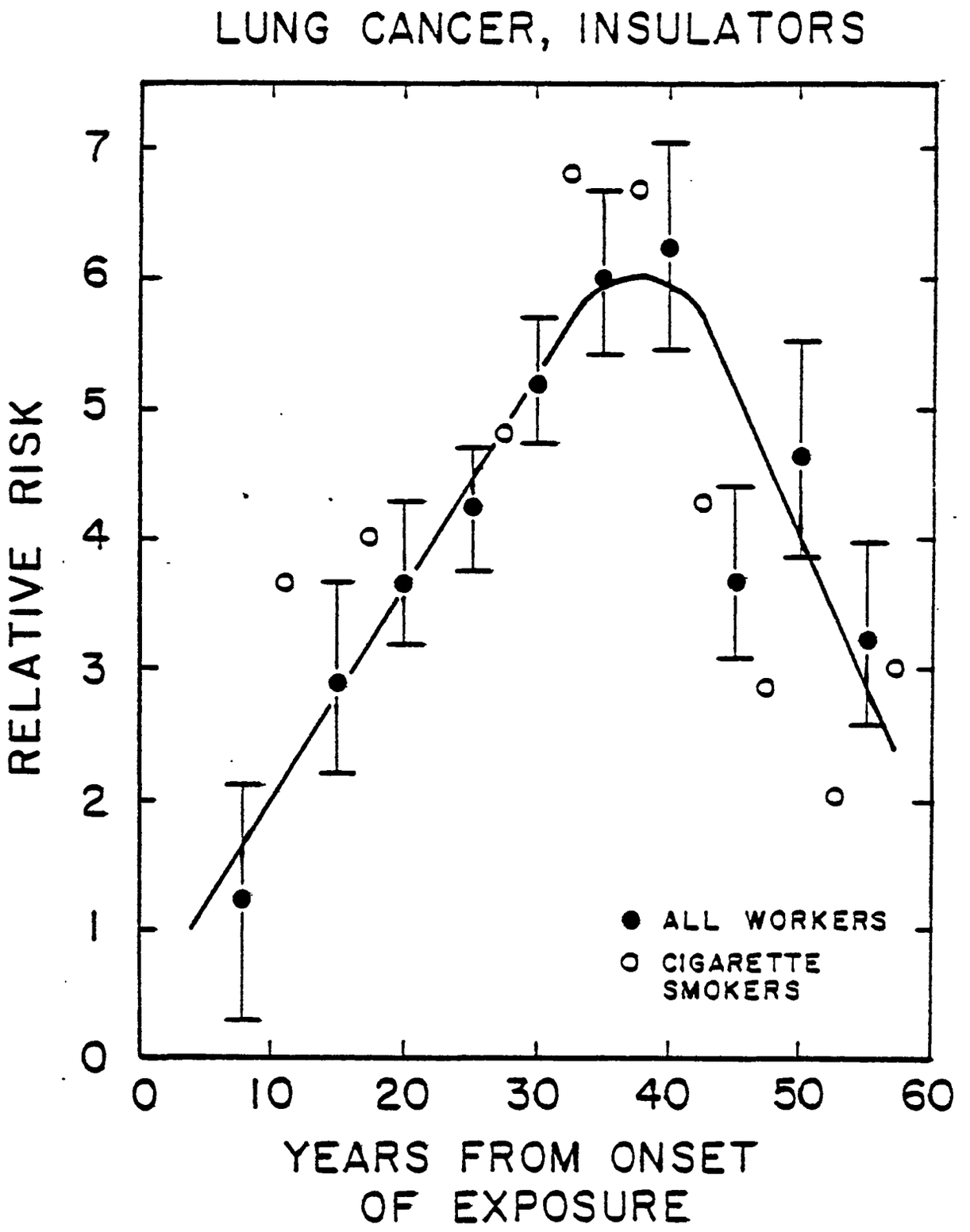
The Ratio of Observed to Expected Deaths (Relative Risk) from Lung Cancer Among Insulation Workers According to Age of Observation and Age at Onset of Employment.



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Figure J - 3

The Ratio of Observed to Expected Deaths (Relative Risk) from Lung Cancer Among Insulation Workers (Aged 15-34 Years at Onset of Employment) According to Time from Onset of Employment.[a]



[a] Open circles refer to workers who were cigarette smokers at the start of observation.

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linear increase with time from onset of exposure is seen for 35 to 40 years (to about the time when many insulators terminate employment).

After 40 years the relative risk fell, rather than remaining constant after cessation of exposure as might be expected from the observation of a linear increase with continued exposure. The decrease was, in part, the result of the earlier deaths of smokers from the group under study from lung cancer and cardiovascular disease. However, the decrease was not solely the result of the early deaths of smokers since a similar rise and fall occurred among those individuals who were smokers at the start of the study compared to smokers in the general population. (In calculating the relative risk of lung cancer in smokers, smoking specific data from the American Cancer Society study of one million people were utilized.) Another possible factor is the confounding of the period of first exposure and the time since first exposure as the period of observation in this study is relatively short. Such a cohort effect would occur if those first employed prior to 1935, who contributed to the long follow-up groups, had an average exposure less than those first employed after 1935, who contributed to the shorter follow-up groups. One possible period of high exposure would be World War II. Part of the decrease may relate to the elimination of asbestos, particularly chrysotile, from the lung. Finally, differing individual biological susceptibilities may play a role. However, the magnitude of these effects at lower doses can not be estimated from the data on insulation workers. It would be expected that the selection effects discussed above would be less important in less heavily exposed

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cohorts. The rise and fall in relative risk is also seen in mortality studies of groups exposed to certain other carcinogens.

In view of these uncertainties, the model for lung cancer risk that has been adopted does not include an eventual fall of relative risk. It is thus assumed that at lower exposure levels the increase in relative risk will be proportional to cumulative exposure, and will remain constant after exposure ceases. If the rise and fall in relative risk observed in the insulators is a general phenomenon and also occurs at lower levels of exposure, our extrapolation from observations on this or other industrial cohorts could either over or underestimate the lifetime risk depending on the period of follow-up. However, if our assumed model is not correct and the observed fall in relative risk is due entirely to selection effects, our estimates of lifetime risk at low levels will tend to be systematically too low, perhaps by a factor as much as 2 to 3 fold when extrapolation is based on the mortality experience of retired workers such as those studied by Henderson and Enterline (1979)

Figures J-2 and J-3 are also consistent with a linear relationship between cumulative dose and increase in relative risk. The relative risk increases linearly with time since first exposure up to 35 years, a period when most insulators were continuously exposed. Over this period, time since first exposure is therefore roughly proportional to cumulative dose in this cohort. These data also suggest a lag of the order of 10 years, or perhaps even less, before any effect is manifest.

