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FINAL

METHODOLOGY FOR CONDUCTING RISK ASSESSMENTS AT ASBESTOS SUPERFUND SITES PART 2: TECHNICAL BACKGROUND DOCUMENT

INTERIM VERSION

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DISCLAIMER

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1.0 INTRODUCTION

This report presents a protocol for assessing potential human-health risks associated with exposure to airborne asbestos. It is designed specifically for use in performing risk assessments at Superfund sites, although it may be applicable to a broad range of situations.

The protocol itself is presented in Part 1 of the report, under separate cover. Considerations addressed during the development of the protocol are presented in this companion technical background document (Part 2 of the report).

In the protocol presented in Part 1, the risk associated with asbestos exposure can be estimated using either of two procedures. The first procedure, which is preferred when sufficient data exist to support the required inputs, is to apply an appropriate risk model (selected from among those presented, based on the end point health effect of interest) using case-specific data as inputs. The models, the types of data required to support the models, and the procedures to use for evaluating each model are defined within the protocol presented in Part 1.

The second approach, which can be used when supporting data are limited, is to estimate risk by extrapolation from a risk table. Both the risk table and instructions on how to use it are provided in the protocol (Part 1 of this document). Limits to the validity of this approach are also discussed, so that the user can evaluate the confidence that may be placed in risk estimates derived using this latter technique.

Importantly, the protocol also includes guidelines for proper collection and analysis of samples to be used to support estimation of asbestos exposure. Estimates of asbestos exposure in a particular setting can vary by orders of magnitude depending on the particular method(s) employed to collect, prepare, and analyze samples and to report results (Berman and Chatfield 1990). Therefore, both the method(s) to be used to develop exposure data and the exposure index to be used to report results are specified in the protocol. Correspondingly, the risk coefficients employed in the protocol have been adapted for use with the specified exposure index.

The models employed for assessing asbestos-related risks (and for deriving the corresponding risk coefficients) are adapted from those proposed in the Airborne Asbestos Health Assessment Update (U.S. EPA 1986). The approach has been modified, however, to better account for the limitations imposed by asbestos analytical techniques. Studies published since the appearance of the Update have also provided new insights into the relationship between asbestos measurement and biological

activity. Consequently, a review and evaluation of the new studies and key studies published earlier are presented in this report[1].

The purpose for documenting the data and assumptions used to develop the protocol proposed in Part 1 is to facilitate critical evaluation while highlighting needs for additional research. Considerations addressed in this report that have been documented in the literature are cited accordingly. Considerations that remain largely a subject of conjecture are also noted. Due to the current level of interest and activity provoked by asbestos, further improvements in asbestos sampling, analysis, and evaluation are anticipated.

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[1] Due to a combination of time and budget constraints, the literature review presented in this document is not comprehensive. However, we did attempt to identify and include key studies and reports that were published at least through 1994.

2.0 OVERVIEW

Exposure to asbestos dusts has been linked to several adverse health effects including primarily asbestosis, lung cancer, and mesothelioma (U.S. EPA 1986). Asbestosis, a chronic, degenerative lung disease, has been documented among asbestos workers from a wide variety of industries. However, the disease is expected to be associated only with the higher levels of exposure commonly found in workplace settings and is not expected to contribute substantially to potential risks associated with environmental asbestos exposure. The majority of evidence indicates that lung cancer and mesothelioma are the most important sources of risk associated with exposure to low levels of asbestos.

Gastrointestinal cancers and cancers of other organs (e.g. larynx, kidney, and ovaries) have also been linked with asbestos exposures in some studies. However, such associations are not as compelling as those for the primary health effects listed above and the potential risks from asbestos exposures associated with these other cancers are much lower (U.S. EPA 1986). Consequently, the protocol presented in Part 1 is focused on risks associated with the induction of lung cancer and mesothelioma.

A variety of human and animal studies have provided insight into the nature of the relationship between asbestos exposure and disease. Ideally, human epidemiology studies are employed to determine the quantitative dose/response relationships and the attendant risk coefficients for asbestos exposure. Risk coefficients have been estimated for asbestos from approximately 15 epidemiology studies for which adequate dose-response data exist. Such factors vary widely, however, and the observed variation has not been reconciled.

Animal studies indicate that asbestos potency is a complex function of several characteristics of asbestos dusts including fiber size and, possibly, fiber type (i.e., fiber mineralogy). The influence of such effects cannot be evaluated in the existing epidemiological studies because the analytical techniques used to monitor asbestos exposure in these studies are not capable of resolving all of the characteristics of asbestos dusts that other studies indicate are important. Thus, the exposure indices employed in the existing epidemiology studies do not correspond precisely with the characteristics of asbestos that best relate to biological activity. This hinders the ability to compare the risk (dose-response) factors derived from the different studies. It also limits the confidence with which risk coefficients derived from the existing epidemiology studies can be applied to assess risks from asbestos exposure in other environments.

Ideally, it should be possible to define an exposure index that correlates precisely with biological activity. Using such an index would assure that risk and exposure are linked by a single, universal relationship in any exposure environment. Asbestos exposures expressed in terms of such an index would therefore provide an accurate measure of relative risks. Further, if risk coefficients could also be derived based on such an

index, they could be paired directly with exposure estimates (using appropriate models) to provide estimates of absolute risk that would remain comparable across exposure environments.

Based on the approach developed for evaluating asbestos-related cancer risk in U.S. EPA (1986), risk is estimated by a mathematical function that depends on time, the level of exposure, the duration of exposure, and a risk coefficient that is appropriate for the disease endpoint of interest. The risk coefficient for lung cancer is generally denoted, "K_L" and the one for mesothelioma is "K_M."

Detailed descriptions of both the lung cancer and mesothelioma models are provided in Section 6.2. The models differ depending on whether lung cancer or mesothelioma is being considered.

For lung cancer, the model estimates *relative* risk, which means that the increase in lung cancer mortality that is attributable to asbestos exposure is a function of the background lung cancer mortality in the exposed population. Background cancer mortality is the rate of deaths from cancer that would be expected to occur in the population in the absence of asbestos exposure. In other words, background lung cancer mortality is the rate of lung cancer mortality for an exposed population that is attributable to all causes other than asbestos.

The model for mesothelioma is an *absolute* risk model. This means that the increase in mesothelioma attributable to asbestos is independent of the background rate of mesothelioma, which is negligible in the general population.

Ideally, the risk coefficients derived from the existing epidemiology studies can be combined with measurements from other exposure settings (using the corresponding models) to estimate lung cancer and mesothelioma risks in these other exposure settings. However, such risk estimates are only valid if both of the following conditions are met:

(1) asbestos is measured in the exposure setting of interest in the identical manner in which it was measured in the study from which the corresponding risk coefficients are derived; and

(2) such measurements reflect the characteristics of asbestos exposures that determine risk.

A growing body of evidence indicates that the way in which asbestos concentrations were measured in the existing epidemiology studies do not reflect the characteristics of asbestos exposure that determine risk. Therefore, measuring asbestos concentrations in exposure settings of interest would not be sufficient to assure validity of risk

estimates derived using the published risk coefficients (and the corresponding models). This is because the second of the above-listed conditions would not be satisfied.

An alternate approach, which was adopted to develop this protocol, is to:

- reconcile existing literature by addressing the capabilities and limitations of the analytical techniques used to measure asbestos in the existing studies;
- evaluate the literature and perform studies to define the characteristics of asbestos that determine risk,
- define a method for measuring asbestos that adequately reflects such characteristics;
- adjust published risk coefficients for asbestos so that they are normalized and applicable to the same method for measuring asbestos; and
- identify the appropriate dose-response models (incorporating appropriately adjusted risk coefficients) that indicate how to relate asbestos exposure (that is properly measured and reported) to risk.

Due to the interrelationship between the steps identified above, the process is necessarily iterative.

Note that, asbestos measurements that are derived using a well-defined and standardized analytical method are said to reflect a specific index of exposure. Such a method must specify the sizes, shapes, and mineralogical characteristics of the asbestos structures that are to be included in the determination of asbestos concentrations. Therefore, the second of the above-listed steps for developing this protocol is to define an *exposure index* for asbestos that adequately reflects the various asbestos characteristics that determine risk.

Unfortunately, several of the details concerning the characteristics of asbestos that determine biological activity remain a subject of controversy that cannot be entirely resolved with existing data. Also, the data set required to adjust existing risk coefficients for the limitations of analytical methods is incomplete at this time. Consequently, the approach adopted in this report for deriving asbestos risk coefficients and applying them using the recommended protocol represent compromises among several alternatives. Where major uncertainties remain, research needs are identified.

In the remaining chapters of this report:

- Chapter 3 provides background information that includes the definition of asbestos, a characterization of asbestos dusts, and a comparison of the capabilities and limitations of the various analytical techniques and methods that are used to measure asbestos exposures.

- Chapter 4 presents a characterization of the asbestos literature. It includes definitions and descriptions of the types of asbestos-related studies that are available and their relative strengths and limitations.

- Chapter 5 presents an evaluation of the asbestos literature, which was conducted to develop an exposure index for asbestos that reflects asbestos characteristics that best relate to biological activity.

- Chapter 6 presents models that are recommended for estimating asbestos risks. The models incorporate risk coefficients that are derived by adjusting published coefficients for use with an asbestos exposure index that relates to risk.

- Conclusions and recommendations are summarized in Chapter 7.

- References are provided in Chapter 8.

3.0 BACKGROUND

Asbestos is a term used to describe the fibrous habit of a family of hydrated metal silicate minerals. The most widely accepted definition of asbestos includes the fibrous habits of six of these minerals: chrysotile, amosite, crocidolite, anthophyllite, tremolite, and actinolite (IARC 1977). Although other minerals may also occur in a fibrous habit, they are not generally included in the definition of asbestos either because they do not exhibit properties typically ascribed to asbestos (e.g. high tensile strength, the ability to be woven, heat stability, and resistence to attack by acid or alkali) or because they do not occur in sufficient quantities to be exploited commercially.

The first four of the six asbestos minerals listed above have been exploited commercially (IARC 1977). Of these, chrysotile alone accounts for more than 90% of the asbestos found in commercial products.

Chrysotile is the fibrous habit of the mineral serpentine (Hodgson 1965). The smallest fibrils of chrysotile occur as rolled sheets or hollow tubules of this magnesium silicate mineral. The larger fibers of chrysotile form as tightly packed bundles of the unit fibrils.

The general chemical composition of serpentine is reported as $Mg_3(Si_2O_5)(OH)_4$ (Hodgson 1965). However, the exact composition in any particular sample may vary somewhat from the general composition. For example, aluminum may occasionally replace silicon and iron, nickel, manganese, zinc or cobalt may occasionally replace magnesium in the crystal lattice of chrysotile (serpentine).

The five other common varieties of asbestos are all fibrous forms of amphibole minerals (Hodgson 1965). These are ferro-magnesium silicates of the general composition:

$$A_{2-3}B_5(Si,Al)_8O_{22}(OH)_2$$

where:

A = Mg, Fe, Ca, Na, or K; and
B = Mg, Fe, or Al.

Some of these elements may also be partially substituted by Mn, Cr, Li, Pb, Ti, or Zn.

The fibrous habits of the amphibole minerals tend to occur as extended chains of silica tetrahedra that are interconnected by bands of cations (Hodgson 1965). Each unit cell typically contains eight silica tetrahedra.

3.1 MORPHOLOGY OF ASBESTOS DUSTS

Structures comprising the fibrous habits of the asbestos minerals come in a variety of shapes and sizes. Not only do single, isolated fibers vary in length and thickness but

such fibers may be found combined with other fibers to form bundles (aggregates of closely packed fibers arranged in parallel) or clusters (aggregates of randomly oriented fibers) or combined with equant particles to form matrices (asbestos fibers embedded in non-asbestos materials). Consequently, dusts (even of one mineral variety) are complex mixtures of structures. For precise definitions of the types of fibrous structures typically found in asbestos dusts, see Chatfield and Berman (1990).

Detailed descriptions of the characteristics of dusts typically encountered at environmental and occupational asbestos sites have been reported in the literature and the following summary is based on a previously published review (Berman and Chatfield 1990). Typically, the major components of the dust observed in most environments are non-fibrous, isometric particles. Fibrous structures consistently represent only a minor fraction of total dust. Asbestos structures represent a subset of the fibrous structures.

The magnitude of the fraction of total dust represented by fibers and the fraction of fibers composed of asbestos minerals vary from site to site. However, the fraction of asbestos in total dusts has been quantified only in a very limited number of occupational and environmental settings (see, for example, Lynch et al. 1970 or Cherrie et al. 1987).

The gross features of structure size distributions appear to be similar among asbestos dusts characterized to date (Berman and Chatfield 1990). The major asbestos fraction of all such dusts are small structures less than 5 μm in length. Length distributions generally exhibit a mode (maximum) between 0.8 and 1.5 μm with larger fibers occurring with decreasing frequency. Fibrous structures longer than 5 μm constitute no more than approximately 25% of total asbestos structures in any particular dust and generally constitute less than 10%.

Diameters appear to exhibit a narrow distribution about a mean for each specific length. Both the mean and the spread of the diameter distribution increases as the length of the structures increase. The increase in diameter with length appears to be more pronounced for chrysotile than for the amphiboles, presumably due to an increase in the fraction of chrysotile bundles contributing to the overall distribution as length increases.

Only a few studies have been published that indicate the number of complex structures in asbestos size distributions. The limited data available indicate that complex structures may constitute a substantial fraction (up to one third) of total structures, at least for chrysotile dusts (see, for example, Sebastien et al. 1984). Similar results were also obtained during a re-analysis of dusts generated from the asbestos samples evaluated in the animal inhalation studies conducted by Davis et al. (Berman et al. unpublished). This is the same re-analysis used to support a recent study of asbestos

Table 3-2: COMPARISON OF APPLICABLE METHODS FOR MEASURING ASBESTOS IN AIR

	NIOSH 7400[1]	NIOSH 7402[2]	YAMATE[3]	AHERA[4]	ISO[5,6]
Analytical Technique	PCM	TEM	TEM	TEM	TEM
Preparation Methodology	Direct (no transfer)	Direct	Direct (Indirect Optional)	Direct	Direct (Indirect Optional)
Magnification	450x	10,000x	20,000x	15,000x - 20,000x	20,000x (total structures) 10,000x (structures longer than 5 µm)
Dimensions Counted					
Length (L):	L .> 5 µm	L > 1 µm	L > 0.06 µm	L > 0.5 µm	L > 0.5 µm, total structures L > 5 µm, long structures
Width (W):	W > 0.25 µm	3.0 > W > 0.04 µm	W > 0.02 µm	W > 0.02 µm	W < 3.0 µm (respirability)
Aspect Ratio (AR):	AR > 3	AR > 3	AR > 3	AR > 5	AR > 5
Sensitivity:					
s/cm²				0.005	Adjustable
s/mm²				70	10 for total structures 0.1 for long structures
Mineralogy Determined	No	Yes	Yes, except matrix particles	Yes, except matrix particles	Yes
Maximum Number Counted	100 structures	100 structures	100 structures	50 structures	100 total structures 100 long structures
Maximum Area Scanned	100 fields	100 grid openings	10 grid openings	Blanks: 10 openings Samples: 10 openings (assuming defined sensitivity is achieved with the collected air volumes).	Adjustable

Table 3-2 (Page 2)

	NIOSH 7400	NIOSH 7402	YAMATE	AHERA	ISO
Statistically Balanced Counting[7]	No	No	No	No	Yes
Counting Rules					
Structures	Count all structures exhibiting L > 5 µm, W < 3.0 µm, and AR > 3.	Count all structures exhibiting L > 1 µm, W < 3.0 µm, and AR > 3. Note PCME[8] fraction within count.	Count all structures exhibiting an AR > 3.	Count all structures with L > 0.5 µm exhibiting an AR > 5. Record individual fibers within all groupings with fewer than 3 intersections. Count structures with L > 5 µm separately (PCME[9]).	Count all structures with L > 0.5 µm or containing components with L > 0.5 µm that also exhibit an AR > 5. Separately identifiable components of parent structures that satisfy dimensional criteria are also separately enumerated. Conduct a similar count to that indicated above for structures with L > 5 µm.
Bundles	Bundles meeting overall dimensional criteria generally counted as single fibers unless up to 10 individual fiber ends can be distinguished within the bundle (representing 5 individual fibers).	Bundles meeting overall dimensional criteria generally counted as single fibers.	Bundles meeting overall dimensional criteria generally counted as single entities and noted as bundles on the count sheet.	Bundles of 3 or more fibers that meet the overall dimensional criteria are counted as single entities and noted as bundles on the count sheet.	Count parent bundles with L > 0.5 µm containing at least one component fiber that exhibits an AR > 5. Qualifying bundles that are components of other parent structures are also separately enumerated. For counts of structures with L > 5 µm, include only bundles longer than 5 µm.
Clusters	Within a cluster, count up to 10 individual fiber ends from (up to 5) fibers that meet the overall dimensional criteria. Otherwise, count a cluster as a single entity.	Within a cluster, count up to 3 individual fibers that meet the overall dimensional criteria. Otherwise, clusters that contain more than 3 fibers that meet the overall dimensional criteria are counted as single clusters.	Within a cluster, count up to 3 individual fibers that meet the overall dimensional criteria. Otherwise, clusters that contain more than 3 fibers that meet the overall dimensional criteria are counted as single clusters.	A collection of fibers with more than 2 intersections where at least one individual projection meets the overall dimensional criteria is counted as a single cluster.	Distinguish "disperse" and "compact" clusters. Count all clusters containing at least one component fiber or bundle satisfying appropriate dimensional criteria. Separately enumerate up to 10 component structures satisfying appropriate dimensional criteria.

Table 3-2 (Page 3)

	NIOSH 7400	NIOSH 7402	YAMATE	AHERA	ISO
Matrices	Count up to 5 fibers emanating from a clump (matrix). Each individual fiber must meet the dimensional criteria.	Count individually identifiable fibers within a matrix. Fibers must individually meet the dimensional criteria.	Count as a single matrix, all matrices with at least one protruding or embedded fiber that meets the dimensional criteria.	Count as a single matrix, all matrices with at least one protruding fiber such that the protruding section meets the dimensional criteria.	Distinguish "disperse" and "compact" matrices. Count all matrices containing at least one component fiber or bundle satisfying appropriate dimensional criteria. Separately enumerate up to 10 component structures satisfying appropriate dimensional criteria.

1. National Institute for Occupational Safety and Health (1985). *Method for Determination of Asbestos in Air Using Positive Phase Contrast Microscopy.* NIOSH Method 7400. NIOSH, Cincinnati, Ohio, U.S.A.

2. National Institute for Occupational Safety and Health (1986). *Method for Determination of Asbestos in Air Using Transmission Electron Microscopy.* NIOSH Method 7402. NIOSH, Cincinnati, Ohio, U.S.A.

3. Yamate, G., Agarwal, S.C., and Gibbons, R.D. (1984). *Methodology for the Measurement of Airborne Asbestos by Electron Microscopy.* U.S. EPA Report No. 68-02-3266. U.S. Environmental Protection Agency, Washington, D.C., U.S.A.

4. U.S. Environmental Protection Agency (1987). *Asbestos Hazard Emergency Response Act: Asbestos-Containing Materials in Schools.* Final Rule and Notice (Appendix A: AHERA Method). Federal Register, 40 CFR 763, Vol. 52, No. 2, pp. 41826-41903, October.

5. ISO 10312: *Ambient Air - Determination of Asbestos Fibres - Direct-Transfer Transmission Electron Microscopy Method.* (Developed by Chatfield, E.J. 1993).

6. Note that the ISO Method is closely related to to the Interim Superfund Method: Chatfield, E.J. and Berman, D.W. (1990). *Superfund Method for the Determination of Asbestos in Ambient Air. Part 1: Method Interim Version..* Prepared for the U.S. Environmental Protection Agency, Office of Emergency and Remedial Response, Washington, D.C. EPA/540-2-90/005a. May. Both methods derive from a common development effort headed by Eric Chatfield. The ISO Method incorporates counting rules that are further refined over what was presented in the Superfund Method, which was published first.

7. Statistically balanced counting is a procedure incorporated into some asbestos methods (e.g. the Superfund Methods and the ISO Methods) in which long structures (typically longer than 5 µm) are counted separately during a lower magnification scan than used to count total structures (which are predominantly short). This procedure assures that the relatively rare longer structures are enumerated with comparable precision to that of the shorter structures.

8. PCME stands for phase contrast microscope equivalent and indicates the fraction of structures observed by transmission electron micrscopy that would also be visible by phase contrast microscopy.

characteristics that promote biological activity (Berman et al. 1995), which is discussed further in Section 5.6.2.

Historically, fibrous structures have been arbitrarily defined as structures exhibiting aspect ratios (the ratio of length to width) greater than 3:1 to distinguish them from isometric particles (Walton, 1982). However, alternate definitions for fibers have also been proposed, which are believed to better relate to biological activity (see, for example, Wylie et al. 1993 or Berman et al. 1995). The degree to which fibers are combined within complex structures in a particular dust may also affect the biological activity of the dust (Berman et al. 1995). Therefore, proper characterization of asbestos exposure requires that the relative contributions from each of many components of exposure be simultaneously considered. Factors that need to be addressed include the distribution of structure sizes, shapes, and mineralogy in addition to the absolute concentration of structures. Such considerations are addressed further in Chapter 5. Thus, unlike the majority of other chemicals frequently monitored at hazardous wastes sites, asbestos exposures cannot be adequately characterized by a single concentration parameter.

3.2 CAPABILITIES OF ANALYTICAL TECHNIQUES USED TO MONITOR ASBESTOS

Due to a complex history, a range of analytical techniques and methods have been employed to measure asbestos in the various studies conducted over time (Walton 1982). Use of these various methods has affected the comparability of results across the relevant asbestos studies (Berman and Chatfield 1990). Therefore, the relative capabilities and limitations of the most important methods used to measure asbestos are summarized here. Later sections of this report incorporate attempts to reconcile effects that are attributable to the limitations of the different methods employed in the various studies evaluated.

Analytical techniques used to measure airborne asbestos concentrations vary greatly in their ability to fully characterize asbestos exposure. The capabilities and limitations of four analytical techniques (midget impinger, phase contrast microscopy, scanning electron microscopy, and transmission electron microscopy) need to be considered here.

Midget impinger (MI) and phase contrast microscopy (PCM) are the two analytical techniques used to derive exposure estimates in the majority of epidemiology studies from which the existing risk coefficients are derived. Scanning electron microscopy (SEM) is an analytical technique that has been employed in several key animal studies. Transmission electron microscopy (TEM) provokes interest because it is the only analytical technique that is potentially capable of distinguishing all of the characteristics of asbestos that potentially affect biological activity.

Although PCM is widely used to characterize occupational exposures, its inability to distinguish between asbestos and non-asbestos and its lack of sensitivity limits its usefulness in environmental settings (Berman and Chatfield 1990). Consequently, TEM is the technique that has been recommended for use at Superfund sites (Chatfield and Berman 1990 and Berman and Kolk 1997).

A general comparison of the relative capabilities and limitations of the analytical techniques introduced above is presented in Table 3-1.

Table 3-1:
Capabilities and Limitations of Analytical Techniques Used for Asbestos Measurements[1]

Parameter	Midget Impinger	Phase Contrast Microscopy	Scanning Electron Microscopy	Transmission Electron Microscopy
Range of Magnification	100	400	2,000 - 10,000	5,000 - 20,000
Particles Counted	All	Fibrous Structures[2]	Fibrous Structures[2]	Fibrous Structures[2,3]
Minimum Diameter (size) Visible	1 µm	0.3 µm	0.1 µm	< 0.01 µm
Resolve Internal Structure	No	No	Maybe	Yes
Distinguish Mineralogy[4]	No	No	Yes	Yes

1. The capabilities and limitations in this table are based primarily on the physical constraints of the indicated instrumentation. Differences attributable to the associated procedures and practices of methods in common use over the last 25 years are highlighted in Table 3-2.

2. Fibrous structures are defined here as particles exhibiting aspect ratios (the ratio of length to width) greater than 3 (see Walton 1982).

3. TEM counts frequently resolve individual fibrous structures within larger, complex structures. Based on internal structure, several different counting rules have been developed for handling complex structures. See the discussion of methods presented below.

4. Most SEM and TEM instruments are equipped with the capability to record selected area electron diffraction (SAED) spectra and perform energy dispersive X-ray analysis (EDXA), which are used to distinguish the mineralogy of structures observed.

Importantly, the physical limitations of the various analytical techniques (instrumentation) is only part of the problem. To provide reproducible results that can be compared meaningfully to other analyses in other studies, one must also consider the choice of procedures (methods) that address everything from sample collection and preparation to rules for counting and quantifying asbestos structures.

Multiple methods have been published for use in conjunction with several of the analytical techniques mentioned above (particularly TEM). Such methods differ in the procedures incorporated for sample preparation and for the manner in which asbestos structures are counted. The sample preparation requirements, conditions of analysis, and structure counting rules for several of the most commonly employed methods are presented in Table 3-2 to illustrate how the choice of method can result in substantially different measurements (even on duplicate or split samples).

The second column of Table 3-2 describes the specifications of the PCM method currently mandated by the Occupational Safety and Health Agency (OSHA) for characterizing asbestos exposure in occupational settings. Although this method is in common use today, several alternate methods for counting fibrous structures by PCM have also been used historically (see Walton 1982). Therefore, PCM measurements reported in earlier studies (including the available epidemiology studies) may not be comparable to PCM results collected today.

The last four columns of Table 3-2 describe TEM methods that are in current use. Comparison across these methods indicates:

- the shortest lengths included in counts using these methods vary between 0.06 and 1 μm. Given that structures shorter than 1 μm represent a substantial fraction of total asbestos structures in almost any environment (Section 3.1), this difference alone contributes substantially to variation in measurement results across methods;

- the definitions and procedures for counting complex structures (i.e. bundles, clusters, and matrices) vary substantially across methods, which further contribute to variation in measurement results. For example, the ISO Method requires that component fibers of clusters and matrices be counted separately, if they can be readily distinguished. In contrast, clusters are counted as single structures under the AHERA Method; and

- although all of the methods listed incorporate sample preparation by a direct transfer process, several of the methods have also been paired with an optional indirect transfer process. Measurements derived from split samples that are prepared, respectively, by direct and indirect transfer, can vary by factors as large as several 100 (Berman and Chatfield 1990). More typically, however, counts of asbestos structures on samples

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Analytical Technique	PCM	TEM	TEM	TEM	TEM
Preparation Methodology	Direct (no transfer)	Direct	Direct (Indirect Optional)	Direct	Direct (Indirect Optional)
Magnification	450x	10,000x	20,000x	15,000x - 20,000x	20,000x (total structures) 10,000x (structures longer than 5 µm)
Dimensions Counted					
Length (L):	L > 5 µm	L > 1 µm	L > 0.06 µm	L > 0.5 µm	L > 0.5 µm, total structures L > 5 µm, long structures
Width (W):	W > 0.25 µm	3.0 > W > 0.04 µm	W > 0.02 µm	W > 0.02 µm	W < 3.0 µm (respirability)
Aspect Ratio (AR):	AR > 3	AR > 3	AR > 3	AR > 5	AR > 5
Sensitivity:					
s/cm³				0.005	Adjustable
s/mm²				70	10 for total structures 0.1 for long structures
Mineralogy Determined	No	Yes	Yes, except matrix particles	Yes, except matrix particles	Yes
Maximum Number Counted	100 structures	100 structures	100 structures	50 structures	100 total structures 100 long structures
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Bundles	Bundles meeting overall dimensional criteria generally counted as single fibers unless up to 10 individual fiber ends can be distinguished within the bundle (representing 5 individual fibers).	Bundles meeting overall dimensional criteria generally counted as single fibers.	Bundles meeting overall dimensional criteria generally counted as single entities and noted as bundles on the count sheet.	Bundles of 3 or more fibers that meet the overall dimensional criteria are counted as single entities and noted as bundles on the count sheet.	Count parent bundles with L > 0.5 µm containing at least one component fiber that exhibits an AR > 5. Qualifying bundles that are components of other parent structures are also separately enumerated. For counts of structures with L > 5 µm, include only bundles longer than 5 µm.
Clusters	Within a cluster, count up to 10 individual fiber ends from (up to 5) fibers that meet the overall dimensional criteria. Otherwise, count a cluster as a single entity.	Within a cluster, count up to 3 individual fibers that meet the overall dimensional criteria. Otherwise, clusters that contain more than 3 fibers that meet the overall dimensional criteria are counted as single clusters.	Within a cluster, count up to 3 individual fibers that meet the overall dimensional criteria. Otherwise, clusters that contain more than 3 fibers that meet the overall dimensional criteria are counted as single clusters.	A collection of fibers with more than 2 intersections where at least one individual projection meets the overall dimensional criteria is counted as a single cluster.	Distinguish "disperse" and "compact" clusters. Count all clusters containing at least one component fiber or bundle satisfying appropriate dimensional criteria. Separately enumerate up to 10 component structures satisfying appropriate dimensional criteria.