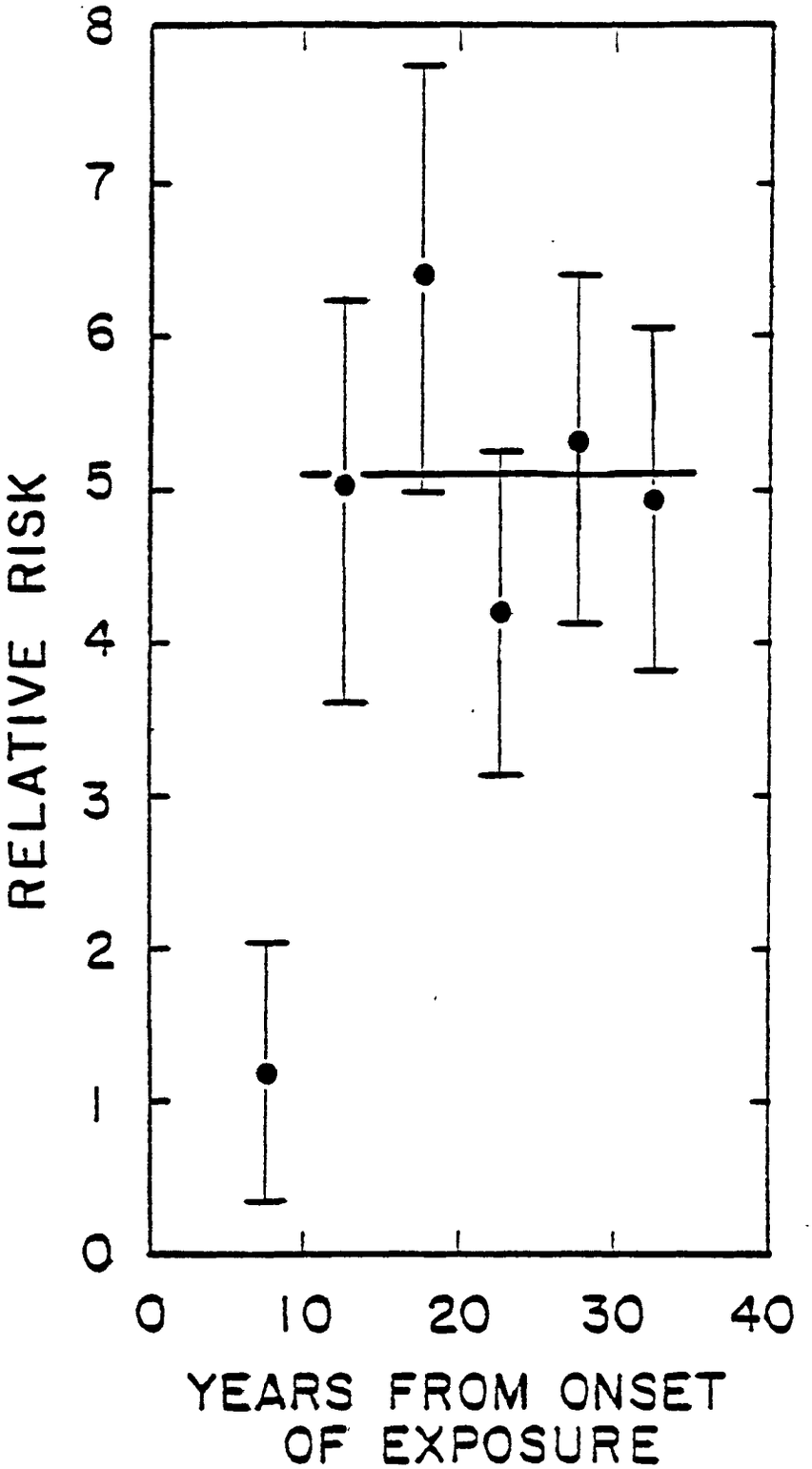
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The data of Seidman et al (1979) also show that the effect of external exposure to asbestos is to multiply the pre-existing risk of lung cancer in the absence of exposure and, that the multiplied risk becomes manifest in a relatively short time. Figure J-4 depicts the time course of the lung cancer mortality beginning five years after onset of exposure for lung cancer of a group exposed for short periods of time. Because 77% of the population was employed for less than two years, exposure had largely ceased prior to the beginning of the follow-up period. As can be seen, the relative risk is significantly elevated within ten years, and then remains constant throughout the observation period of the study. Furthermore, the relative risk from a specific exposure is independent of the age at which the exposure began, whereas the attributable risk would increase considerably with the age of exposure. Table J-3 shows the relative risk of death from lung cancer for individuals exposed for less than and greater than nine months according to the age at the time of entrance into a ten year observation period. Within a given age category, the relative risk is similar at different decades from onset of exposure, as was seen in Figure J-4 with the overall data. However, the relative risk also is independent of the age decade at entry into a ten-year observation period (see lines labeled "All" in each exposure category). There is some reduction in the oldest groups. This can be attributed to the same effects manifest at older ages in insulators and to relatively fewer cigarette smokers who might be present in the older age groups because of selective mortality.

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Figure J - 4

Short Time Amosite Workers[a]



[a]The ratio of observed to expected deaths from lung cancer among amosite insulation production employees according to time from onset of exposure.

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Table J - 3

Relative Risk of Lung Cancer during Ten Year Intervals at Different Times from Onset of Exposure[a]

Years from onset of exposure	Age at start of period of observation		
	30-39	40-49	50-59
	Shorter exposure (<9 months)		
5	0.00 [0.35]	3.75 (2)	0.00 [3.04]
15	6.85 (1)	4.27 (3)	2.91 (4)
25	—	2.73 (2)	4.03 (6)
All	3.71 (1)	3.52 (7)	2.58 (10)
	Longer exposure (>9 months)		
5	0.00 [0.66]	11.94 (4)	9.93 (8)
15	19.07 (2)	11.45 (5)	5.62 (5)
25	—	13.13 (6)	7.41 (8)
All	11.12 (2)	12.32 (16)	7.48 (21)

[a] Seidman et al 1979.
( ) = Number of cases
[ ] = Number of cases "expected" on the basis of the average relative risk in the overall exposure category.
— = No cases seen.

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These results can be summarized by the formula:

L_L (a, s, d, f) = L_U (a, s) x (1 + K_L x d x f). (Equation J-1)

L_L (a, s, d, f) denotes lung cancer incidence among asbestos workers aged a who smoke s cigarettes per day and have been exposed for a total duration of d years at an average level of f fiber/ml. L_U (a, s) denotes lung cancer incidence at the same age a in an unexposed population with similar smoking habits, and K_L is a constant, probably characteristic of the mineral type and distribution of fiber dimensions of the asbestos. The relative risk, which equals 1 + K_L x d x f, is thus increased in proportion to d x f, the cumulative dose (fiber/ml years). In applying Equation J-1, it is necessary to take into account a lag time of about 10 years for the effect of a given exposure to be manifest.

d. Mesothelioma

For both pleural and peritoneal mesothelioma, there is a clear increase in risk with increasing duration of exposure (Newhouse and Berry, 1979; Hobbs et al, 1980). Incidence rises as the third or fourth power of time in some studies (Peto et al, 1982), and the risk is more or less independent of smoking (Hammond et al, 1979) and age at first exposure (Peto et al, 1982). This incidence pattern suggests that asbestos acts as an initiator of mesothelioma. Such a pattern would be

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expected if the effect of each day of exposure is an addition to overall incidence proportional to the intensity of exposure on that day (Peto, 1979), and either proportional to the cube of time since that day, or to the square of time with a latency of 10 years. For either of these models, the incidence 20 or more years after first exposure will be roughly proportional to a power of time since first exposure of between 3 and 4 for any duration of exposure.

The model incorporating a delay of 10 years in the response function provides a better fit to the observed data both in earlier and later periods however, and predicts a less steep increase at times more than 50 years from onset of exposure, where our knowledge of time dependence is lacking. The corresponding formula, which we will use as a model for mesothelioma incidence is the function:

Equation J-2

$$L_M(t, f, d) = K_M f\,[(t - 10)^3 - (t - 10 - d)^3] \qquad t > 10+d$$

$$= K_M f\,(t - 10)^3 \qquad 10+d > t > 10$$

$$= 0 \qquad 10 > t$$

where t denotes years since first exposure, f is level of exposure in fiber/ml, and d is duration of exposure in years. The constant K_M depends on the type and fiber dimensions of the asbestos.

In practice, of course, the exposure level f will vary over time, and if the increase in incidence caused by each increment of exposure is indeed proportional to the product of level of exposure and the square

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of time since the exposure occurred with a lag of 10 years, the incidence at time T + 10 years will be proportional to the integral up to time T of f(t), the exposure level at time t, multiplied by $(T - t)^2$. Such a complex model is of little value, however, as variations in past exposure are never accurately known.

The model represented in equation J-2 accords with current theories of carcinogenesis, and provides a satisfactory explanation of the epidemiological data on mesothelioma incidence up to 45 years after first exposure. In the two studies (Selikoff et al, 1979; Nicholson et al, 1983) where individuals first exposed 45 or more years previously were included, the risk rose as a power of time but ceased to rise or fell in the longest time periods from onset categories. This flattening or decrease could, however, be due to the selection effects at high exposure and perhaps cohort effects, discussed above in relation to lung cancer. The incidence predicted by equation J-2 depends strongly on time from onset of exposure and is independent of age. Some "lag" between first exposure to asbestos and first appearance of the disease is supported by the epidemiological data, but it cannot be estimated accurately, and the choice of 10 years in equation J-2 is somewhat arbitrary.

The equation implies that asbestos acts early in the development of mesothelioma rather than later. The predicted eventual incidence is not strictly proportional to duration of exposure, and is hardly increased by prolonging exposure beyond 20 years. Asbestos may also act at a later stage in the development of mesothelioma, as it appears to for

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lung cancer. It is imposible to assess with any confidence the effect this might have on the incidence formula. The suggested equation for mesothelioma incidence is obviously subject to uncertainty, and should be refined as further data become available.

At first sight it seems paradoxical that the suggested incidence for mesothelioma at a given time after exposure is independent of age while the lifetime risk is far greater when exposure occurs at a young age. This is because the risk increases rapidly with time since exposure, and lifetime risk is therefore greater in those whose life expectancy is greatest at the time of first exposure.

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2. Dose-Response Slopes (K_L) for Lung Cancer

a. Data Quality Considerations

Since the validity of a study's inferences depends on the accuracy of the underlying data, this review of epidemiologic studies in which dose-response relationships have been reported includes: an assessment of the quality of the exposure data, the detail of the risk assessment, the apparent appropriateness of the comparison population, and evidence of internal consistency as demonstrated by the observation of a risk gradient with increasing exposure.

It should be noted that asbestos exposures have been expressed differently over the years. In early studies the measure of exposure intensity involved counting collected particles of all types, most of which were not asbestos. More recent measurements enumerate asbestos fibers longer than 5 μm. In this report, unit risks for lung cancer and mesothelioma will be expressed in relation to cumulative fiber exposures. Thus, conversions of particle counts, expressed as millions of particles per cubic foot (mppcf), to fiber concentrations in f/ml must be made. No single conversion factor applies to all asbestos work places. The conversion factors for a given process are uncertain because of limitations in the number of side-by-side determinations of particle and fiber concentration and their considerable variability. Nevertheless, the uncertainly of an average conversion factor for a

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given process is very much less than the differences in unit risks found in different studies.