Table 3-2 (Page 3)

	NIOSH 7400	NIOSH 7402	YAMATE	AHERA	ISO
Matrices	Count up to 5 fibers emanating from a clump (matrix). Each individual fiber must meet the dimensional criteria.	Count individually identifiable fibers within a matrix. Fibers must individually meet the dimensional criteria.	Count as a single matrix, all matrices with at least one protruding or embedded fiber that meets the dimensional criteria.	Count as a single matrix, all matrices with at least one protruding fiber such that the protruding section meets the dimensional criteria.	Distinguish "disperse" and "compact" matrices. Count all matrices containing at least one component fiber or bundle satisfying appropriate dimensional criteria. Separately enumerate up to 10 component structures satisfying appropriate dimensional criteria.

1. National Institute for Occupational Safety and Health (1985). *Method for Determination of Asbestos in Air Using Positive Phase Contrast Microscopy.* NIOSH Method 7400. NIOSH, Cincinnati, Ohio, U.S.A.

2. National Institute for Occupational Safety and Health (1986). *Method for Determination of Asbestos in Air Using Transmission Electron Microscopy.* NIOSH Method 7402. NIOSH, Cincinnati, Ohio, U.S.A.

3. Yamate, G., Agarwal, S.C., and Gibbons, R.D. (1984). *Methodology for the Measurement of Airborne Asbestos by Electron Microscopy.* U.S. EPA Report No. 68-02-3266. U.S. Environmental Protection Agency, Washington, D.C., U.S.A.

4. U.S. Environmental Protection Agency (1987). *Asbestos Hazard Emergency Response Act: Asbestos-Containing Materials in Schools.* Final Rule and Notice (Appendix A: AHERA Method). Federal Register, 40 CFR 763, Vol. 52, No. 2, pp. 41826-41903, October.

5. ISO 10312: *Ambient Air - Determination of Asbestos Fibres - Direct-Transfer Transmission Electron Microscopy Method.* (Developed by Chatfield, E.J. 1993).

6. Note that the ISO Method is closely related to to the Interim Superfund Method: Chatfield, E.J. and Berman, D.W. (1990). *Superfund Method for the Determination of Asbestos in Ambient Air. Part 1: Method Interim Version.*. Prepared for the U.S. Environmental Protection Agency, Office of Emergency and Remedial Response, Washington, D.C. EPA/540-2-90/005a. May. Both methods derive from a common development effort headed by Eric Chatfield. The ISO Method incorporates counting rules that are further refined over what was presented in the Superfund Method, which was published first.

7. Statistically balanced counting is a procedure incorporated into some asbestos methods (e.g. the Superfund Methods and the ISO Methods) in which long structures (typically longer than 5 µm) are counted separately during a lower magnification scan than used to count total structures (which are predominantly short). This procedure assures that the relatively rare longer structures are enumerated with comparable precision to that of the shorter structures.

8. PCME stands for phase contrast microscope equivalent and indicates the fraction of structures observed by transmission electron micrscopy that would also be visible by phase contrast microscopy.

prepared by an indirect transfer procedure are greater than those derived from directly prepared samples by factors of between 5 and 50.

Given the combined effects from the physical limitations of the various techniques employed to analyze for asbestos and the varying attributes of the methods developed to guide use of these techniques, the relative capabilities and limitations of asbestos measurements derived, respectively, from paired methods and techniques in common use can be summarized as follows:

- MI, PCM, SEM, and TEM are all particle counting techniques and the latter three count fibrous particles;
- neither MI nor PCM are capable of distinguishing asbestos from non-asbestos (i.e. they are incapable of determining structure mineralogy);
- counting rules used in conjunction with MI do not distinguish isometric particles from fibers;
- counting rules used in conjunction with PCM limits counting to fibrous structures longer than 5 μm with aspect ratios greater than 3:1;
- the range of visibility associated with PCM limits counting to fibers thicker than approximately 0.3 μm;
- under conditions typically employed for asbestos analysis, the range of visibility associated with SEM limits counting to fibers thicker than approximately 0.1 μm, which is only marginally better than PCM;
- SEM is capable of distinguishing asbestos structures from non-asbestos structures;
- TEM is capable of resolving asbestos structures over their entire size range (down to thicknesses of 0.01 μm);
- TEM is capable of distinguishing the internal components of complex asbestos structures; and
- TEM is capable of distinguishing asbestos structures from non-asbestos structures.

More detailed treatments of the similarities and differences between asbestos techniques and methods can also be found in the literature (see, for example, Berman and Chatfield 1990).

Due to the differences indicated, measurements from a particular environment (even from duplicate samples) that are derived using different analytical techniques and methods can vary substantially and are not comparable. In fact, results can differ by two or three orders of magnitude (Berman and Chatfield 1990). More importantly, because the relative distributions of structure sizes and shapes vary from environment to environment, measurements derived using different analytical techniques and methods do not even remain proportional from one environment to the next. Therefore, the results from multiple asbestos studies can only be meaningfully compared if the effects that are attributable to use of differing analytical techniques and methods can be quantified and reconciled. To complicate the situation, however, few of the existing studies document analytical procedures in sufficient detail to reconstruct exactly what was done.

4.0 THE ASBESTOS LITERATURE

This is a description of the common types of studies in the asbestos literature and an overview of the sources of potential error commonly associated with each. Such limitations must be considered when drawing conclusions from the available studies and, more importantly, when comparing inferences across studies.

The types of studies available for examining relationships between risk and asbestos exposure include human epidemiology studies, human pathology studies, animal studies, and in-vitro tissue or cultured cell studies. Because results from such studies need to be compared and contrasted, the methods employed for asbestos characterization in each of these studies need to be reconciled and the procedures employed for evaluating study effects need to be compared and contrasted.

When evaluating the asbestos literature, it is particularly important to assess the analytical methodologies employed in each study (Section 3.2). The only instrument capable of completely delineating structure size distributions is TEM (or TEM combined with other techniques). Thus, conclusions regarding variations in biological effects due to differences in size distributions must be viewed with caution when size distributions are derived using only PCM, SEM, or other analytical techniques. As also indicated previously, the specific methods chosen to define the protocols for sample preparation and structure counting also affect the outcome of measurements so that structure size distributions derived using different methods cannot be directly compared (even, for example, when the measurements are all obtained using TEM).

Epidemiology studies, which track the incidence of disease within a defined group (cohort) sharing comparable exposures, have been performed on cohorts of workers exposed to asbestos and other mineral fibers in a variety of occupational and environmental settings. Among these, studies that include quantification of exposures are particularly useful for evaluating dose/response relationships and deriving risk coefficients. However, because exposure measurements from most of the available quantitative epidemiology studies are based on midget impinger measurements or PCM measurements, detailed characterization of the size distribution or the mineral type of fibrous structures is generally lacking.

In some cases, the limited exposure characterization presented in specific epidemiology studies can be augmented by pairing such studies with published TEM characterizations of dusts from the same or similar exposure settings, to the extent the appropriate supplemental studies are available. In fact, this is the procedure adopted in this protocol to adapt the existing risk coefficients to exposure indices thought to better relate to biological activity (Section 6.2). Such an approach is limited, however, to the extent that the published asbestos characterizations actually represent exposure conditions in the corresponding epidemiology studies.

Human pathology studies provide a characterization of disease morphology and correlations between causes of death and the types of asbestos fibers retained in the lungs and other bodily tissues. These studies generally involve microscopic examination of tissue samples for indications of morphologic changes characteristic of disease and/or microscopic examination of digested tissue specimens to characterize the mineral fibers extracted from the tissue.

The results of human pathology studies need to be evaluated carefully by addressing effects that are attributable to the way that tissue samples are prepared for analysis (e.g. ashing or bleach digestion), the choice of methods employed for characterization of asbestos, and the choice of locations from which tissue samples are collected for analysis. Fiber concentration estimates have been shown to vary substantially depending on whether tissue samples are ashed or digested in bleach prior to asbestos analysis (HEI-AR 1991). The ways in which choice of analytical methods can affect the outcome of these kinds of studies was described in the last Chapter (Section 3.2). Effects attributable to choice of tissue location are described further below.

In animal studies, various species are exposed to measured doses of size-selected mineral fibers and the resultant biological responses are monitored. Animals may be dosed either by inhalation, intratracheal installation, implantation, or injection (U.S. EPA 1986). Such studies are conducted for several purposes. As with human pathology studies, animal pathology studies are those in which the transport of asbestos structures is tracked through the various organs and tissues of the animal and the attendant cellular and molecular changes are characterized. In parallel with quantitative epidemiology studies, animal dose/response studies track the incidence of disease among a population that has been exposed in a controlled manner. One of the advantages of animal dose/response studies over human epidemiology studies is that exposures are controlled and can be well characterized. The major disadvantage is that uncertainties are introduced when extrapolating the results of animal data to predict effects in humans.

As with human epidemiology and pathology studies, the validity of conclusions drawn from animal studies depends strongly on the techniques and methods used to characterize asbestos structures. The ability to reconcile conclusions derived from many animal studies with the rest of the asbestos literature is limited because SEM was commonly employed to measure asbestos in the animal studies but not other studies. Even many of those studies in which TEM was employed for asbestos analysis suffer from use of non-standard methods that cannot be easily reconciled with the more traditional TEM methods.

The route of exposure employed in a particular animal study is also important to consider. Each of the routes of exposure commonly employed in these studies (inhalation, intratracheal installation, and injection or implantation) delivers different

injection or implantation studies deliver 100% of all size categories of structures to the target tissue. However, the efficiency that each size category is delivered by inhalation is a function of the aerodynamic properties of the asbestos structures and the air flow characteristics of the lungs. Thus, the relationship between dose and exposure depends upon the route of exposure employed.

Regarding the measurement of health effects, many of the results in animal studies suffer from a lack of statistical significance because only small numbers of tumors are observed. Consequently, trends cannot be established conclusively. Interestingly, some studies draw conclusions regarding the relative potency of different sample types when variations within the dose/response trend of a single sample type is larger than observed differences between types.

In both human and animal pathology studies, the location of a tissue sample excised for analysis is a critical factor that governs the quality of the study. Numerous authors have reported that asbestos is non-uniformly distributed in lung parenchyma and other tissues following exposure (see, for example: Davis et al. 1986, Bignon et al. 1979, or Pooley 1982). The incidence of lesions and other pathological effects attributed to asbestos exposure correspondingly exhibit a non-uniform distribution.

To sample deep lung tissue reproducibly, it is necessary to select a specific section of lung parenchyma from a defined portion of the bronchio-alveolar tree. Pinkerton et al. (1986) showed that the deposition of asbestos in the lungs is an inverse function both of the pathlength and the number of bifurcations between the trachea and the site. Thus, analyses of samples from different animals of the same species can only be compared meaningfully if the samples are collected from identical locations in the bronchio-alveolar tree. Similar, nonuniform depositional patterns have also been observed in humans (Raabe 1984). Unfortunately, few of the available animal and human pathology studies have considered this important factor when selecting tissue samples for analysis.

For animal inhalation studies, meaningful comparison of the relative deposition of asbestos dusts between species is not direct. To extrapolate results between species, differences in physiology between species need to be addressed. However, if measurements are available for both species, it is possible to compare relative tissue doses (mass of asbestos per mass of tissue).

In-vitro tissue studies typically involve the dosing of isolated tissue cultures with various types and quantities of asbestos while monitoring for changes in levels of various enzymes or metabolites within the system. In some cases, cultures are monitored for morphological changes within the cells of the system or for changes in the growth or survivability of the culture as a whole. Limitations in such studies may include:

- uncertainties introduced by the methods employed for characterizing the asbestos samples used for dosing;

- uncertainties introduced when attempting to equate dosing carried out in in-vitro cultures and dosing associated with real-world exposures of interest; and

- effects attributable to uncontrolled differences between the environment of the tissue culture and the in-vivo environment being simulated.

At the same time these types of studies are particularly useful for elucidating the biophysical and biochemical mechanisms that contribute to the induction of asbestos-related disease.

Many studies in the current literature also incorporate combined aspects of several of the four general study types described above. For these studies, a corresponding combination of the considerations described above must be addressed when evaluating such studies and comparing their results with inferences derived from the rest of the literature.

5.0 ASBESTOS CHARACTERISTICS THAT RELATE TO BIOLOGICAL ACTIVITY

As indicated in Chapter 2, the first two steps of the process required to develop a protocol for assessing asbestos risk are: (1) to reconcile the existing literature by considering the capabilities and limitations of the methods employed for data development and (2) to identify the characteristics of the asbestos that determine risk. Accordingly, the principal processes that determine the biological response to asbestos are identified below and the relevant literature characterizing such processes is evaluated. Based on the analysis presented, the characteristics of asbestos that determine biological activity are also identified.

It is generally recognized that risks posed by exposure to asbestos dusts depend predominantly on the physical dimensions of the fibrous structures in the dust (e.g. U.S. EPA 1986, Mossman et al. 1990). However, other factors that relate to mineralogy and, therefore, fiber type (such as surface chemistry and in-vivo durability) have also been shown to affect biological activity in at least some studies (Mossman 1993).

Traditional methods of characterizing exposure have not proven adequate to develop a dose/response relationship for asbestos that uniformly applies under all exposure circumstances. This is likely due to inadequate understanding both of the critical range of dimensional parameters that best correlate with risk and of the degree to which fiber type affects risk.

The principal outstanding issues are:

- whether short fibers (which were excluded from the asbestos analyses performed in the majority of available epidemiology studies) contribute substantially to risk;
- whether thin fibers (which cannot be detected by the analytical methods used in the majority of the available epidemiology studies) contribute substantially to risk;
- whether asbestos aggregates (bundles, clusters, and matrices) should be ignored, counted as single entities, or weighted in proportion to the number of individual fibers present in each aggregate;
- whether fibers exhibiting the same dimensions but of varying mineralogy (i.e. varying fiber type) contribute uniquely to risk;
- whether fiber types in addition to those included in the currently accepted definition of asbestos contribute to risk (assuming that they also exhibit appropriate dimensional characteristics);

- whether factors addressing fiber size and fiber type relate to the induction of each of the asbestos-related diseases (primarily asbestosis, pulmonary cancer, and mesothelioma) in the same manner; and

- whether the currently accepted dose-response models for each of the asbestos-related diseases adequately describe the induction of each respective disease.