Similarly considerable uncertainties exist in studies where past asbestos exposure estimates are based on fiber concentrations measured in what are believed to be work activities characteristic of those of past years. Processes, materials and ventilation conditions may have changed with time and estimating the effect of these changes introduces uncertainties in past fiber exposure estimates. However, these uncertainties are also much less than the differences in unit risks found in different studies.

For both exposure data and risk detail, two levels of completeness are considered. The exposure data available to studies consist either of job histories and industrial hygiene measurements made at the relevant exposure site (Level 1 exposure data), or of surrogate measures of exposure time, with hygiene measurements adopted from other exposure sites (Level 2 exposure data).

In analyzing risk in order to obtain a dose-response relationship, two approaches were used in the studies reviewed: (1) risks are calculated separately for several subgroups having different (cumulative) exposures, which should increase with increasing exposure. A dose-response relationship is obtained by fitting a regression equation to these data points, and (2) overall risk and mean (cumulative) exposure are estimated for the entire populations, with a

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dose-response relationship based on this single data point, assuming the dose-response line passes through the origin (no excess risk for zero exposure).

The first, more detailed, approach allows examination of the consistency of a study's findings; inferences from studies demonstrating such consistency should be given greater attention than studies without evidence of such consistency. For example, if risk is reported for separate exposure groups but no sensible pattern of risk with increasing exposure levels is observed, then the validity of the dose estimation and/or the risk estimation must be questioned. If risk at very low exposure levels is found to be substantially elevated, then the possibilities of systematic underdetermination of dose or overestimation of risk, perhaps because of an inappropriate comparison population or the inclusion of a highly susceptible sub-population, must be considered. Conversely, demonstration of a gradient of risk with exposure, with a reasonable level of risk for the lowest exposure group, provides important validation (on an ordinal scale) of the exposure estimates and choice of comparison population. High risk at low levels of exposure could also imply the existence of a highly sensitive sub-population.

Studies reporting only a single data point (overall risk for a population with an estimated overall mean exposure) do not provide any measure of internal validation for the exposure estimation procedure. Moreover, accurate estimation of the mean (cumulative) exposure is usually difficult if there are no estimates of exposure for individuals

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in the cohort. Estimating this mean as the product of the mean intensity and the mean exposure time is the most reasonable procedure in the absence of individual exposure histories. However, this process will not always provide an accurate estimate of the mean exposure.

Such a problem occurred in estimating mean cumulative levels in a British textile factory (Peto et al, 1977). Early estimates of exposure were too high; the error was discovered when subsequent examination of individual job histories showed that employees had spent more time in the less dusty areas than originally believed. This error was correctable because industrial hygiene data and job histories were available to provide reliable estimates of the mean exposure intensity and duration. Obtaining an accurate estimate of mean cumulative exposure in the absence of such information is, of course, more difficult.

Clearly accurate information is also important for estimates of the cumulative exposures of individual workers. However, this is not always available. Complete job histories are not always available for each worker; sometimes only employment durations may be known. Relatively few dust counts were made prior to 1970 and exposure data may not exist for many jobs in a plant. Worker mobility during a work day may significantly alter his exposure from that determined at a specific work station. To the extent that such circumstances exist, there will be uncertainties in the estimates of individual exposures.

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A final data quality consideration is the statistical precision of a given study. If few deaths are observed or the relative risk of lung cancer as expressed the study is low, the 95% confidence limits (from statistical considerations alone) on the calculated estimates of K_L are very large; in some of the studies reviewed the 95% confidence range exceeds an order of magnitude.

b. Review of Studies

This review first considers studies with Level 1 exposure data (job histories available, industrial hygiene measurements made at the site of exposure), followed by those without such information (Level 2). The estimates of the increase in the standardized mortality ratio for lung cancer per unit dose, from these studies, are summarized in Table J-4.

Level 1 Exposure Data Studies

(1) Canadian chrysotile miners and millers (McDonald et al, 1980) (n = 11,379, 245 lung cancers, earliest exposure data for cohort - 1949)

Two analyses estimating a dose-response relationship were performed, one based on a case-control approach with adjustment for smoking, the other using the full cohort.

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Table J - 4

Estimates of Increase in Standardized Mortality Ratio for Lung Cancer (SMR) per Unit Increase in Cumulative Asbestos Exposure

Occupational Exposures	Fiber Type	Number of Lung Cancer Deaths	Increase in SMR per Unit Increase in Dose* Dose In mppcf-yr	Dose In f/ml-yr
Level 1 Exposure Data				
A. Studies with an observed gradient of risk with mean exposure level				
Mining (McDonald, 1980)	Chrysotile	245	.14	
Retirees (Henderson et al, 1979)	Mixed	63	1.3+ (.66)	
U.S. Cement (Weill et al, 1979)	Mixed	51	.44	
U.S. Textile (Dement, 1982)	Chrysotile	26	6.8+ (13.1)	
B. Studies without an observed gradient of risk with mean exposure level				
Mining (Rubino et al, 1979)	Chrysotile	11		.17
Friction Materials (Berry and Newhouse, 1983)	Mixed	106		.06
British Textile (Peto, 1980)	Mixed	30		1.00
Canadian Cement (Finkelstein et al, 1983a)	Mixed	20		4.82
Level 2 Exposure Data				
A. Studies without sufficient data given an observed gradient of risk with exposure level				
Mining (Nicholson et al, 1979)	Chrysotile	28	.30	
Amosite Products Users (Seidman et al, 1979)	Amosite	83-93		6.8
Insulation Workers (Selikoff et al, 1979)	Mixed	492-486		1.01

*Cumulative asbestos dose measured in million particles per cubic foot-years (mppcf-yr) or fibers per milliliter-years (f/ml-yr)

+After adjustment for possible biases

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In the case-control analysis, the dose-response relationship for lung cancer was found to be:

$$SMR = 100 + .14\ x,$$

where x is asbestos exposure in mppcf-yrs (accumulated to 9 years before death of the cases). A low gradient of risk with smoking in the high dust exposed groups casts doubt on the accuracy of the information on smoking and/or on the dust exposures or suggests some unknown bias in the estimate of excess lung cancer risk.

Results of the cohort analysis, using five exposure groups, were presented by McDonald et al, 1980 in a figure. A regression based on values estimated from this figure yields a slope similar to the case-control approach:

$$SMR = 100 + .146\ x.$$

An earlier report (McDonald et al, 1971) for this cohort reported that lung cancer rates in the mining region were two-thirds Quebec rates, which were used in this study. If regional rates were used for the calculation of expected lung cancer deaths, then the resulting slope would be estimated to be approximately .22.

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(2) Manufacturing retirees (Henderson and Enterline, 1979) (n = 1075, 63 lung cancers, earliest exposure data for cohort - approximately 1962).

Regression of the date for five exposure subgroups provide the relationship:

$$SMR = 101 + .66\ x,$$

where x is is mppcf-yrs.

Because the earliest industrial hygiene measurements were apparently made in the early 1960's (Enterline and Henderson, 1973), considerable extrapolation to earlier time periods was necessary (the cohort, consisting of all men retiring during 1941-1967, had an average employment duration of 25 years). The observed linear gradient of risk with cumulative exposure with an intercept of approximately 100 provides support for the expected rates used and the exposure groupings.

However, since follow-up of this group began at age 65, it is essentially a study of a survivor population and as such may have underestimated the maximum relative risk actually experienced by the entire manufacturing cohort. If this peak relative risk provides the best basis for predicting the long-term experience of individuals exposed at lower levels, then the fitted slope should be increased, perhaps by a factor of 2.0. This would yield an estimated equation of:

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$$SMR = 100 + 1.3\ x.$$

(3) Asbestos cement manufacturing workers (Weill et al, 1979). (n = 5,645, 51 lung cancer cases, earliest exposure data for cohort - 1952)

SMR's reported on workers with over 20 years of follow-up from initial exposure in five disjoint exposure categories resulted in a linear regression of:

$$SMR = 78 + .48\ x \text{ (x in mppcf-yrs)}.$$

Forcing an intercept of 100 yields:

$$SMR = 100 + .40\ x.$$

The low value of 78 for the estimated intercept may represent deficiencies in tracing this population overall, a result of relying solely on records of the Social Security Administration. If it is assumed that the SMR's for all exposure groups were 78% of the correct value, then all values should be increased by 28%, which would result in an estimated slope of .61.

However, with trace over 90% in the two upper exposure categories it is unlikely that substantial underestimation of the SMR's for these groups has occured; the effect of the low trace rate in the low exposure

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$$SMR = 160 + 11.0\ x.$$

(Note: Similar weighted regressions for other studies with risk reported for separate exposure categories did not produce substantially different slopes.)

The estimated intercept of 160 calls into question the appropriateness of the comparison population, as does the authors' report that lung cancer rates in the county of the plant are substantially higher than those of the U.S., the population used for comparison. Age-adjusted rates presented in the paper show that county rates are 1.75 those for the U.S., a ratio similar to the weighted regression intercept of 1.60. The authors, however, made a strong argument in support of the U.S. rates as the most appropriate comparison population.