To date, the main emphasis has been placed on animal implantation and injection studies for identifying the characteristics of asbestos that determine biological activity. Consequently, there are questions concerning the exact relationship between effects observed in such studies and effects that obtain when exposure is via inhalation. Another issue that remains unresolved is the extent to which animal data can be extrapolated to human exposures. These issues are considered more fully in the following sections of this Chapter.

Given the considerations addressed in Chapters 3 and 4, selected studies from the available literature provide a consistent picture of asbestos characteristics that relate to biological activity. The objectives are to identify the specific morphological characteristics (e.g. length, surface area, mass, surface charge, chemical composition) of asbestos structures that best correlate with biological activity and to delineate the range of values for each characteristic over which biological activity is important.

The biological activity of inhaled asbestos depends on the following factors:

- the extent that asbestos structures are respirable and the pattern of deposition of inhaled structures;

- the extent that deposited structures are subsequently cleared or degraded;

- the extent that deposited structures are translocated from the lung to neighboring tissues; and

- the extent that retained structures induce a biological response in the surrounding tissue.

5.1 FACTORS AFFECTING RESPIRABILITY AND DEPOSITION

Discounting systemic affects resulting from other forms of exposure, factors affecting respirability are common to all of the toxic end points associated with asbestos exposure considered in this study (asbestosis, pulmonary carcinomas, and mesothelioma). To be respirable, an inhaled particle must pass the blocking hairs and

tortuous passageways of the nose and throat and be deposited in the lungs. Particles deposited in the naso-pharengeal portion of the respiratory tract are not considered respirable.

Not all of the inhaled particles that reach the lungs will be deposited. Small particles may not impact lung surfaces during inhalation and are subsequently exhaled. Once a particle impacts on a surface, however, it is likely to remain because the surfaces of the lungs are wetted with a surfactant (Raabe 1984).

Adverse health effects potentially result when particles are deposited in the lungs and remain in contact with tissue within the lungs for a sufficient period of time for biological effects to occur. For mesothelioma, an offending particle must also be translocated from the lung to surrounding mesenchyme.

It is the long-term retention of particles in the respiratory tract that potentially leads to adverse health effects. Consequently, the interplay between deposition and removal (clearance) is an important determinant of biological activity and separating the impact of these two processes is difficult. The term "retention" is used here to represent the fraction of particles remaining in the lungs beyond the time frame over which only the most rapid removal processes are active. The factors affecting retention are addressed further in Section 5.2.

Published inhalation studies divide the respiratory tract into three units (see, for example, Raabe 1984). The naso-pharyngeal portion of the respiratory tract extends from the nares in the nose through the entrance to the trachea. The tracheo-bronchial portion of the respiratory tract includes the trachea and all of the branching bronchi down to the terminal bronchioles. The terminal bronchioles and the alveoli, which are collectively referred to as the "deep lung", are the bronchio-alveolar (or pulmonary) portion of the respiratory tract.

The dimensional requirements for respirability have been studied and reviewed by several authors (see, for example, Raabe, 1984 or U.S. EPA 1986). Much of the data reviewed by these authors is based on earlier studies in which researchers exposed animals or human volunteers to a series of monodisperse spherical particles. In this manner, the impact of the diameter of spherical particles on respirability was elucidated. The respirability of fibrous materials (such as asbestos) tends to be described in terms closely associated with those employed for spherical particles, but with adjustments for density and shape.

5.1.1 Respirability of Spherical Particles

Spherical particles larger than 10 μm in diameter are considered non-respirable because virtually all particles in this size range are trapped in naso-pharyngeal passageways and blocked from entering the lungs. As the diameter of the particles fall,

an increasing fraction traverses the nose and throat and may be deposited in the lungs. About half of particles 5 μm in diameter are blocked before entering the lungs. Virtually all particles smaller than 1 μm enter the lungs, although other factors determine whether they are in fact deposited or simply exhaled. Figure 5-1 (Source: Raabe 1984) is a representation of the relative deposition in the various compartments of the respiratory tract as a function of particle diameter.

Within the lungs (Figure 5-1), the greatest fraction of respirable particles (over the entire range of diameters down to less than 0.01 μm) are deposited in the deep lung (the broncho-alveolar portion of the respiratory tract). Generally, the fraction of particles deposited in the deep lung increases regularly with decreasing diameter until a maximum of 60% deposition in the deep lung is reached at about 0.1 μm diameter.

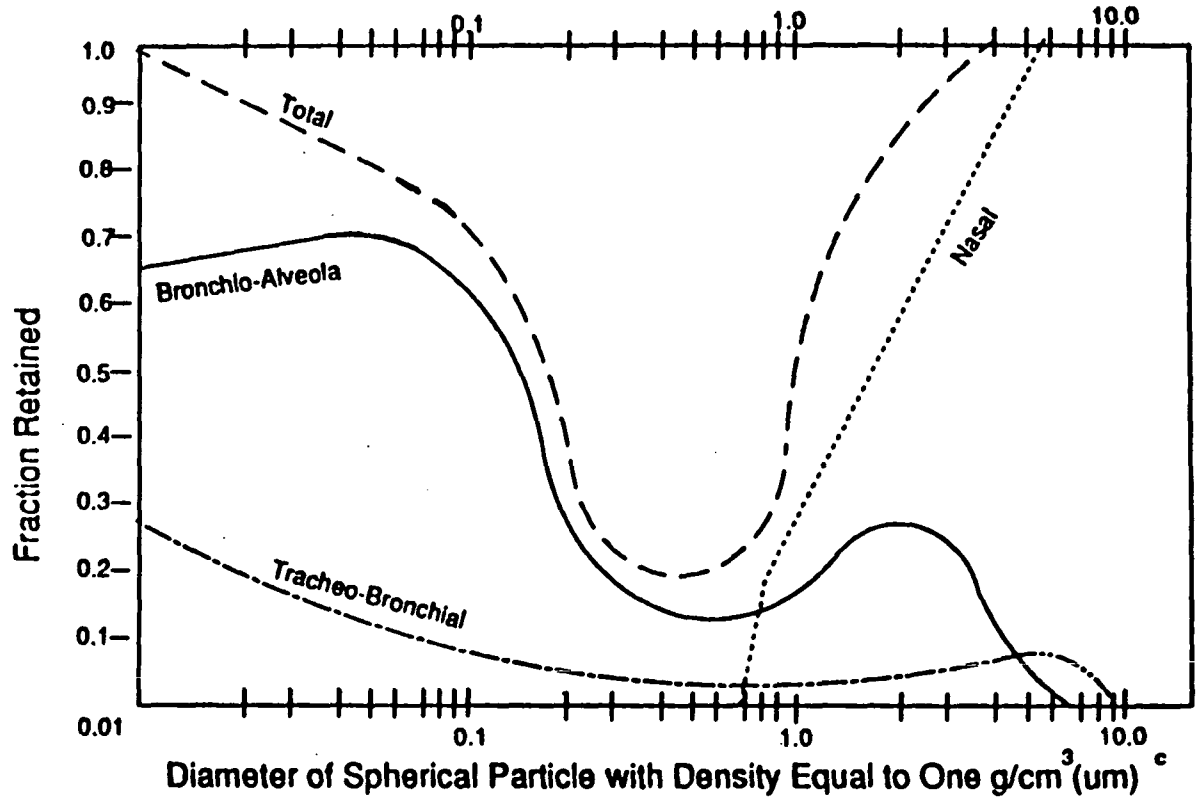
As indicated in Figure 5-1, a transition occurs at particle diameters between 0.5 and 1 μm. For particles in this range and smaller, deposition in the deep lung competes primarily with deposition in the tracheo-bronchial tree and with exhalation; smaller particles have an increasing probability of being exhaled without ever impacting the surface of an air passageway. For particles larger than this transition range, broncho-alveolar deposition is limited chiefly by the fraction of particles that are removed from the air stream prior to reaching the deep lung (either by deposition in the naso-pharyngeal or the tracheo-bronchial portions of the respiratory tract).

The transition between naso-pharyngeal competition with deep-lung deposition and competition from other removal processes is important because during mouth breathing, a process that bypasses the tortuous pathways of the nose and throat, it has been observed that larger particles (up to several micrometers in diameter) may be deposited in the deep lung (Raabe 1984). Because most people spend at least small amounts of time mouth breathing, especially during exertion or during snoring, this mechanism for allowing larger particles to settle in the deep lung should not be ignored.

A diameter of 0.5 μm also happens to represent the transition between the regime where inertial flow and the regime where diffusional flow becomes the major factor controlling deposition in the lungs. Below the 0.5 μm transition, the diffusional diameter becomes more important in determining deposition than the aerodynamic equivalent diameter (defined below).

FIGURE 5-1

FRACTIONS OF RESPIRABLE PARTICLES DEPOSITED IN THE VARIOUS COMPARTMENTS OF THE HUMAN RESPIRATORY TRACT AS A FUNCTION OF AERODYNAMIC EQUIVALENT DIAMETER[a,b]



[a] Source: Raabe 1984.

[b] Assumes a typical tidal value of 1450 cm^3 and a rate of 15 breaths per minute.

[c] Aerodynamic equivalent diameter.

5.1.2 Respirability of Fibrous Structures

Several authors have investigated the effect of the shape of non-spherical particles (including fibers) on respirability and deposition (see, for example, Harris and Timbrell 1977, Strom and Yu 1994, or Yu et al. 1995). It has been found that the behavior of non-spherical particles can be related to the behavior of spherical particles by introducing a concept known as the aerodynamic equivalent diameter. The aerodynamic equivalent diameter is the diameter of a hypothetical spherical particle of unit density that would exhibit the same settling velocities and aerodynamic behavior as the real, non-spherical particle of interest. Factors that affect the aerodynamic equivalent diameter are density, true diameter, true length (for elongated particles such as fibers) and the regularity of the particle shape.

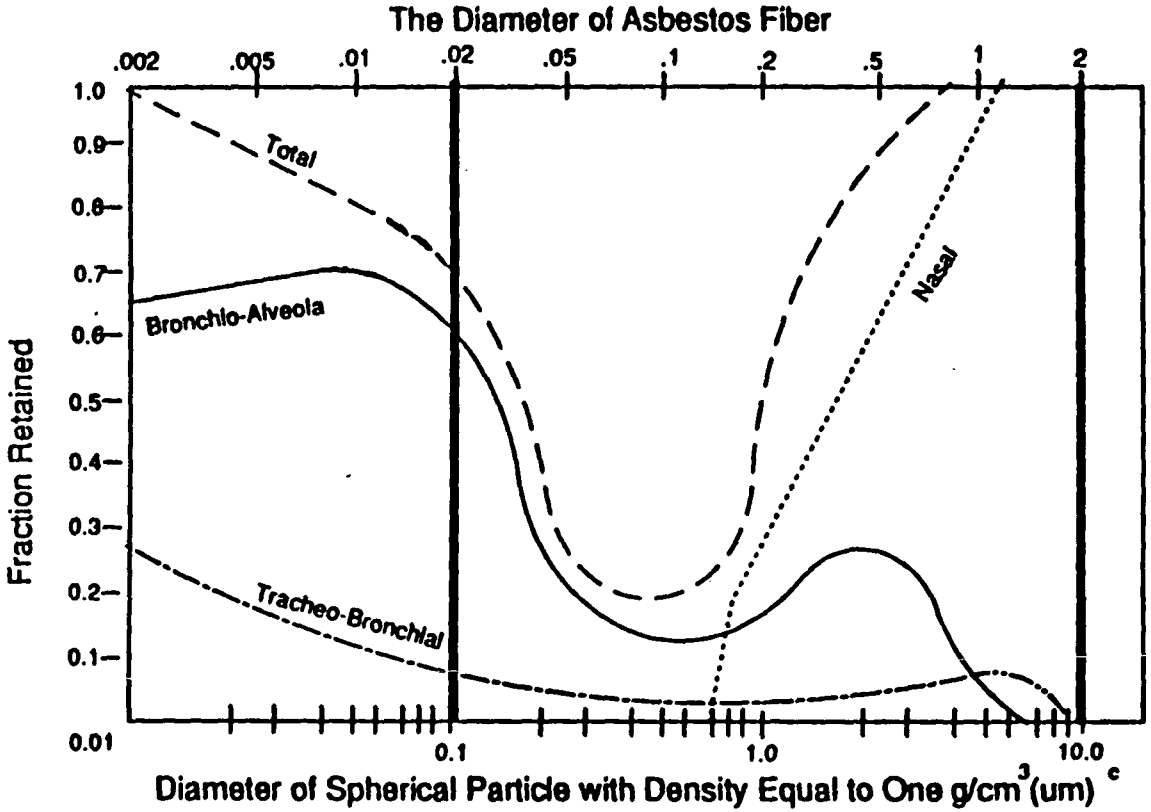
Because fibrous particles tend to align primarily along the axis of travel under the flow conditions found in the lungs, respirability is predominantly a function of the diameter of a fiber and the effect of length is secondary (Harris and Timbrell 1977). Fibrous structures (of unit density) with aspect ratios greater than 3:1 behave like spherical particles with diameters up to 3 times larger (the aerodynamic equivalent diameter) and exhibit only a very weak dependence on length. This is demonstrated in Figure 5-2 where the true diameter of a fiber is graphed on the top horizontal axis against spherical (aerodynamic equivalent) diameters on the bottom horizontal axis. Figure 5-2 is an overlay of Figure 5-1. Note that, to adjust for the density of asbestos, the true diameters listed in the figure have been shifted to the right of where they would appear if the relationship was exactly one third of the aerodynamic equivalent diameter.

Two vertical dashed lines in Figure 5-2 represent effective limits to the range of respirable asbestos. The left line in the figure represents the limiting diameter of the smallest chrysotile fibril (about 0.02 µm true diameter) and thus represents a lower limit to the deposition chart that is of concern when considering asbestos. The right vertical line represents the cutoff where deposition in the deep lung becomes unimportant due to removal of such particles by the naso-pharyngeal passageways. This latter cutoff corresponds to a true fiber diameter of 2.0 µm, which theoretically represents the upper limit to the size of asbestos that is respirable. As indicated in the figure, however, deposition in the deep lung drops precipitously for fibers thicker than about 0.7 µm so that no more than a few percent of asbestos fibers thicker than approximately 1 µm actually reach the deep lung.