With no evidence of a possible differential bias in the estimated SMR's among the various exposure categories (as contrasted with the Weill et al, 1979 study), it may be postulated that all data points were overestimated by a factor of 1.6. If this correction factor is employed, the equation becomes:

$$SMR = 100 + 6.8\ x.$$

These calculations have attempted to adjust for sources of variability and bias in the measurement of risk; if systematic error in

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categories may be evaluated by calculating the line using only the two upper categories and projecting through the origin. This yields the equation:

$$SMR = 100 + .44\ x.$$

Thus, problems of trace in the lowest exposure categories had little effect on the slope of the regression line.

(4) Chrysotile textile workers (Dement et al, 1982). (n = 768, 26 lung cancer cases, earliest exposure data for cohort - 1930)

The data reported for three exposure groups (in mppcf-yrs) exhibited an increasing trend in risk with increasing exposure and yielded a regression equation (using the mid-point of the exposure groups as the estimated mean exposure):

$$SMR = 120 + 13.1\ x.$$

The data point for the highest exposure group has a major effect on the regression equation (both the slope and intercept), but because the variance associated with it is high, less weight should be given to this point than to the other two. Using a weighted least squares regression taking into account the estimated variance of each point (based on a Poisson model for the observed (0) deaths in each exposure group), the equation becomes:

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the estimation of dose has occurred, then the slope would require further adjustments. Underestimation of exposure levels for this population might have occurred in view of the fact that estimated levels are far lower than those reported in a British textile factory which was in operation during the the same time period (Peto, 1980), although, as indicated earlier, early estimates from the British study were too high.

(5) British textile workers (Peto, 1980)

(n = 679 with at least 10 years of follow-up, 30 lung cancers, earliest exposure data for cohort -1951)

Although extensive fiber counting throughout the factory was performed beginning in 1951, individual exposure profiles were developed for only a portion of the population. Among men first exposed in 1951 or later and with at least 20 years of follow-up from initial exposure, there was an overall excess of lung cancers: 8 observed, 1.62 expected, for an SMR of 494.

A case-control analysis of these 8 cases and 40 matched controls, which included individual exposure reconstruction, found no gradient with exposure. This casts doubt on the validity of the exposure estimates.

Further questions, concerning the dose estimates arise because, contrary to a statement by Steel (1979) that static samplers provide a lower value for asbestos exposure than personal samplers, static

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samplers in this factory found levels 75% greater than those measured by personal samplers.

If reservations concerning the exposure estimates are set aside and if the mean cumulative exposure of those in the case/control analysis (300 f/ml-yr) is used as an estimate of the overall mean, then this (single-point) dose-response equation for the post-1950 cohort is:

$$SMR = 100 + 1.30\ x,$$

where x is in f/ml-yr.

Men exposed before 1951 did not exhibit SMR's as high as the post-1950 cohort, suggesting that exposure levels were not significantly higher during the earlier period. The SMR after 20 years from initial exposure for the two cohorts combined was 194 (30/15.5). Assuming an overall mean exposure of 300 f/ml-yrs and using a single-point extrapolation yields:

$$SMR = 100 + .31\ x.$$

The lack of agreement of these two slopes, together with the observation of no dose-response relationship in the case/control analysis, casts doubt on using the dose-response slope derived from this study.

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A previous analysis based on a single-point extrapolation (Peto, 1978) suggested a slope of 1.0. Since this value lies between those calculated above, this will be taken as the best estimate currently available.

(6) British friction materials workers (Berry and Newhouse, 1983). (n = 9,087, 106 lung cancers, earliest exposure data for cohort - 1967)

Estimates of early exposure levels were based on records of production, ventilation, etc., as well as on fiber counts made during simulation of past conditions. Individual exposure histories were constructed for those in the case/control analysis (based on 106 lung cancer cases occurring ten or more years after initial exposure.)

Relative risks for lung cancer exhibited no trend with exposure, a result which raises questions concerning dose estimation or indicating no association between cancer and exposure in this population. No excess risk was observed overall, which is consistent with the latter interpretation, or which raises questions about the appropriateness of the population from which expected numbers were calculated.

The published matched analysis found the relationhip:

$$SMR = 100 + .058\ x,$$

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where x is in f/ml-yr.

(7) Italian chrysotile miners and millers (Rubino et al, 1979) (n = 952, 11 (12?) lung cancers, earliest exposure data for cohort - 1969)

As in the Berry and Newhouse (1983) study, estimates of early exposure levels were based on past related records and fiber counting conducted during simulation of past conditions. Job histories were available for the entire cohort and were used with the estimated exposure levels to obtain individual cumulative exposure estimates. An analysis of those with 20 or more years since initial employment found an SMR of 115. Summarized measures of cumulative exposure suggest an overall mean of 323 f/ml-yr; the one-point dose-response relationship from these data is:

$$SMR = 100 + .05\ x,$$

where x is in f/ml-yr.

A case-control study of 12 lung cancer cases (smokers) and 41 controls found a higher risk in the upper exposure category. Mean exposures for the two exposure categories for the case-control study were not provided; these values for the entire cohort are not clear but values of 26 and 476 f/ml-yr may be inferred from one of the published

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tables. Using these values for the case-control study yields a slope of .29.

The paucity of data concerning exposure levels makes it difficult to have confidence in either dose-response result, and without measured levels in early years of operation of the mine, no other validation is possible. The best available estimate will be taken as the mean of the two slopes, 0.17.

(8) Canadian asbestos cement workers (Finkelstein, 1983a) (n = 241 exposed, 20 lung cancers, earliest exposure data - 1949)

Estimates of exposure levels were based on fiber counting performed in 1969-1970. Particle counts, available at various times starting in 1949, were used to estimate changes in exposure levels over time; these estimates of changes were applied to the 1969-1970 fiber counts to obtain estimated fiber levels for earlier periods.

A high lung cancer SMR of 606 (20/3.3) was found for this population, but subdivision of the cohort into three cumulative exposure categories found no gradient of risk with increasing exposure. In fact, the lowest age-adjusted lung cancer rate (11.9 per 1000 man-years) occurred in the highest exposure category, while a somewhat higher rate (13.6) was reported for the lowest category, and a rate approximately twice these (26.1) was found for the middle exposure group. No sensible dose-response for lung cancer can be inferred from these results.

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Possible explanations for these results are incorrect exposure estimates and/or very high competing risks for the heavily exposed persons.

If reservations concerning exposure levels are ignored, a one-point extrapolation using the overall SMR of 606 at the estimated overall mean 18-year cumulative exposure of 105 f/ml-yr results in the equation:

$$SMR = 100 + 4.82\ x.$$

(9) Level 2 Studies

(No job histories or industrial hygiene measurements available for the cohort, exposure estimates made from best available sources.)

(a) Long-term Canadian miners and millers (Nicholson et al, 1979) (n = 544, 28 lung cancers)

This cohort of workers, all of whom had worked at least 20 years by 1961, showed a overall lung cancer SMR of 252.

Job histories were not available, so individual exposure reconstruction could not be performed. This study population is a subset of that studied by McDonald et al, 1980. McDonald reported that the 3105 men in the two mines combined who had accumulated 20 years of employment by 1966 had an average cumulative exposure of 503 mppcf-yrs, based on individual dose reconstructions. Since the group in the

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smaller study had accumulated 20 years by 1961, it is possible that they were exposed to higher concentration levels, since some of their exposure occurred earlier. Concentration levels in Thetford Mines, the site of employment for the great majority of those in the smaller study, are reported to have been "always higher" (McDonald et al, 1980) than in the other mine. For these reasons 503 mppcf-yrs may be an underestimate of the actual mean exposure of this cohort, although the amount of underestimation cannot be estimated. If this value (503 mppcf-yrs) is used in a one-point extrapolation through the origin, then the dose-response equation is

$$SMR = 100 + .302\ x,$$

where x is in mppcf-yrs.

(10) Amosite factory workers (Seidman et al, 1979) (n = 820, 83 lung cancers by death certificate, 93 by best evidence of cause of death)

The majority of this cohort of workers in a Paterson, N.J. factory was recruited between 1941 and 1945, and the plant closed in 1954. Sixty-two percent of the men were employed for less than one year; the average duration of employment of all workers was 1.46 years.

No dust measurements were made in the plant. The best exposure estimates available for this plant are based on measurements made in two

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plants, (in Pennsylvania and Texas) during 1967-1971, using the same or similar equipment and producing the same product as the Paterson plant. These estimates were made at least 20 years after the majority of the cohort was employed, in different plants with possible different ventilation conditions.

Comparison mortality was calculated using New Jersey general population white male rates. Expected deaths were calculated on a generation life table basis and not on a person years at risk basis. The ratio of the overall observed percentage of deaths from lung cancer to the expected percentage, adjusted to a person-years-at-risk basis, is 4.46.

If the risk data are interpreted as similar to SMR's and if the estimated mean concentration of 35 f/ml is accepted, then the estimated mean cumulative exposure is 51.1 f/ml-yrs. and a one point extrapolation through the orgin produces a slope of 6.8. However, the very shortest employment groups (1 month, 1-2 months) have a more than two fold elevated risk. This calls into question the appropriateness of the analysis and/or the comparison rates, or implies the existence of a highly susceptible population, all of which raise questions about the validity of the linear dose-response relationship.

(11) Insulation workers (Selikoff et al, 1979)

(n = 17800, 429 lung cancers by DC, 486 by BE)

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This study of men who were members of the insulation workers' union in 1967 followed these workers over the ten-year period 1967-1977. For 12051 men (68%), follow-up occurred at a time 20 or more years after initial enrollment; overall, 29% of the cohort enrolled in the union prior to 1948, and an additional 39% enrolled between 1948 and 1956. After 20 or more years from onset of exposure using best evidence of cause of death, 450 lung cancer deaths were observed, compared with 93.7 expected (SMR=480).

Estimating the exposure of this cohort is extremely difficult because employment occurred in a wide range of industries and jobs, and no employment records other than union membership are available. Few dust measurements were made in these industries during the relevant time periods.

One of the few areas in which any measurements were made was shipyard work. However, it is not known what proportion of the cohort were in shipyards, although a substantial number may have been, at least during World War II. Measurements by Fleischer et al, in four shipyards in 1946 found very high average levels on board ships in three yards (means of 49-142 mppcf), but substantially lower in the fourth (11 mppcf). Levels in the shops of these yards were lower (means of 14-32 mppcf) but only 12% of workers in the four yards were employed in the shop. A study of conditions in some of these yards showed the same particle concentrations in 1965 - 1966 (Murphy et al, 1971).

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Levels would be expected to have decreased considerably since that time. A study by Harries in 1971 reported this general trend in a survey of British ship repairing, although concentration levels (f/ml) varied dramatically among the areas sampled and some mean concentrations were very high.

These shipyard data relate to only one type of work performed by members of this union. The individual work activities in commercial and industrial construction varied considerably and took place in a wide variety of structures with different ventilation conditions. In spite of these difficulties an estimate of 15 f/ml as the average fiber exposure of insulators has been derived (Nicholson, 1976) using the Fleischer (1946) study and measurements made in 1968 - 1970 by several research groups.

Using 15 f/ml as the estimated average concentration of exposure for this cohort and assuming an average of 25 years of exposure, a one-point dose-response estimation yields:

$$SMR = 100 + 1.01\ x,$$

where x is in f/ml-yr.

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c. Conversion of Particle Counts to Fiber Counts

For all four studies reporting a gradient of risk with increasing asbestos exposure level, the industrial hygiene data for the early years of exposure were measured in the number of (millions of) particles per cubic foot of air (mppcf). Since modern industrial hygiene methods count the number of fibers per milliliter (f/ml), it is necessary to establish a conversion factor which will estimate the number of f/ml which is equivalent to one mppcf.

There is general agreement that no single conversion factor can be relied upon as accurate for all segments of the asbestos industry nor for all stages of processing within any one segment of the industry.

Nevertheless, in spite of extensive variability in the observations, best estimates of these factors have been made (Ayer et al, 1965; Hammad et al, 1979; McDonald et al, 1980; Dement et al, 1982). These estimates have confirmed the expected trend: the highest factor occurs in textiles, where the greatest proportion of particles are asbestos fibers, while the lowest factor occurs in asbestos cement manufacturing, where, because of mixing with other substances, the lowest proportion of particles are asbestos fibers.

In the textile industry, Ayer (1965) derived an estimated factor of 6.0. Dement (1982), as part of his epidemiologic study of

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a textile factory derived a factor of 8.0 for the preparation area and 3.0 for all other areas. The factor of 3.0 is used to convert the slope of the Dement study to f/ml-yr. For the asbestos cement study (Weill et al, 1979), a factor of 1.4 derived by Hammad et al (1979) for these factories will be used. McDonald et al (1980) reported that the conversion factor in the Canadian chrysotile mines falls in the range 1-5; the value of 2.5 will be used here. For the study of manufacturing retirees, a value of 2.0 will be used since much, though not all, of these exposures are believed to have involved asbestos cement. Using these conversion factors the slopes obtained from the four studies reporting a gradient of increase in SMR with asbestos exposure measured in mppcf were converted to increases in SMR per unit exposure of asbestos measured in f/ml-yrs. as shown in Table J-5.

d. Estimates of Mesothelioma Carcinogenicity

Four of the above studies provide information on the incidence of mesothelioma (pleural and peritoneal combined) according to time from the onset of exposure and data on the duration and intensity of asbestos exposure. Thus, values for K_M, the proportionality constant (exposure gradient) for mesothelioma risk (Equation J-2) can be estimated. Other studies have reported cases of mesothelioma, but incidence data are lacking. The four studies, however, are not representative of all asbestos exposure circumstances. Other studies, with few identified cases of mesothelioma, are not amenable to analysis, in part, because data were not provided and in part because those studies with

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TABLE J-5

Estimates of Increase in Standardized Mortality Ratio for Lung Cancer (SMR) per Unit Increase in Cumulative Asbestos Exposure, Measured in f/ml-yr

	Increase in SMR for Dose in mppcf-yrs	Conversion* Factor	Increase in SMR per unit Dose in f/ml-yrs
Level 1 Exposure Data			
A. Studies with an observed gradient of risk with mean exposure level			
Mining (McDonald, 1980)	.14	2.5	.06
Retirees 1.3+ (Henderson et al, 1979)	(.66)	2.0	.50+(.33)
U.S. Cement (Weill et al, 1979)	.44	1.4	.31
U.S. Textile 6.8+ (Dement, 1982)	(13.1)	3.0	2.3+(4.4)
B. Studies without an observed gradient of risk with mean exposure level			
Mining (Rubino et al, 1979)			1.7
Friction Materials (Berry and Newhouse, 1983)			.06
British Textile (Pero, 1980)			1.0
Canadian Cement (Finkelstein et al, 1983a)			4.8
Level 2 Studies			
A. Studies without sufficient data to give an observed gradient of risk with exposure level			
Mining (Nicholson et al, 1979)	.30	2.5	.12
Amosite Products (Seidman et al, 1979)			6.8
Insulation Workers (Selikoff et al, 1979)			1.0

*Number of f/ml for each mppcf
+After adjustment for possible biases

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insufficient data tended to be those that reported a lower risk of lung cancer. The estimate of K_M for each of the four studies was made by calculating a relative mesothelioma incidence using Equation J-2 and data on duration and intensity of asbestos exposure. The relative incidence curves were then superimposed on the observed incidence data in each study. These fits are depicted on Figures J-5 and J-6. The four studies are described below and summary data listed in Table J-6

(1) Insulation workers (Selikoff et al, 1979; Peto et al 1982)
(n = 17,800, 236 mesotheliomas by BE)

A follow-up through 1979 of the cohort of insulators provides data on the incidence of mesothelioma with time from onset of exposure (Peto et al, 1982). It has been estimated that their time-weighted average exposure was 15 f/ml (Nicholson et al, 1976) . Using these data and 25 years for their average duration of exposure, a value of $K_M = 1.5 \times 10^{-8}$ is estimated.

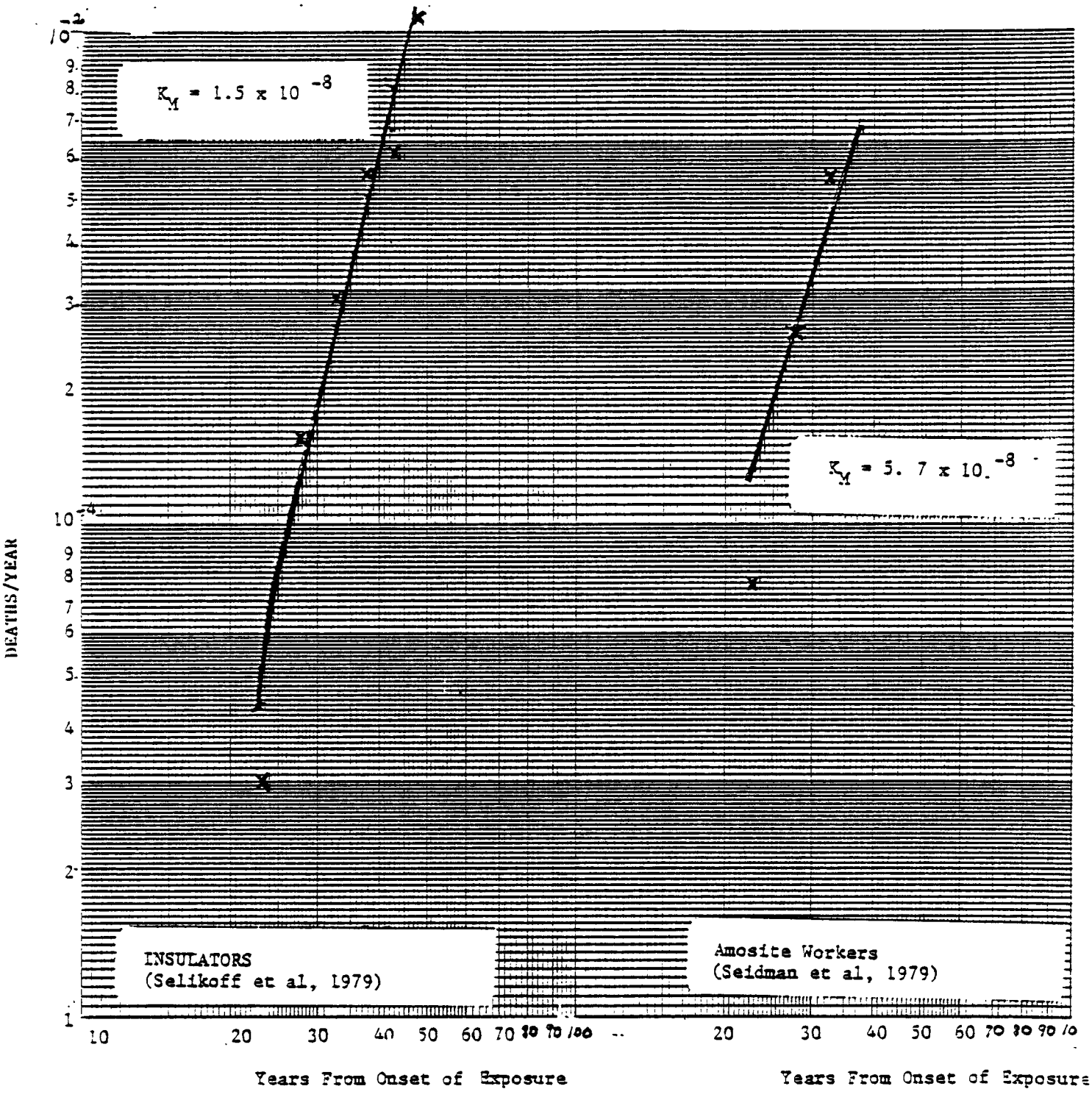
(2) British textile workers (Peto, 1980; Peto et al, 1982)
(n = 679, 7 mesotheliomas)