Harris and Timbrell (1977) also evaluated the relationship between the overall shape of a particle and the extent of deposition. Over the range of diameters that potentially represent the range of asbestos fibers likely to be encountered, pulmonary deposition decreases with increasing complexity of shape beyond simple cylinders at the expense of increasing naso-pharyngeal or tracheo-bronchial deposition. Thus, fewer clusters and matrices, which exhibit complex shapes, are deposited in the deep lung than fibers

FIGURE 5-2

FRACTIONS OF RESPIRABLE PARTICLES DEPOSITED IN THE VARIOUS COMPARTMENTS OF THE HUMAN RESPIRATORY TRACT AS A FUNCTION OF THE TRUE DIAMETER OF ASBESTOS FIBERS[a,b,c]



[a] Source of original: Raabe 1984.

[b] Assumes a typical tidal value of 1450 cm^3 and a rate of 15 breaths per minute.

[c] The relationship between true diameters and aerodynamic equivalent diameters derived from Harris & Timbrell (1977). Diameters adjusted for shape and density of asbestos fibers.

[d] Aerodynamic equivalent diameter.

and bundles, which are essentially cylinders. This change also becomes increasingly important as the length of the structure increases.

For structures less than 25 μm in length, the difference in deposition between simple fibers and complex clusters or matrices may vary by up to a factor of 2 with the complex structures being more likely to be removed in the naso-pharyngeal portion of the respiratory tract and the fibers more likely to be deposited in the deep lung. At 100 μm lengths, the fraction of complex structures that survive passage through the nose and throat in comparison with simple fibers may vary by a factor of five. This means that large structures become relatively less respirable as their complexity increases. However, during mouth breathing large clusters and matrices may enter the deep lung.

When all of the factors that Harris and Timbrell (1977) addressed are considered, the efficiency of the deposition of asbestos structures in the deep lung is maximal for short, thin, single fibers (less than 10 μm in length with a true diameter less than 0.7 μm). The efficiency decreases slowly with increasing length (up to an effective limit of 200 μm), moderately with increasing complexity of shape, and rapidly with increasing diameter (up to an effective limit of 2.0 μm, true diameter). Thinner fibers, down to the lower limit of the range for asbestos fibers (0.02 μm, true diameter), are deposited with roughly the same efficiency. Approximately 20 to 25% of the fibers within this range are deposited in the deep lung.

In a series of studies, Yu and coworkers combined an improved model of human lung physiology (Asgharian and Yu 1988) with a series of more rigorous equations to describe fiber mobility (Chen 1992) and used these to evaluate the deposition of various types of fibrous materials in the lung. The trends indicated in their studies show general agreement with those reported by Harris and Timbrell but with several notable refinements.

In a study of refractory ceramic fibers (Yu et al. 1995), a maximum deposition efficiency of 15% is reported for fibers that are approximately 6 μm long and approximately 1 μm in diameter. This is close to the fiber size at which maximal deposition is reported by Harris and Timbrell (1977). As with Harris and Timbrell, Yu et al. also report that deposition efficiency decreases precipitously for thicker structures and more slowly for thinner structures. For thinner structures, deposition efficiency increases with both decreasing width and length. As fibers get longer, optimum deposition occurs with decreasing thickness. Thus, for example, a maximum deposition rate of 10% occurs for fibers that are 20 μm long at a thickness of 0.8 μm.

In a study of silicon-carbide whiskers (Strom and Yu 1994), the deposition model is extended to fiber widths as narrow as 0.01 μm. Results from this study indicate that fibers between 0.01 and 0.1 μm in thickness are deposited with a minimum efficiency of 5% up to lengths of approximately 40 μm before efficiency drops below 5%. For thin fibers (thinner than 0.5 μm), shorter fibers tend to be deposited in the deep lung much

more efficiently than longer fibers. More than 25% of thin fibers shorter than 1 μm are deposited in the deep lung following inhalation. Strom and Yu also report that the efficiency of deposition in the deep lung of long structures increases substantially during mouth breathing.

Comparing the results reported for refractory ceramic fibers (density = 2.7 g/cm^3) and silicon-carbide whiskers (density = 3.2 g/cm^3), it also appears that the efficiency of deep-lung deposition increases for thinner and for longer structures as the density of the structures increases. Given the observed density effect, longer and thinner chrysotile fibers would be deposited in the deep lung less efficiently than (denser) amphibole fibers of the same size. However, shorter and thicker chrysotile structures would be deposited somewhat more efficiently than similarly sized amphiboles. This suggests that a greater fraction of the mass of chrysotile that gets deposited in the deep lung will be composed of bundles than the mass fraction of bundles in the air breathed.

Based on the deposition efficiencies predicted by Yu and coworkers, fibrous structures that reach the deep lung in humans are effectively limited to those thinner than approximately 1 μm. It is also apparent that aspect ratio constraints affect only the shortest fibers (i.e., those shorter than approximately 3 μm). The thickness constraint for all longer structures is best described as a maximum width (rather than an aspect ratio).

Yu and coworkers also modified their models to evaluate the rates that fibrous materials are deposited in rat lungs and compared these with results for humans. Such comparisons have implications for the manner in which results from animal inhalation studies are extrapolated to humans.

Results from Yu et al. (1994) suggest that pulmonary deposition of all fibrous structures with lengths between about 1 and 100 μm and thinner than approximately 1 μm occurs at much higher rates in rats than in humans. Fibers as long as 90 μm are deposited in rat lungs at efficiencies exceeding 20% while fewer than 5% of structures this long are deposited in the pulmonary region of human lungs. In fact, it is only structures between 1 and about 20 μm within a very narrow range of thicknesses (centered around 1 μm) that are deposited more efficiently in the deep lungs of humans than in rats.

Yu et al. (1995) also indicate that, even when deposition efficiencies are comparable in rats and humans, due to differences in the total lung mass and breathing dynamics across species, the resulting lung burdens (i.e. the mass or number of structures per mass of lung tissue) are five to 10 times higher in the rat than in humans for any given exposure. Lung burden per lung surface area are also higher in the rat than in humans.

5.1.3 The Effects of Electrostatic Charge on Particle Respirability

Electrostatic charge has been shown to affect the retention of particles within the lungs (see, for example, Vincent 1985). Since processes that generate airborne particles generally involve some form of abrasion, airborne dust particles frequently exhibit varying degrees of electrostatic charge. Although this potentially leads to variation in the efficiency of particle retention in the lungs as a function of the source of the dust, a detailed relationship between surface charge and retention has not been elucidated.

Davis et al. (1988b) report that animals exposed to dusts containing fibrous chrysotile, whose surface charge is reduced with a beta minus source, retain substantially less chrysotile than animals dosed with dusts containing particles whose surface charge has not been reduced. However, the magnitude of the difference in the mass of fibers retained is less than a factor of two, implying that the absolute variation due to this effect may be small. Further research in this area is needed.

Chen and Yu (1993) report that, based on modeling of lung deposition, overall deposition increases with increasing charge density on the particles inhaled. However, due to the pre-filtering by the naso-pharyngeal and tracheo-bronchial portions of the respiratory tract, the effects of electrostatic charge on deep lung deposition appear to be only slight to modest.

Given the results of the above studies, the overall effects of electrostatic charge on particle deposition in the deep lung appear to be relatively minor. Therefore, such effects do not need to be considered explicitly when evaluating the health consequences of asbestos.

5.2 FACTORS AFFECTING DEGRADATION AND CLEARANCE

Degradation and clearance mechanisms compete with deposition to determine the fraction of asbestos that is retained in the lungs. These factors affect all of the toxic end points of interest.

The three units of the respiratory tract defined in the last section (naso-pharyngeal, tracheo-bronchial, and bronchio-alveolar units) differ primarily by the types of clearance mechanisms operating in each section (Raabe, 1984). The structures of the nose and throat are bathed in a continual flow of mucous, which is ultimately swallowed or expectorated. The mucous traps deposited particles and carries them out of the respiratory tract. The air channels of the tracheo-bronchial section of the respiratory tract are lined with cilia and mucous secreting cells. As in the nose and throat, the mucous traps particles deposited in these air pathways and the ciliary escalator transports the mucous up to the throat where it may be swallowed or expectorated.

The terminal bronchioles and alveoli of the deep lung are not ciliated. Particles deposited in this section of the respiratory tract can only be cleared by the following mechanisms:

- if the deposited particles are soluble or if their structural integrity is insufficient to withstand the physical stresses of the lung environment, they may be degraded by splitting or dissolution and their components transported away from the lungs by blood or lymph;

- if they are sufficiently compact to be taken up through phagocytosis into the cells lining the air passageways of the deep lung, they may be transported into cell interiors or transported through to the basement membranes of the lungs or to the lymphatic system; or

- if they are sufficiently compact, they may be taken up by macrophages and transported into the lymphatic system or transported outward to the ciliary escalator of the tracheo-bronchial portion of the respiratory tract.

Due to a combination of chemical and physical stresses in the environment of the lung, asbestos structures may degrade by splitting. Longitudinal splitting, primarily of bundles, produces thinner structures and transverse splitting produces shorter structures. Observations from several studies suggest that chrysotile asbestos commonly undergoes longitudinal splitting in the deep lung while amphiboles appear relatively resistant to splitting (see, for example, Roggli et al. 1987). By changing the size and number of structures that were initially deposited in the lungs, splitting may affect the rates at which the various other degradation and clearance mechanisms operate.

The clearance mechanisms described above for the deep lung may be common to other tissues potentially invaded by asbestos such as the mesenchyme (see, for example, Stanton 1977).

The different clearance mechanisms that are active within the respiratory tract operate over different time frames (Raabe, 1984). Muco-ciliary transport in the nose and throat generally exhibits a half life for clearance of 4 minutes. Clearance of the tracheo-bronchial section of the respiratory tract is a function of the distance from the trachea and generally varies from a half life of 30 minutes for the largest bronchi to approximately 5 hours for the smallest and most remote bronchi. In healthy humans, material deposited in this region is generally cleared within 24 hours. In contrast, the clearance mechanisms operating in the deep lung, beyond the muco-ciliary escalator, operate over time frames of many days to years.

Once in the lungs, the majority of fibers with diameters greater than 2 μm tend to be deposited in the upper bronchioles, which efficiently clear such particles. For asbestos

to remain within the lung long enough to cause a biological response, it generally must be deposited in the terminal bronchioles or the alveoli beyond the ciliary escalator. As indicated in the last section, more than one half of asbestos fibers less than 3 μm in diameter that are deposited in the lungs are expected to be removed by ciliary actions and subsequently swallowed.

It is primarily the asbestos particles that are deposited in the deep lung, beyond the ciliary escalator, that present a substantial potential for causing adverse health effects. Clearance in the other portions of the respiratory tract is sufficiently rapid that biological effects associated with asbestos exposure are seldom manifested. Although there are a small number of studies that indicate a potential connection between asbestos exposure and cancers of the nose and throat, the evidence is much less compelling than the overwhelming evidence supporting a link between asbestos inhalation and lung cancer or mesothelioma (U.S. EPA 1986). Similarly, a number of studies show that asbestos deposition in the deep lung are heaviest at alveolar duct bifurcations and biological responses appear to be initiated where deposition is heaviest (see, for example, Brody et al. 1981, Davis et al. 1987, and Johnson 1987).

Detailed knowledge of clearance and degradation mechanisms have been developed primarily from animal retention studies and human pathology studies. Dynamic models have also been developed.

5.2.1 Retention Studies

Retention studies track the time-dependence of the lung burden of asbestos (the concentration of asbestos in the lung) during or following exposure. Thus, such studies are designed to indicate the degree to which inhaled structures are retained. Depending on the time frame evaluated, however, effects due to deposition and those due to clearance may not easily be distinguished in such studies.

Results from retention studies must be evaluated carefully. This is because lung burden estimates from such studies may be affected by the manner in which asbestos is isolated from lung tissue for measurement and the manner in which the concentration of asbestos is quantified. For example, lung burden estimates may vary substantially depending on whether lung tissue is ashed or dissolved in bleach during sample preparation (Chapter 4).

Retention studies that track lung burden following a single, short term exposure tend to confirm that deposition rates for similarly sized amphibole and chrysotile structures are comparable (see, for example, Roggli et al. 1987). Thus, respirability and deposition are processes that do not depend on mineral type. Roggli and coworkers report that 19% of the mass of crocidolite structures inhaled by rats is retained in the lungs immediately following exposure. Similarly, 23% of the mass of inhaled chrysotile is retained.

Like several other studies, Roggli et al. observed in this study that clearance mechanisms are size dependent and that short structures are cleared more readily than long structures. They also observe that chrysotile splits longitudinally in the lung environment, which increases the number concentration of (thinner) structures in the short term (before clearance mechanisms become dominant). In contrast with several other studies, they also report that clearance rates are independent of mineral type. Thus, for example, after four weeks, Roggli et al. report that 75% of crocidolite structures and a comparable 81% of chrysotile structures were cleared from the lungs of the rats studied in this experiment.

In contrast to the above, retention studies that track lung burden during chronic exposure suggest that clearance mechanisms may depend on mineralogy (and, thus, fiber type). Wagner et al. (1974), for example, report that amphibole lung burdens increase continually as long as exposure to amphiboles continues and that amphibole concentrations in lung tissue decrease only slowly following cessation of exposure. In contrast, chrysotile lung burdens reach a plateau despite continued exposure. This indicates that a steady state between deposition and clearance is reached for chrysotile while removal processes for amphiboles are much slower. The concentration at which chrysotile reaches a plateau is shown to be a function of the level of exposure. Corresponding results have also been reported in other, similar studies.

- Davis and coworkers (1978, 1980, 1988a, and 1988b) report that retention of asbestos (measured in terms of mass) appears to be a function of fiber type and surface charge in addition to fiber size. With regard to fiber type, for example, Davis et al. (1978) report that substantially more amphibole (amosite) asbestos appears to be deposited and retained in the lungs of exposed rats than chrysotile. Chrysotile is also apparently cleared more readily than amosite.

- Jones et al. (1988) report that the lung-tissue concentration of amosite (an amphibole asbestos) increases continually with exposure and the rate of increase is proportional to the level of exposure. A leveling off of amphibole concentrations in lung-tissue was not observed in this study as long as exposure continued, even for the lowest level of exposure (0.1 mg/m^3) studied. The lowest exposure concentration evaluated in this study is only 1% of the concentration at which chrysotile lung burdens were shown to reach equilibrium in other retention studies.

Several related animal studies suggest ways in which mineralogy may affect the efficiency of clearance, particularly with regard to susceptibility to degradation. For example, Bellman et al. (1986), Roggli et al. (1984 and 1987), and Wright and Kushner (1975) all indicate that glass and certain other materials (including chrysotile asbestos) appear to dissolve and degrade in vivo.