A value of 30 f/ml is suggested by the data presented by Peto (1980). However, some uncertainty exists concerning this value as discrepancies in the relative exposures measured using personal samplers and static samplers exist (see above). If the exposures measured by personal samplers are less than static samplers, as suggested by the data of Smither and Lewinsohn (1973), the average exposure could be about 15 f/ml. However, using 30 f/ml and an employment period of 20 years a value of $K_M = 0.7 \times 10^{-8}$ is estimated. Using 15 f/ml as the estimated exposure yields a K_M of 1.4×10^{-8}.

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Figure J - 5

The Fit of Observed Mesothelioma Incidence to that Calculated Using Equation J-2 for Two Studies of Asbestos-Exposed Workers[a]

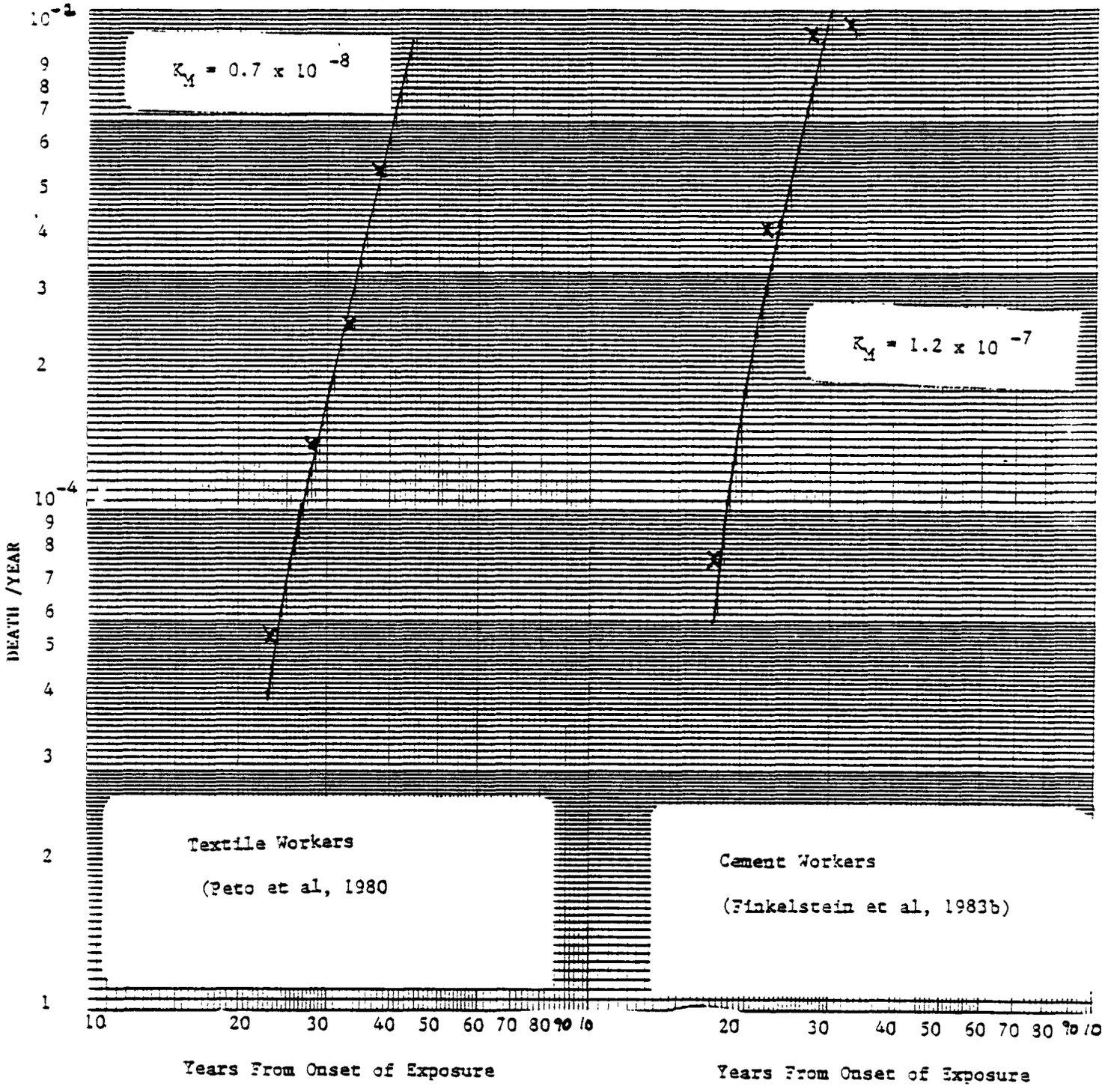


[a]Selikoff et al, 1979; Peto et al, 1980; Seidman et al, 1979

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Figure J - 6

The Fit of Observed Mesothelioma Incidence to that Calculated Using Equation J-2 for Two Studies of Asbestos-Exposed Workers[a]



[a] Peto et al, 1980; Peto et al, 1982; Finkelstein et al, 1983

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TABLE J-6

Summary of the Data on K_M, the Measure of Mesothelioma Risk Per Fiber Exposure, in Four Studies of Asbestos Workers

Study	Average Employment Duration	Average Exposure (f/ml)	Number Mesotheliomas	K_M	K_M/K_L*
Insulators (Selikoff et al, 1979; Peto et al, 1982)	25	15	175	1.5×10^{-8}	1.5×10^{-6}
Textile workers (Peto, 1980; Peto et al, 1982)	25	30	7	0.7×10^{-8}	0.7×10^{-6}
Amosite factory workers (Seidman et al, 1979)	1.5	35	14	5.7×10^{-8}	0.8×10^{-6}
Cement factory workers (Finkelstein et al, 1983b)	12	9	11	12.0×10^{-8}	2.5×10^{-6}

*Note: See Table J-7

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(3) Amosite factory Workers (Seidman et al, 1979)
(n = 820, 14 mesotheliomas by BE)

The average employment time of all individuals in this factory was 1.46 years. This value and the previously used value of 35 f/ml for yields of:

$$K_M = 5.7 \times 10^{-8}$$

(4) Cement workers (Finkelstein et al, 1983b)
(n = 186, 11 mesotheliomas)

It was stated that the cumulative exposure of the cohort over 18 years was 105 f/yr. Only men with 9 or more years of employment were included in the cohort. While data on the exact duration and intensity of exposure are unavailable, using a value of 12 years for duration of exposure and 9 f/ml for the intensity of exposure. This yields a value of $K_M = 1.2 \times 10^{-7}$.

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3. Evidence for Fiber Type Effects

a. Lung Cancer

The evidence for differences in lung cancer potential for the different fiber types is mixed and not conclusive. Although some studies have suggested that a greater lung cancer risk occurs from crocidolite exposure (Henderson and Enterline, 1979; Weill et al, 1979). The evidence is limited, particularly on a unit exposure basis. Further, no such evidence emerged in a recent study of three asbestos factories (McDonald and Fry, 1982). The evidence on lung cancer risk per cumulative fiber exposure from eleven studies does not point to any fiber types as being uniquely carcinogenic. A review of the values of K_L in Table J-5 shows that the lowest value and one of the highest was found in studies in which the only exposure was to chrysotile. Similarly, studies of groups with crocidolite exposure (manufacturing retirees and cement workers) give both high and low values of K_L, as did studies of groups with amosite exposure. Methodological difficulties could explain some but not all of the differences.

b. Mesothelioma

In order to compare the risk of pleural mesothelioma and lung cancer, it would be desirable to estimate the ratio of the constants

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K_L for lung cancer (Equation J-1) and K_M for pleural mesothelioma (Equation J-2, ignoring peritoneal mesothelioma) for all studies, but the necessary data are generally lacking. Duration of exposure is often not reported, for many cohorts the incidence of mesothelioma has not been published in a suitable form, and in some reports, the total number of mesotheliomas is given without distinguishing pleural and peritoneal tumors. A further difficulty is the selection of appropriate death-rates for lung cancer (I_U in Equation J-1) on which to base the expected number. If one compares the limited data on K_M and K_L that are available, the ratio between the two are reasonably close (0.8-2.5)(See Table J-6). If an adjustment is made for the percentage of mesotheliomas that are peritoneal (by multiplying by the ratio of the numbers of pleural mesotheliomas to total mesothelioma), the ratio of $K_M(Pl)/K_L$ changes to:

Group	Exposure	Number Mesotheoliomas Pl	Per	$K_M(Pl)/K_L$
Insulators	Amos. Chrys.	63	112	0.5×10^{-6}
Brit. textiles	Chrys.	7	0	0.7×10^{-6}
Amosite mfg.	Amosite	7	7	0.4×10^{-6}
Canadian cement	Chrys. Croc.	6	5	1.4×10^{-6}

The agreement in the ratio is still good.

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Differences between cohorts appear to be greater for peritoneal than for pleural mesotheliomas (see below). The overall ratio of excess lung cancer to pleural mesotheliomas among male asbestos workers is about 4 when the results of published studies are combined (Peto, 1983). Some individual studies show a significantly higher or lower ratio than this average figure, but this variation may be due at least partially to methodological difficulties. Crocidolite does not seem to cause as high a relative incidence of mesothelioma as has often been suggested. For example, the ratio of excess lung cancer to pleural mesotheliomas was 4.6 among Canadian chrysotile miners and 2.0 among non-migrant Australian crocidolite miners, and the extraordinary excess of mesothelioma among migrant crocidolite miners (8 mesotheliomas, and an excess of 3 lung cancers) may therefore have been inflated artifactually, perhaps by selective inclusion and incomplete follow-up (Peto, 1983). Nonetheless, the highest relative mesotheliomas rates did occur in crocidolite miners and in workers in chrysotile factories in which crocidolite was also used.

c. Relative Incidence of Pleural and Peritoneal Mesothelioma

The most striking difference between the mortality experience of different cohorts of asbestos workers is the variation in incidence of peritoneal mesothelioma. In cohorts that were sufficiently heavily

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exposed to suffer substantially increased lung cancer risks and a high incidence of pleural mesothelioma, peritoneal mesothelioma has sometimes been completely absent and sometimes has been more common than pleural mesothelioma. Peritoneal mesothelioma appears to be most common in workers exposed to amosite, less often to crocidolite, and rarely or never to chrysotile. However, data on a unit exposure basis are lacking and misclassification of peritoneal mesothelioma is extremely common (see Table H-2). Further, this simple classification can hardly explain the observation that none of the 30 mesotheliomas among Australian crocidolite miners was peritoneal (Hobbs et al, 1980), while 6 of the 9 cases among Canadian crocidolite gas-mask workers were (McDonald and Fry, 1982). Other factors, particularly fiber dimension, are therefore likely to be relevant. Pleural and peritoneal cases can be combined in estimating the overall risk, as their incidence patterns are similar (Selikoff et al, 1979) and both are quickly fatal; but these differences illustrate the uncertainty in any extrapolation from the experience of a particular cohort to predict the effects of different types or sizes of fiber, or other conditions of exposure.

One other feature suggested by several studies is a lower dose-specific risk of malignancy, particularly mesothelioma, in the mining work environment than in asbestos using industries, with the possible exception of crocidolite for which no exposure data are available. A low value of K_L was observed in chrysotile mining and relatively few mesotheliomas have been observed among miners of

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chrysotile (McDonald et al, 1980; Rubino et al, 1979), amosite (Webster, 1970), or anthophyllite (Meurman et al, 1974). Many of the studies of production and users of asbestos products show high dose-specific risks of death from lung cancer and mesothelioma from both chrysotile and amosite exposure (no data are available on anthophyllite or crocidolite). This suggests that dimensionality relating to use may be an important factor separate from fiber type.

4. Cancer Risks at Low Exposure

All data that relate asbestos disease to exposure are derived from studies of workers exposed in occupational environments. In order to estimate cancer risks at low exposure a model for dose extrapolation must be utilized. As mentioned previously, the available data are compatible with a linear dose-response relationship, with no evidence of a threshold. However, the limited data indicating the validity of this relationship are for exposures two or three orders of magnitude higher than those of concern from the use of consumer products or from the ambient environment.

The extrapolation to the various lower exposure circumstances will utilize the previously discussed models for the time and dose dependence of lung cancer and mesothelioma (Equations J-1 and J-2).

Table J-7 displays the values of K_L and K_M found in all studies analyzed in Section J-2. Values of K_L span a 100-fold range

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TABLE J-7

Values of K_L and K_M (Equations J-1 and J-2) Obtained in the Analysis of Eleven Studies of Asbestos Workers[a]

Mortality Study	K_L[b]	K_M
McDonald et al, 1980	6×10^{-4}	
Henderson and Enterline, 1979	$3.3\text{-}5.0 \times 10^{-3}$	
Weill et al, 1979	3.1×10^{-3}	
Dement et al, 1982	$2.3\text{-}4.4 \times 10^{-2}$	
Rubino et al, 1979	1.7×10^{-3}	
Berry and Newhouse, 1983	6×10^{-4}	
Peto, 1980	1.0×10^{-2}	0.7×10^{-8}
Finkelstein et al, 1983a,b	4.8×10^{-2}	12.0×10^{-8}
Nicholson et al, 1979	1.2×10^{-3}	
Seidman et al, 1979	6.8×10^{-2}	5.7×10^{-8}
Selikoff et al, 1979	1.0×10^{-2}	1.5×10^{-8}

[a] In f-yr/ml.

[b] Increase in SMR per f-yr/ml/100.

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and those of K_M a 17-fold range. However, as mentioned previously K_M could not be determined for several studies, notably those with lower values of K_L.

Tables J-8A and J-8B list a range of calculated sex and smoking specific lifetime risks (per 100,000) of mesothelioma and lung cancer for a continuous exposure to 0.01 f/ml for various time periods. Values of $K_L = 0.3 \times 10^{-2}$ to 3×10^{-2} and values of $K_M = 3 \times 10^{-9}$ to 3×10^{-8}, were used in these calculations. 1977 United States mortality rates were utilized except that female lung cancer rates were increased by a factor of 2 to reflect the current rapid rise in these rates. Nonsmoking male and famale lung cancer rates were taken from data published by Garfinkel (1981). Data from Hammond (1966) on the ratio of total mortality among smokers to that among nonsmokers were used to adjust current male and female total mortality rates. The adjustments are approximate and their effect is to cause slight differences in smoking specific mesothelioma risks due to the different lifespans of smokers and nonsmokers. Since non-smokers live longer than smokers, they have a greater probability of eventually developing (and dying from) mesothelioma.

The choice of lung cancer rates is inevitably arbitrary. Lung cancer rates in the United States are still rising in men aged 50 or over, and are increasing even more rapidly in women, due more to past patterns of cigarette consumption than to recent changes, and these trends are likely to continue for some time even if current smoking rates do not change (Doll and Peto, 1981). The rates we have assumed in

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TABLE J-8A

The Range of Lifetime Risks of Death per 100,000 Males from Mesothelioma and Lung Cancer from a Continuous Asbestos Exposure of 0.01 f/ml According to Age, Duration of Exposure and Smoking for Various Time Periods

Age at onset of exposure	Years of exposure 1	5	10	20
		Mesothelioma in male smokers		
0	3.2 - 31.9	14.5 - 144.9	25.7 - 256.6	41.2 - 412.4
10	2.0 - 19.7	8.8 - 88.2	15.5 - 154.6	23.4 - 233.5
20	1.1 - 10.9	4.9 - 49.1	8.4 - 84.0	12.3 - 123.5
30	0.5 - 5.9	2.4 - 24.3	4.0 - 40.3	5.5 - 55.4
50	0.1 - 0.8	0.3 - 3.4	0.5 - 4.6	0.5 - 5.5
		Lung cancer in male smokers		
0	0.8 - 8.4	4.2 - 41.6	8.4 - 83.6	16.7 - 166.7
10	0.8 - 8.4	4.2 - 42.0	8.4 - 84.0	16.8 - 167.6
20	0.8 - 8.4	4.2 - 42.4	8.4 - 84.4	16.7 - 166.7
30	0.8 - 8.4	4.2 - 42.4	8.4 - 84.0	15.8 - 158.3
50	0.7 - 7.1	3.2 - 32.3	5.7 - 56.7	8.1 - 80.6
		Mesothelioma in male nonsmokers		
0	3.7 - 37.4	17.1 - 170.9	30.7 - 307.0	49.4 - 493.5
10	2.4 - 23.5	10.6 - 105.8	18.8 - 187.7	29.2 - 291.9
20	1.3 - 13.4	6.1 - 61.3	10.5 - 105.4	15.7 - 157.1
30	0.7 - 7.1	3.2 - 31.5	5.3 - 52.5	7.4 - 73.9
50	0.1 - 1.3	0.5 - 4.6	0.7 - 6.7	0.8 - 8.0
		Lung cancer in male nonsmokers		
0	0.1 - 0.8	0.5 - 4.6	0.9 - 8.8	1.8 - 17.6
10	0.1 - 0.8	0.5 - 4.6	0.9 - 8.8	1.8 - 17.6
20	0.1 - 0.8	0.5 - 4.6	0.9 - 8.8	1.8 - 17.6
30	0.1 - 0.9	0.5 - 4.6	0.9 - 8.8	1.8 - 17.2
50	0.1 - 0.8	0.4 - 3.8	0.7 - 6.7	1.2 - 11.8