- Bellman et al. (1986) showed that chrysotile and glass structures instilled into rats rapidly biodegrade. Acid treated structures degrade even more rapidly. Chrysotile was also observed to split longitudinally in this study. In contrast, long crocidolite structures, which do not degrade in vivo, were removed only slowly, with a half life greater than 1000 days.

- While amphiboles appear relatively immune to chemical attack, Thommassin et al. (1980) have demonstrated that chrysotile readily loses magnesium in acid solution. In strong acid, the loss occurs in stepwise fashion where the surface magnesium is lost first. Although the process is slower, acids of the Krebs cycle (found in living tissue) also leach magnesium from chrysotile.

- Le Bouffant et al. (1978) also confirm chrysotile bundles dissociate in vivo over time.

A range of studies also indicate that chrysotile asbestos undergoes longitudinal splitting in the environment of the lung (see, for example, Roggli et al. 1987, Kauffer et al. 1987, or Kimizuka et al. 1987). In contrast, amphiboles are not observed to undergo longitudinal splitting in the lung.

Several retention studies indicate that clearance mechanisms operating in the deep lung exhibit dimensional selectivity. For example, a number of animal studies indicate that short structures are preferentially cleared from the deep lung.

- Bellmann et al. (1986) found that fibrous structures shorter than 5 µm were cleared with a half life of 150 days from rats receiving glass, chrysotile, or crocidolite via intratracheal installation.

- In two studies (Roggli et al. 1987 and Roggli and Brody 1984), short crocidolite and chrysotile structures were preferentially cleared from rat lungs following inhalation.

- Wright and Kushner (1975) intratracheally instilled paired samples each of glass, fluoramphibole, and crocidolite into guinea pigs. For each mineral tested, a sample with predominantly short structures and another with predominantly long structures were evaluated. The long structures uniformly caused fibrosis while the short structures were uniformly phagocytized and removed to thoracic lymph nodes. Based on the relative size distributions of the samples analyzed, structures up to 10 µm in length appear to be efficiently scavenged by macrophages. Glass structures also underwent biodegradation so that longer structures broke down into shorter structures that could be phagocytized.

- In a study by Morgan et al. (1978), structures shorter than 10 μm were efficiently scavenged from the lungs of rats inhaling radiolabled anthophyllite. Structures up to 40 μm were partially removed by the process. However, the efficiency of phagocytosis appears to decrease substantially for structures longer than 10 μm, based on the observation that such structures remain in the lung for extended periods.

- In a study of rats inhaling chrysotile for a single, 5-hour period, Kauffer et al. (1987) report that the average length of fibers observed in lungs increases over time (suggesting that shorter structures are preferentially cleared). In this study, fibers shorter than approximately 8 μm are preferentially cleared.

In contrast, a small number of studies present a lack of evidence that clearance mechanisms are dependent on size (see, for example, Roggli et al. 1987). However, the manner in which the Roggli study was conducted may limit the ability to detect time-dependent changes in size distributions (see below).

Among the considerations that must be addressed when interpreting the results of retention studies is the limitations attributed to the procedures employed to count and to characterize the dimensions of the fibers encountered. For example, studies that employ optical microscopic techniques to characterize lung burdens may report higher clearance rates for chrysotile asbestos than the true rate of clearance because (with time) longitudinal splitting simply causes the remaining chrysotile fibers to become too thin to observe (see Section 3.2). However, because documentation of the procedures and analytical techniques employed is severely limited in most of these studies, it is not possible to evaluate the effects that may be due to limitations in measurement.

Another limitation in these studies (except Kauffer et al. 1987) is the lack of consideration of the effect of fiber diameter. Therefore, results relating to size dependence should likely be interpreted qualitatively rather than quantitatively. A strict cutoff in the length of fibers below which removal by phagocytosis is 100% effective has not been identified. Rather, the effectiveness of phagocytosis appears to decrease rapidly for structures between 5 to 20 μm. Structures longer than 20 μm are not effectively cleared. The selectivity of clearance with respect to diameter is less clear.

Given the body of evidence provided by the available retention studies, it appears that:

- deposition efficiency is dependent on structure size and shape but independent of chemistry or mineralogy;

- clearance mechanisms are dependent on mineralogy at least to the extent that mineral type determines susceptibility to mechanical splitting or dissolution; and

- at least a subset of clearance mechanisms exhibit a size dependence with smaller fibers being preferentially cleared.

The last of the above conclusions, however, remains somewhat controversial, due to conflicting results from different studies. Also unresolved is the mechanism(s) contributing to the observed difference in retention of chrysotile and amphiboles. Given limits to the rates of dissolution, solubility is unlikely to account for the difference. Among other possibilities, two are worth noting:

(1) in some studies, longitudinal splitting of chrysotile fibers may rapidly reduce the bulk of chrysotile to structures that are not detectable by many of the procedures traditionally employed to measure them; or

(2) amphiboles may induce a stronger toxic response than chrysotile in the tissues that the asbestos structures contact. This, in turn, may facilitate sequestration and hinder clearance of the amphibole as repair mechanisms respond to the damaged tissue surrounding the offending fibers. Alternately, such responses may contribute to overload mechanisms that have been reported in several studies to hinder clearance in general (see Sections 5.2.3 and 5.4).

Further research is required to distinguish among these and other possible explanations for the observed difference in retention of chrysotile and the amphiboles.

5.2.2 Human Pathology Studies

Human pathology studies provide additional information concerning the nature of asbestos deposition, clearance, and retention. These are studies in which lung burdens are measured in samples of lung tissue and correlated with the exposures received by the individuals from which the lung samples derive.

Among the advantages of human pathology studies is that they provide direct insight into the behavior of asbestos in humans. They are also limited, however, by the lack of ability to obtain time-dependent estimates of lung burden (because samples are derived from deceased individuals), by the manner in which samples are prepared for asbestos analysis, by the manner in which asbestos is analyzed, and by the limited ability to re-construct the uncontrolled exposures experienced by study subjects (Chapter 4).

Observations from human pathology studies generally reinforce conclusions drawn from animal retention studies. For example, several studies indicate that chrysotile is cleared much more rapidly and completely than amphiboles from the human lung.

- In a study of lung burdens in mesothelioma victims, Churg et al. (1984) showed that amphiboles structures were 5 to 15 times as plentiful as chrysotile despite the predominantly chrysotile exposure. This is likely due to differential clearance since deposition efficiencies appear to be similar (Section 5.1).

- Similarly, Pooley (1976) found substantial concentrations of tremolite (an amphibole) in the lungs of deceased Quebec chrysotile workers despite the fact that tremolite is an extremely minor contaminant of the chrysotile ore being mined. Based on this observation, chrysotile is preferentially cleared from the lung.

Similarly, some pathology studies indicate that at least some clearance mechanisms show a dependence on fiber size. Notably, for example, Timbrell (1982) studied deceased workers and relatives from the Paakkila anthophyllite mine in Finland. He found that structures shorter than 4 μm and less than 0.6 μm in diameter are completely cleared from healthy lungs. The efficiency of clearance decreases slowly with increasing size. Structures longer than 17 μm and thicker than 0.8 μm in diameter are not significantly cleared. The study is based on a comparison of structure size distributions in lungs compared to the structure size of the material in the original dust exposure. Timbrell also noted that asbestosis suppresses the removal process.

When considering the dependence of clearance on size (particularly via mechanisms involving phagocytosis), it is necessary to address differences in human and animal physiology. Due to differences in morphology, for example, human macrophages have been shown capable of phagocytizing larger particles and longer fibers than macrophages found in mice and rats (Krombach et al. 1996). Thus, the range of fibrous structures that are efficiently cleared from human lungs is expected to include longer fibers than the range efficiently cleared in mice or rats. Unfortunately, given the limited precision of the available data, the size ranges that are reported to be cleared efficiently in rats and humans, respectively, cannot be easily compared.

5.2.3 Dynamic Models

Due to the complexity of the processes involved, only a small number of dynamic models for fiber retention have been developed. Interpretation of the results of these models requires that the meaning of the term "retention" first be reconciled across studies.

- Dement and Harris (1979) report that, based on a mathematical model, the fraction of structures retained in the deep lung is unlikely to vary by more than a factor of two for different asbestos mineral types. In this study, however, the term retention appears to refer primarily to a very

short time period that primarily includes consideration of deposition but not clearance processes.

- Using a definition for retention that reflects long-term residence in the lung, Yu et al. (1990a) developed a model of chrysotile retention that explicitly incorporates longitudinal splitting, dissolution, and size-dependent clearance. Time-dependent lung burden estimates derived using the model were shown to compare reasonably well with published data (Abraham et al. 1988) both in terms of fiber concentrations and fiber size-distributions.

- In a later modification of their retention model for chrysotile, Yu et al. (1991) also considered the effect of airway asymmetry on fiber retention. In this version of the model, Yu and coworkers incorporated information concerning the geometry of the bronchio-alveolar tree (including the mean distance and the mean number of airway bifurcations between the trachea and the alveoli in each section of the lung) and studied the effects of such considerations. The modified model predicts a non-uniform distribution of the asbestos that is retained in the lung and the predictions reasonably reproduce the distributions observed by various researchers and measured formally by Pinkerton et al. (as cited by Yu et al.).

- Yu et al. (1990b) also modeled the long term retention of amosite in rat lungs. In contrast to the models employed for chrysotile, the model presented for amosite incorporates a term for the clearance rate that is not a constant but, rather, is a function of the lung concentration of asbestos. This modification was apparently required to adequately mimic the suppression of clearance with increasing lung burdens that has been observed by several research groups (e.g. Wagner et al. 1974 or Davis et al., 1978). Conditions under which elevated asbestos (or dust) concentrations are observed to reduce clearance are referred to as "overload" conditions. Model predictions were shown to reasonably reproduce the time-dependence of amosite lung burdens in several studies.

That Yu and coworkers found it necessary to consider the effects of overloading in modeling amosite retention but not when modeling chrysotile is consistent with observations that amphibole lung burdens tend to increase with chronic exposure while chrysotile lung burdens tend to level off (see, for example, Wagner et al. 1974 or Davis et al, 1978). These observations may suggest, among other possibilities, that the tissue-specific responses induced by the amphiboles are more pronounced than those induced by chrysotile, which might therefore contribute to the suppression of

clearance mechanisms at lower concentrations for amphiboles than for chrysotile (see Section 5.4.2).

The general conclusions that can be drawn from the dynamic models cited above serve to reinforce the conclusions drawn from the animal and human pathology studies also reviewed and discussed in this Chapter. Briefly:

- during inhalation, deposition efficiency depends on the size, shape, and complexity of a fibrous structure but is entirely independent of chemistry (mineralogy);

- mechanisms that contribute to clearance from the deep lung show a dependence on fiber size in which short fibers (i.e. those shorter than approximately 10 μm) are cleared more rapidly and efficiently than longer structures;

- mineralogy may also effect clearance mechanisms in at least three ways:

  - first, chrysotile structures are soluble and dissolve in vivo over a time scale that is important to clearance, at least in humans. Amphiboles are insoluble over such time scales;

  - second, chrysotile structures apparently degrade by splitting longitudinally in vivo so that complex structures ultimately degrade to their component fibrils. Amphiboles do not similarly degrade; and

  - third, possibly due to differences in tissue toxicity (Section 5.4), amphiboles are retained more effectively than chrysotile during chronic exposure due to an overload effect in which clearance mechanisms are suppressed as amphibole tissue burdens increase. Such an overload effect may only occur at relatively higher concentrations for chrysotile;

5.3 FACTORS AFFECTING TRANSLOCATION

To induce mesothelioma, asbestos structures retained in the lung must be translocated to the surrounding mesenchyme. A number of mechanisms have been proposed for this process. Evidence indicates that fibrous structures are quite mobile in the lungs and surrounding tissues.

- Brody et al. (1981) tracked the distribution of chrysotile following inhalation by rats. Asbestos was initially deposited almost exclusively at

alveolar duct bifurcations. In agreement with Pinkerton et al. (1986), the degree of deposition appeared to be an inverse function of the pathlength and bifurcation number for each alveolar duct. Uptake by macrophages and type 1 epithelial cells were observed following deposition. Asbestos was observed both in lipid vesicles and free in the cytoplasm of type 1 cells. After 8 days, alveolar duct bifurcations became thickened with an influx of macrophages. Asbestos was also observed in basement membrane below the epithelium. Apparently, structures had been transported through type 1 cells to the basement membrane. Once in the basement membrane, asbestos may enter the interstitium. Predominantly short structures were monitored in this study. Long structures were not readily observed.

- Bignon et al. (1979) studied the rate of translocation of various materials in rats. Chrysotile, crocidolite, and glass fibers were intrapleurally injected into rats and their concentration was monitored as a function of time in lung parenchyma and other tissues remote from the pleura. Within one day following injection, asbestos was detectable in lung parenchyma. After 90 days, asbestos was found in all of the tissues analyzed. Based on the rate of translocation to the lung, crocidolite migrates about 10 times more rapidly than chrysotile (on a mass basis). The rate of migration of glass is in between the two asbestos types. Structures initially found in the lung were significantly shorter than the average size of structures injected. After seven months, however, the average lengths of structures in all tissues monitored were longer than the average length of structures originally injected. Thus, short structures migrate more rapidly than longer structures (possibly by a different mechanism) but long structures eventually translocate as well. Within a target tissue, preferential clearance of short structures also contributes to observed increases in the average length of the structures with time.

- Le Bouffant (1980) studied the concentrations, mineralogy, and size distributions of asbestos fibers found in the lungs and pleura of deceased asbestos workers. Based on the analysis, he found that the average ratio of chrysotile fiber concentrations found in the lung versus the pleura is 1.8 while for amosite the ratio is 34. This indicates that chrysotile migrates from the lung to the pleura more rapidly than amphiboles resulting in a higher fraction of total fibers in the pleura being composed of chrysotile (3% in the lungs versus 30% in the pleura). With regard to size, the researchers found the size distribution of amosite is virtually identical in the lung and pleura while chrysotile fibers found in the pleura are much shorter than chrysotile fibers found in lung tissue. This suggests that the movement of chrysotile is a result of a combination of translocation and degradation to shorter fibers. Chrysotile fibers apparently degrade to

shorter fibers more rapidly than amosite and translocate to the pleura more rapidly than amosite. Thus, a greater fraction of chrysotile fibers (albeit short fibers) reach the pleura than amosite fibers over fixed time intervals. However, the results of this study also confirm that the longer amosite fibers do eventually translocate, although on a much more extended time scale than the translocation of chrysotile.

Based on the above studies, the efficiency of translocation is a function both of mineralogy and fiber size. Chrysotile appears to translocate more rapidly than amosite possibly due to chemical reactivity and shorter fibers appear to translocate more rapidly also. Translocation of the shortest fibers (less than 10 μm) likely competes with clearance to the lymphatic system and clearance becomes increasingly important as the length of the fiber decreases. Longer fibers (up to 20 μm in length) also translocate from the lung to the pleura but over a much longer time scale than the movement of short fibers.

5.4 FACTORS GOVERNING BIOLOGICAL RESPONSE

For inhaled structures that survive degradation or clearance, a series of complex reactions between the deposited structure and surrounding tissue may induce a biological response. Asbestosis (fibrosis), pulmonary carcinomas, or mesotheliomas may result. Mesotheliomas would be associated with structures translocated to the mesenchyme following retention in the lung.

The best studies available for addressing the gross effects of biological responses in target tissues are the series of implantation and injection studies performed by several groups of researchers. Many of the details of the mechanisms that mediate biological response have also been elucidated in a number of in-vitro studies of isolated tissues, cells, or chemical assemblies.

5.4.1 Gross Features of Biological Response Elucidated by Injection and Implantation Studies

Because the fibrous materials in injection and implantation studies are placed immediately against the target tissue, the effects of processes associated with inhalation, retention, and translocation are avoided. The only active mechanisms that need to be considered in these studies are those that occur directly in the target tissue (including degradation, clearance, and biological responses) Fibrous materials placed against the tissue surface are subject to dissolution, phagocytosis by macrophages, and phagocytosis by the cells of the target tissue. A range of biologic responses have also been observed.

Numerous researchers have performed these types of studies.

The work of Stanton et al. In a series of studies, Stanton et al. (1972, 1977, and 1981) implanted fibrous materials and induced mesotheliomas in rats. In the studies, a pledgette composed of coarse glass is loaded with hardened gelatin containing sample material and is surgically implanted immediately against the left pleura of the rats. Control studies demonstrate that the coarse glass of the pledgette does not induce significant tumors in the absence of other tumorigenic agents in the gelatin.

Although the mass dose of material implanted was the same for all experiments (40 mg), the observed incidence of mesothelioma varied among samples. By characterizing the dimensions of fibrous structures in the samples using a microscope, the researchers were able to explore the relationship between fiber size and the incidence of mesothelioma. By studying a wide range of fibrous materials, Stanton and his coworkers concluded that the induction of mesothelioma is determined primarily by the physical dimensions of fibers and that mineral composition is secondary. Further, potency appears to increase with the length and decrease with the diameter of fibrous structures. The researchers also concluded that the incidence of malignant tumors correlates with the degree of fibrosis induced by the presence of the fibrous materials. This does not necessarily imply, however, that fibrosis is a necessary step in the induction of asbestos-induced tumors.

The hypothesis that lung tumor induction is associated with the onset of fibrosis was further examined by Davis and Cowie (1990). These researchers found that rats that developed pulmonary tumors during inhalation experiments exhibited a significantly greater clinical degree of fibrosis than rats that did not develop tumors. Furthermore, Davis and Cowie reported suggestive evidence that the pulmonary tumors that did develop in the dosed rats tended to develop within portions of the rat's lungs that were already scarred by fibrosis.

Lack of a strong relationship between tumor incidence and mineral type for fibrous dusts is in direct contrast to the behavior of hazardous isometric dusts where toxicity is a strong function of the chemical nature of the dust (Elmes 1982). Effects observed in association with fibers occur at much lower doses than the doses at which hazardous dusts exhibit toxicity.

Conclusions from the Stanton et al. studies indicating that mineralogy is not a factor in biological response also conflicts with evidence concerning mechanisms presented in Section 5.4.2. However, the Stanton et al. studies have been shown to suffer from certain methodological limitations (Berman et al. 1995) so that results from these studies should be considered more qualitative than quantitative.

Due to limitations in the ability to produce samples composed of uniform fibers, quantitative relationships between size and potency were explored by Stanton et al.

(1972, 1977, and 1981) using a regression analysis. Structures longer than 8 μm with diameters less than 0.25 μm or longer structures with diameters less than 1.5 μm were found to represent the range of sizes that best correlate with carcinogenicity. It was further stated that such correlations did not eliminate the possibility that other size ranges also contribute to potency, only that the two size ranges identified appear to correlate best. Samples that varied substantially from the reported correlations were attributed to errors in the characterization of structure size distributions in those samples. However, other methodological limitations might also have contributed to the observed deviations or such "outliers" may also suggest evidence for a mineralogical effect that is similar to what is reported in other studies (see Section 5.4.2 and Berman et al. 1995).

The precision of estimates for the ranges of sizes that contribute to biological activity that are derived from the Stanton et al. studies is limited so that such estimates should also be considered qualitative. Size distributions were determined by characterizing 200 to 1,000 structures using TEM and there is no indication that statistically balanced counting rules were employed (Chapter 4). Under such conditions, counts of structures longer than 8 μm are likely small and subject to large uncertainties for most of the samples characterized. Confidence intervals are not provided for any of the counts presented in these studies.

Potentially larger errors in the Stanton et al. studies could have been introduced by the method employed to relate fiber counts to sample mass. As indicated in Chapter 4, estimating contributions to mass by sizing total particles and assuming that this is proportional to total sample mass is subject to error from the limit to the precision of characterizing structure dimensions (particularly diameter) and by not accounting for nonasbestos (and possibly nonfibrous) material in the samples.

Thus, for example, there is no discussion of the precision with which the cut point of 8 μm was determined in these studies. Based on the manner in which size distribution data is presented, it is unlikely that cut points that vary by up to a factor of 2 would lead to substantial difference in the quality of the correlation. For example, a cut point of 5 μm may not be distinguishable from 8 μm within the database examined.

Re-analysis and extension of the Stanton studies. Several researchers have re-evaluated data from the implantation studies to test additional hypotheses. Using the Stanton data, Bertrand and Pezerat (1980) examined the relationship between mesothelioma incidence and several characteristics not evaluated by Stanton et al. including: average fiber length, average fiber diameter, average fiber aspect ratio, total fiber surface area, and total fiber volume. Results from the regression analysis indicate that potency varies directly with average length and inversely with average diameter but that neither parameter is a good indicator alone. Combining the effects of length and diameter, average aspect ratio is highly correlated with potency. Biological activity does not correlate highly with structure count, surface area, or volume except when

fiber sizes are restricted to the long, thin structures that Stanton defined. Results of this study are not inconsistent with those originally presented by Stanton, except that they emphasize a set of characteristics that relate parametrically to biological activity rather than expressing exposure as a single restricted size range of structures.

It is important to note that Bertrand and Pezerat were able to find good correlations between response and specific "average" characteristics of the samples that are not proportional to the quantity of the material present in the sample ("intensive" characteristics). Such intensive characteristics as average aspect ratio, average length, or average diameter are properties that are independent of the mass of material in a sample. Since response must be a function of the quantity of sample present, intensive characteristics should have to be multiplied by characteristics that are proportional to the mass of a sample (e.g. fiber number, sample mass, or sample volume) in order to relate them to response. Properties that vary with the mass of a sample are termed "extensive" properties.

The correlations between intensive properties and response reported by Bertrand and Pezerat likely succeed within the Stanton database because a constant sample mass (40 mg) was employed for all of the implantation experiments. However, to apply dose/response relationships that are dependent only on intensive characteristics beyond the Stanton data (where mass dose will not be constant), it is necessary to pair intensive characteristics with extensive characteristics (such as mass or number of fibers per sample). Therefore, it is unclear how the conclusions from this paper may be generalized to other data sets.

In a similar study, Bonneau, et al. (1986) also examined parametric relationships between structure characteristics and mesothelioma induction. The paper examined specifically correlations between carcinogenicity and dose in terms of two specific relationships: dose expressed as fibers longer than 8 μm that are thinner than 0.25 μm ("Stanton" fibers) and dose expressed as mean aspect ratio. The researchers conclude that mean aspect ratio provides an excellent indication of carcinogenicity for individual fiber types but that each fiber type must be treated separately. Poorer correlations are found for the relationship between the concentration of "Stanton" fibers and mesothelioma, even when fiber types are considered independently. Although these results appear to be consistent with findings reported from mechanistic studies (Section 5.4.2) in that they posit a role for fiber mineralogy, the relationships evaluated by Bonneau et al. also suffer from the limitation of expressing dose only in terms of intensive quantities, as discussed above. Direct comparison with other studies is therefore difficult.

Following up on the reported problems characterizing crocidolite in Stanton's work, Wylie et al. (1987) reanalyzed seven crocidolite samples originally studied by Stanton. She and coworkers then used the new size distributions to reevaluate the "Stanton hypothesis" (that the concentration of Stanton fibers in a sample correlates with

carcinogenicity). Wylie and coworkers note that substantial deviations from the Stanton hypothesis occur for specific samples. They conclude that a specific structure size range alone is not sufficient to characterize biological activity and that a parametric relationship with other structure characteristics (potentially including mineral type) may be necessary to sufficiently describe biological activity.

Conclusions from the Wylie et al. paper must be interpreted carefully because the researchers evaluated only the relationship between carcinogenicity and the single specific size range indicated ("Stanton" fibers). Thus, the possibility that improved correlations exist between biological activity and different size ranges or a combination of size ranges cannot be ruled out. Qualitatively, conclusions presented in this paper are not inconsistent with the conclusions reported by Stanton et al. regarding the general relationship between response and fiber dimensions.

The Wylie et al. study appears to suffer from several methodological problems. These relate to the manner in which the sample reanalysis was performed. The drop method for preparing electron microscopy grids (used in this study) is not satisfactory for preparing grids. In fact, as reported in the study itself, grids prepared as duplicates by this method were shown to be non-uniform at the 95% confidence interval using a chi squared test. In addition, only 100 to 300 fibers were counted for each sample. Since there is no indication that statistically balanced counting was performed, the uncertainty associated with counts of Stanton fibers may be substantial. Such errors would be further multiplied by uncertainty introduced during the sizing of total particles to determine the number of fibers per unit mass.

In a later study, Wylie et al. (1993) examined the effect of width on fiber potency. In this latter study, results from animal injection and implantation studies were pooled and subjected to regression analyses to identify correlations between exposure and tumor incidence. The animal studies selected for inclusion in this analysis were performed on a variety of tremolite samples exhibiting a range of morphological and dimensional characteristics.

In their regression analyses, Wylie et al. evaluated a range of exposure indices that emphasize different morphological or size characteristics to help elucidate the characteristics of asbestos that induce a biological response. Because all of the animal studies included in their analysis involved tremolite, mineralogy was not an issue.

Results from the Wylie et al. study suggest that fibers longer than 5 μm and thinner than 1 μm best correlate with tumor incidence among the animal injection and implantation studies examined. Further, they suggest that a width limit, rather than a limit on aspect ratio, better reflects the bounds of the asbestos characteristics that determine biological activity. They also suggest that complex structures (bundles and clusters) need to be evaluated as part of the determination of exposure because such structures can breakdown and contribute to the population of thinner fibers.

Although the results of the Wylie et al. study are interesting and tend to support the general conclusions in this document (see Section 5.6.2), as the authors themselves indicate, such results should be considered qualitative due to the limitations imposed on their study by the methodology employed. This study was conducted by:

- combining results from multiple studies without careful consideration of variation introduced by methodological differences across the studies;
- employing asbestos concentrations determined by SEM and without careful consideration of differences in the counting methodologies employed by differing research groups across studies; and
- considering injection and implantation studies, which (as opposed to inhalation studies) do not account for all of the mechanisms that affect the dose-response relationship in humans.

The limitations imposed by the above constraints are highlighted in Chapters 3 and 4 of this report.

Other injection studies. A series of injection studies were conducted by several research groups. In these studies, fibrous materials were suspended in saline and injected into rats immediately adjacent either to the pleura or peritoneum. A large number of fibrous materials have now been studied by this process, as reported by Pott et al. (1974, 1976, 1978, 1982, and 1987), Muhle et al. (1987), Bolton et al. (1982, 1984, and 1986), Davis et al. (1985, 1986a, 1986b, 1987, and 1988a), and Wagner et al. (1976, 1980, 1982, 1984, and 1985). Results confirm that it is the fibrous nature of the materials that is the primary factor leading to the induction of tumors and that potency appears to depend directly on length and inversely on diameter.

The authors of these studies tend to indicate that except where fibers are not persistent in vivo due to solubility or other degradation processes, the mineralogy of the fibers appears to play only a secondary role in determining disease incidence. Researchers conducting injection experiments also tend to report a correlation between tumor incidence and the degree of fibrosis induced by the sample. These observations are consistent with the ideas originally articulated by Stanton et al. Also, the possibility of a relationship between tumor induction and fibrosis is further addressed by Davis and Cowie (1990).

Pott developed Stanton's ideas further by suggesting that carcinogenicity is a continuous function of fiber dimensions, which decreases rapidly for lengths less than 10 μm and also decreases with increasing diameter. The possibility was also raised that the apparent inverse dependence on diameter may be an artifact due to the limited number of thick fibers that can be injected in a sample of fixed mass. However, this contrasts with conclusions drawn by Wylie et al. 1993 (see above)..

Although the published injection studies indicate that potency decreases with decreasing length, researchers have been reluctant to identify a length below which contributions to carcinogenicity can be considered inconsequential. This may be due in part to the skewed distribution of fiber sizes typical of asbestos dusts. Thus, for example, even if structures less than 5 μm are only 1% as potent as structures longer than 5 μm, they may be as much as 100 times as plentiful in some asbestos dusts, so that the total contribution to potency would be equal for both size fractions.

Reasonable dose/response curves have been generated using various sample masses of a single material in some of these studies. This has been demonstrated for UICC crocidolite and UICC chrysotile "A" (Bolton 1984). Results indicate that the relationship between tumor incidence and the log of the dose may be linear and there is no effective threshold. A consistent difference between the two dusts is apparent; the points lie along separate curves and chrysotile appears to be more potent per unit sample mass.

In general, details of the analytical techniques used for quantifying size distributions in these studies are not fully documented. To the extent that they are, it appears that similar approaches were adopted to those described for the implantation studies above. Consequently, similar limitations apply to the interpretation of results. Briefly, large uncertainties are likely associated with counts of long fibers and estimates of the number of fibers per unit sample mass. Counts in several of the studies also suffer from limitations in the ability of SEM or PCM to detect thin fibers (Section 3.2); whenever SEM or PCM was employed, the thinner fibers were likely under represented in reported fiber size distributions.