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TABLE J-8B

The Range of Lifetime Risks of Death per 100,000 Females from Mesothelioma and Lung Cancer from a Continuous Asbestos Exposure of 0.01 f/ml According to Age, Duration of Exposure and Smoking for Various Time Periods

Age at onset of exposure	Years of exposure 1	5	10	20
		Mesothelioma in female smokers		
0	4.2 - 41.6	19.2 - 191.9	34.5 - 345.2	55.9 - 558.6
10	2.7 - 26.9	12.1 - 121.0	21.4 - 214.2	33.6 - 336.0
20	1.6 - 16.0	7.1 - 70.6	12.2 - 122.2	18.4 - 184.0
30	0.8 - 8.4	3.7 - 37.0	6.2 - 61.7	8.8 - 88.2
50	0.2 - 1.7	0.6 - 5.9	0.9 - 8.8	1.1 - 10.5
		Lung cancer in female smokers		
0	0.5 - 5.5	2.7 - 26.9	5.3 - 53.3	10.7 - 106.7
10	0.5 - 5.5	2.7 - 26.9	5.3 - 53.3	10.7 - 106.7
20	0.5 - 5.5	2.7 - 26.9	5.3 - 53.3	10.5 - 105.0
30	0.5 - 5.5	2.6 - 26.5	5.2 - 51.7	9.6 - 95.8
50	0.4 - 3.8	1.8 - 17.6	3.1 - 31.1	4.5 - 45.4
		Mesothelioma in female nonsmokers		
0	4.5 - 44.5	20.5 - 204.5	36.8 - 368.3	59.8 - 598.1
10	2.9 - 28.6	13.1 - 130.2	24.4 - 243.6	36.4 - 363.7
20	1.7 - 17.2	7.7 - 76.9	13.3 - 133.1	20.2 - 201.6
30	0.9 - 9.2	4.1 - 40.7	6.9 - 68.9	9.9 - 98.7
50	0.2 - 1.7	0.7 - 6.7	1.0 - 10.0	1.2 - 12.2
		Lung cancer in female nonsmokers		
0	0.1 - 0.8	0.4 - 3.8	0.8 - 8.0	1.6 - 15.5
10	0.1 - 0.8	0.4 - 3.8	0.8 - 8.0	1.6 - 16.0
20	0.1 - 0.8	0.4 - 3.8	0.8 - 8.0	1.6 - 15.5
30	0.1 - 0.8	0.4 - 3.8	0.8 - 8.0	1.5 - 15.1
50	0.1 - 0.8	0.3 - 3.3	0.6 - 6.3	1.1 - 10.5

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calculating Tables J-8A and J-8B may, therefore, substantially underestimate future lung cancer rates for both sexes. If smoking falls substantially, of course, they may prove too high.

The ten-fold range on K_L encompasses most of the work situations in Table J-7. The three chrysotile mining studies fall outside the selected range, but this work situation might not be characteristic of environmental exposure to consumer products. So too does the study of Berry and Newhouse (British friction material workers), but their K_L value is very uncertain. The 90% upper bound is 8×10^{-3} which is well within the range selected for K_L. On the upper side, the studies of Finkelstein (Canadian cement workers) and Seidman et al (amosite manufacturing workers) fall outside the ranges selected. A tenfold range for K_M was also selected. Its midpoint, 1×10^{-8} was the average of the risks expressed by the studies of Selikoff et al (1979) and Peto (1980). The values for these two studies were used because their values for K_L were at the midpoint of the K_L range.

It must be emphasized, however, that the estimates of risk are very uncertain because of the variability in estimates of K_L and K_M and because of uncertainties in extrapolating results obtained from high exposures in the workplace to environmental exposures two or three orders of magnitude lower. Thus, the actual risk in a given situation can lie outside estimates made from these ranges. Nevertheless the range depicted is believed to be representative of most exposure circumstances.

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The data of Tables J-8A and J-8B show the importance of the difference between the time courses of mesothelioma and lung cancer. The time course of lung cancer is determined by its time course in the absence of asbestos exposure, i.e., on the time course of cigarette smoking risk. On the other hand, mesothelioma risk depends solely on the time from onset of exposure to asbestos and, thus, children exposed in early years of life are especially susceptible because of their long future lifespan.

The data of Tables J-8A and J-8B are estimated risks from a continuous exposure to 0.01 f/ml. Estimates for higher or lower concentrations can be directly scaled by multiplying by the ratio of the intensity. Typical urban asbestos concentrations are about 100 times lower than 0.01 f/ml (Nicholson et al, 1980). Effects for shorter durations of exposure can be estimated by scaling the data in the one year column by the fraction of a year desired. Longer exposures can be approximated by adding risks in appropriate time categories. For example, a forty year risk, beginning at birth, is approximately the sum of the risks at 0 and 20 years from onset of exposure in the 20 year of exposure column. This procedure leads to 70 year risks for smoking males of (55.6 - 557.3)/100,000 for mesothelioma and (49.0 - 489.9)/100,000 for lung cancer.

5. Conversion of Fiber Measurements

Current measurements of low-level environmental pollution utilize electron microscopic techniques which lead to estimates of total mass

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of asbestos present in a given volume of air. To extrapolate dose-response data obtained in studies of working groups to environmental exposures, it is necessary to establish a relationship between optical fiber counts and mass of asbestos as determined by electron microscopy. Some data exist that relate optical fiber counts (longer than 5 μm) to the total mass of asbestos. These are listed in Table J-9 and provide limited estimates of a conversion factor relating fiber concentrations (f/ml) to airborne asbestos mass ($\mu g/m^3$). The proposed standards for asbestos in Great Britain adopted by the British Occupational Hygiene Society (BOHS) stated that a "respirable" mass of 0.12 mg asbestos/m^3 was equivalent to 2 f/ml (BOHS, 1968). Details were not given on how this relationship was determined. If it was estimated from magnesium determinations in an aerosol, the weight determination would be an overestimate because of the presence of other nonfibrous, magnesium-containing compounds in the aerosol. Such was the case in the work of Lynch et al (1970). Thus, the data of containing compounds in the aerosol appear to provide an overestimate of the conversion factor. The data of Rohl et al (1976) are likely to be underestimates because of possible losses in the determination of mass by electron microscopy. No information was given on the procedures used to determine the mass of chrysotile in the data presented by Davis et al (1978).

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TABLE J-9

Measured Relationships Between Optical Fiber Counts and Mass of Airborne Chrysotile

Sampling Situations	Fiber[a] Counts (f/ml)	Mass Concentrations ($\mu g/m^3$)	Conversion Factors $\frac{\mu g/m}{f/ml}$ or $\frac{\mu g}{10^6 f}$	10^3 f/mg
Textile factor BOHS (1968) (weight vs. fiber count)	2	120	60	16
Air chamber monitoring Davis et al (1978)	1,950	10,000	5	200
Monitoring brake repair work Rohl et al (1976) (E.M. mass vs. fiber count)	0.1 to 4.7 (7 samples)	0.1 to 6.6	0.7 to 24[b] mean = 6	170
Textile mill			150[c]	6.7
Friction products mfg.			70[c]	13.9
Pipe mfg. Lynch et al (1970)			45[c]	22.5

[a]All fiber counts used phase-contrast microscopy and enumerated fibers longer than 5 μm.
[b]Coversion factor may be low due to losses in E.M. processing.
[c]Conversion factor may be high because of overestimate of asbestos mass on the basis of total magnesium.

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The range of 5 to 150 $\mu g/m^3/f/ml$ for the conversion factor relating mass concentraion to optical fiber concentration is great, and any average value derived from it has a large uncertainty. However, for the purpose of extrapolating to low mass concentrations from fiber count, the approximate geometric mean, 30 $\mu g/m^3/f/ml$, of the above range of conversion factors would appear to be appropriate. The geometric standard deviation of this value is about 4 and this uncertainty implies that any extrapolation in which it is used must have wide limits. Thus, the values of Table J-6 (for exposures to 0.01 f/ml) correspond to a mass concentration of 300 $\mu g/m^3$. In the case of amosite, the data of Davis et al (1978) suggest that a conversion factor of 18 $\mu g/m^3/f/ml$ is appropriate. However, since these data yielded lower chrysotile values than all other chrysotile estimates, it may also be low for amosite.

Clearly better data on the relationship between fiber counts and mass determinations as well as improved fiber counting techniques at lower concentrations are necessary. This latter possibility may be feasible. Recent work (Spurny et al, 1980) on the use of scanning electron microscopic techniques for the determination of the concentrations of asbestos fibers longer than 5μm in ambient air samples gives promise of improved counting accuracy at low concentrations.

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