Because samples are placed against mesenchyme in the published implantation and injection studies, results of these studies most directly represent processes associated with the induction of mesothelioma. Assuming, however, that clearance and degradation processes are similar in the deep lung, once a fiber reaches a target tissue, results from the implantation and injection studies may also provide a model biological response in lung tissue and the factors that lead to the induction of pulmonary tumors. Such a model must be considered qualitative, however, because it has been shown that the mechanisms of tissue response to the presence of asbestos in lung parenchyma and in the mesenchyme differ in detail (Section 5.4.2). At the same time, It is known that the general nature of clearance and degradation processes in the two tissue types are generally similar.

5.4.2 Implications Regarding the Mechanics of Cancer Induction Derived from In-Vitro Studies

In a 1993 review, Mossman describes the currently accepted model for cancer. In this model, development of cancer requires both that genetic alterations occur in a particular cell line and that the affected cells be stimulated to grow and divide so that

the mutations are inherited and preserved. Such genetic alterations may either occur randomly and spontaneously during cell division or may be induced by one or more specific biological or chemical agents. If the affected cells are chronically stimulated to divide, sufficient genetic mutations (of the right type) eventually accumulate in the cell line to cause growth to become uncontrolled so that tumors develop. Agents that cause genetic alterations are cancer initiators in this model and agents that chronically stimulate cell division are promoters. It is also noted that the long latency periods between an initiating event and the development of clinically observable tumors is a result of the substantial time required for sufficient mutations of the right type to accumulate in the affected cell line to lead to neoplastic behavior.

Mossman (1993) then highlights the results from various in-vitro studies, which indicate that:

- asbestos serves primarily as a promoter of lung cancer although evidence suggests it may serve both as a promoter and an initiator of mesothelioma. Mesothelial cells have been shown to be much more susceptible to genetic damage by asbestos than bronchial and alveolar epithelial cells;

- promotion is facilitated by the genotoxic and cytotoxic effects of asbestos where the resulting cell death stimulates cell division to replace damaged tissue;

- asbestos genotoxicity and cytotoxicity is mediated by production of reactive oxygen species generated either during phagocytosis by monocytes or in reactions catalyzed by iron on the surface of asbestos fibers; and

- the genotoxic and cytotoxic effects of asbestos are size dependent with longer structures showing greater potency than shorter structures. In many of these studies, structures shorter than approximately 10 μm are shown largely to be inactive.

Consistent with the above, evidence from several of the studies cited by Mossman in this and an earlier review (Mossman et al. 1990) indicate that amphiboles are more potent carcinogens than chrysotile, particularly toward the induction of mesothelioma. This is apparently due both to the increased persistence of amphiboles in vivo (relative to chrysotile) and to the higher concentration of iron in most amphibole matrices (particularly crocidolite). The greater persistence suggests that amphibole structures may provide chronic stimulation of cell division in target tissues for a longer period of time than chrysotile and thus serve as a more potent promoter. The greater concentration of iron suggests a greater number of active sites on the surface of each structure at which formation of reactive oxygen species may be catalyzed.

Taken as a whole, these data suggest that it may be prudent to establish distinct risk coefficients for each of the different asbestos fiber types. Because these findings are further reinforced by results of the re-analysis of animal inhalation studies described later (Section 5.6.2), the protocol recommended in this document incorporates separate consideration of fiber types.

5.5 OTHER FACTORS

A range of studies provide further, though indirect, evidence of the overall dependence of biological activity on structure characteristics without distinguishing among the effects due to respirability, clearance, degradation, translocation, or mechanism. Such studies generally confirm conclusions drawn from the specialized studies above, except that the effect of chrysotile biodegradability is emphasized. In addition, a wider range of durable minerals that exist as fibrous structures within the appropriate size range are shown to be biologically active.

- Pooley (1982) showed that the amphibole lung burdens of deceased asbestos workers, which correlate with disease incidence are longer than the chrysotile found in the lungs of workers and controls, which do not correlate with disease.

- In another study, (Pooley 1972) showed that the incidence of mesothelioma appears to correlate best with the incidence of amphibole. The relationship between chrysotile counts and mesothelioma is not clear, but none of the mesotheliomas are associated with high chrysotile concentrations.

- Baris et al. (1987) showed that the distribution of erionite fibers in sheep lungs correlate with the incidence of mesothelioma in various regions of Turkey. Short chrysotile fibers also found in Turkish sheep lungs do not correlate with the incidence of disease.

- Churg et al. (1984) found that the longer amphibole fibers present in the lungs of mesothelioma victims correlate with the incidence of the disease between cases and controls. The relationship between disease and the distribution of shorter chrysotile fibers, also found in the lungs, is less clear.

When evaluating these studies, it is important to consider that, due to the in-vivo degradability of chrysotile, valid tests for correlations between chrysotile lung burdens and any toxic end point require that time since exposure be considered explicitly. Since the studies above do not formally address the time issue, rather than concluding a lack of correlation between chrysotile exposure and disease, there might simply be a

less pronounced effect per unit of chrysotile exposure than per unit of amphibole exposure. Such an interpretation (though not directly testable due to the limitations of the designs of these studies) would place them in closer agreement with the results of the mechanistic studies discussed in Section 5.4.2.

5.6 ANIMAL INHALATION STUDIES

Animal inhalation studies measure response to exposure in controlled systems that model all of the relevant variables associated with asbestos disease mechanisms in humans (including respirability, retention, degradation, clearance, translocation, and tissue-specific response). Thus, the available inhalation studies are the best database from which to evaluate the integrated effects that lead to the development of asbestos-related disease. Such studies can be used both to identify the characteristics of asbestos that determine biological activity and to qualitatively elucidate the nature of the corresponding relationship between exposure (via inhalation) and the induction of disease.

The remainder of this section is divided into two parts. The nature and results of existing animal inhalation studies are described first. Then a project undertaken to overcome the limitations of the existing animal inhalation studies is described. Because this latter project was specifically designed to support the risk protocol presented in this document, the nature and results of this project are described in detail.

5.6.1 The Existing Animal Inhalation Studies

The existing animal inhalation database consists of approximately 30 studies of which approximately 20 contain dose/response information based on lifetime monitoring of exposed animals, including the work of Davis et al. (1978, 1980, 1985, 1986a, 1986b, 1988a, and 1988b), Wagner et al. (1974, 1982, 1985, and 1987), Bellman et al. (1987), Bolton et al. (1982), Le Bouffant et al. (1987), Lee et al. (1981), McConnel et al. (1982, 1995), Muhle et al. (1987), Platek et al. (1985), Smith et al. (1987), Goldstein et al. (1983) and Mast et al. (1995a and b). The studies are similar in overall design, although detailed differences potentially affect the comparability of results from separate studies.

In the inhalation studies, plugs are formed from bulk samples of fibrous asbestos and related materials, which are placed in a dust generator to be aerosolized. The generators (Beckett 1975), usually a modified version of the apparatus originally designed by Timbrell (Timbrell et al. 1970), consist of a rotating brush that sweeps over an advancing plug of bulk material liberating fibers that become entrained in the controlled air flow passing through the device. The airborne dust is then passed either into a delivery system for nose-only exposure or into an exposure chamber where

animals are kept for fixed periods of time (usually 7 hours per day) on a weekly routine (typically 5 days per week). The exposure routine is continued for as long as 2 years in some of the studies. In some, but not all of the studies, fiber-containing air is passed through a cyclone or elutriator prior to the exposure chamber so that exposure consists primarily of particles sized within the respirable range.

Asbestos concentrations in the animal inhalation experiments are monitored by a combination of techniques. The concentration of total dust in the chamber is generally monitored gravimetrically. Simultaneously, membrane filter samples are collected and fibers counted by PCM. The quotient of these two measurements yields the number of (PCM) fibers per unit mass of dust (Section 3.2). The distribution of fiber sizes within the dusts introduced into the animal exposure chambers may also be determined in these studies by any of a variety of methods. As indicated previously (Section 3.2), however, the utility of such measurements depends on the precise manner in which they are derived.

To derive fiber size distributions, dust samples from these studies have generally been collected on polycarbonate filters for analysis by SEM. However, such distributions suffer both from the limitations of SEM (Section 3.2) and from the manner in which they are tied to the inhalation experiments (see Chapter 4).

Theoretically, the dose of any fiber size fraction can be estimated in a two-step process. The procedure incorporates consideration of a size fraction termed the PCM-equivalent fraction (PCME). This is the fraction of structures measured by SEM (or TEM) that correspond to the size range of structures known to be visible and therefore countable by PCM. First, the concentration of the PCM-equivalent fraction of the fiber size distribution (measured by SEM) is normalized by dividing its value by the concentration of the same size fraction per unit dust mass that was derived by PCM in the original inhalation experiment. This ratio is then multiplied by the fractional concentration of any specified size range of interest within the distribution (measured by SEM) to determine the exposure level for that size fraction. However, because bivariate (length by diameter) size distributions have not typically been developed in the available studies and because the number of total fibers longer than 5 μm observed by SEM (without adjustment for width) does not correspond to the number of total fibers longer than 5 μm observed by PCM, it is not possible to derive a true PCME fraction from the SEM data. Therefore, the theoretical approach described above for estimating exposure to specific size fractions cannot generally be applied in the existing studies.

As indicated above, the data within the published animal inhalation studies are further constrained by the limitations of the analytical methods employed to generate the data (Section 3.2). Comparison of data between studies is also hindered by the lack of sufficient documentation to indicate the specific methods and procedures employed in each study. Frequently, for example, it is unclear whether respirable dusts or total dusts have been monitored. Also, several studies fail to report one or both of two

critical pieces of information: fiber-number-to-mass conversion factors and fiber size distributions. In addition, few studies indicate the precise counting rules employed for generating size distributions.

When structure-number-to-mass conversion factors are provided, unless the conversion factor is derived by counting fibers in a specific size range in a known mass of sample and fiber concentrations in other size ranges are then normalized to this count, several types of error may be introduced. For example, if total sample mass is assumed proportional to calculated mass derived from volume characterizations of the particles counted, unless isometric particles are sized along with fibers and both asbestos and nonasbestos particles are included in the count, a bias will be introduced in the conversion factor because total sample mass will have been under represented to the extent that any types of particles are ignored in the estimation of fiber mass. Even if all types of particles are included, substantial uncertainty may result due to the difficulty of estimating the volumes of irregular particles and the limited precision associated with the count of the largest particles (due to their limited number). The uncertainty in the measurement of a fiber's diameter is squared in contributing to the uncertainty associated with a mass estimate.

Among reported variations in study design, differences in the detailed design and operation of the aerosolization chamber and the frequency and duration of exposure also potentially contribute to variation in results between studies. Further, use of differing animal strains and species across the various studies suggest the possibility that physiological differences may contribute to the observed variation in study results. Such differences are discussed further in Chapter 4.

A small subset of the asbestos dusts evaluated in the animal inhalation studies have been analyzed by TEM. However, even the published fiber size distributions from these TEM studies are subject to variation from differences in procedures used for sample preparation, from differences in counting rules, and from precision limitations due to the limited number of fibers actually characterized (Section 3.2). This latter limitation particularly affects the precision with which longer fibers are counted.

Although fiber size distributions are primarily based on SEM analyses rather than TEM analyses in the existing animal inhalation studies, results generally echo the results of the injection and implantation studies. Thus, longer fibrous structures are observed to contribute most to asbestos biological activity, at least qualitatively. For example, dusts containing predominantly long amosite or long chrysotile fibers induce far more pulmonary tumors than samples containing predominantly short structures (Davis et al. 1986 and 1988b). However, dusts evaluated in the existing inhalation experiments have not been characterized sufficiently to distinguish the dependence of biological activity on fiber diameter. Neither are the existing studies sufficient to evaluate the importance of mineralogy (or other potentially important asbestos characteristics) in determining risk.

5.6.2 A Re-analysis of the Davis et al. Studies

Given the problems with the existing animal inhalation studies, a project was undertaken to overcome some of the attendant limitations. To control for effects from variation in study design and execution (including choice of animal strain, animal handling procedures, equipment design, sample handling procedures, dosing regimen, and pathology protocols), the project focused on a set of studies generated from a single laboratory (i.e., the studies published by Davis et al.). Ultimately, the results from six studies covering nine different asbestos samples (including four types of asbestos with samples exhibiting multiple size distributions for two asbestos types) and a total of 13 separate experiments (some samples were studied at multiple exposure levels or in duplicate runs) were pooled for analysis. The database of experiments employed in the project is described in Table 5-1

To overcome the limitations in the Davis et al. studies associated with the characterization of asbestos itself, the dusts studied in the thirteen experiments listed in Table 5-1 were regenerated by the same group who performed the original studies, from the same starting materials, using the same equipment, and reproducing the same conditions under which the original studies were conducted. Samples of the regenerated dusts were then collected and analyzed by TEM using a modified version of the Superfund air method (Chatfield and Berman 1990) to generate bi-variate size distributions that also include detailed characterization of the shapes and complexity of fibrous structures observed.

The total mass concentration of the regenerated dusts and fiber measurements by PCM were also collected to provide the data required to link size distributions in the regenerated dusts to absolute structure concentrations in the original inhalation experiments. The manner in which such calculations are performed has been published (Berman et al. 1995).

The concentration estimates (for asbestos structures exhibiting a range of characteristics of interest) that were derived from the TEM analyses of the regenerated dusts were then combined with the tumor response data from the set of inhalation experiments listed in Table 5-1 and a statistical analysis was completed to determine if a measure of asbestos exposure could be identified that satisfactorily predicts the lung tumor incidence observed. A more limited analysis was also performed to address mesothelioma; the small number of mesotheliomas observed in the Davis et al. data constrained the types of analyses that could be completed for this disease. The detailed procedures employed in this analysis and the results from the first part of the study have been published (Berman et al. 1995). These are summarized below along with results from the parts of the study that remain to be published.

TABLE 5-1:
SUMMARY DATA FOR ANIMAL INHALATION EXPERIMENTS CONDUCTED BY DAVIS AND COWORKERS[1,2]

Fiber Type	Description	Abbreviations	Mass Concentration (mg/m^3)	PCM f/ml	Number of Animals	Number of Benign Pulmonary Tumors	Number of Malignant Pulmonary Tumors	Total Number of Pulmonary Tumors	Mesotheliomas	Reference
Chrysotile	UICC-A	UC	2	390	42	6	2	8	1	Davis et al. 1978
Chrysotile	UICC-A	UC	10	1,950	40	7	8	15	0	Davis et al. 1978
Chrysotile	Long	LC	10	5,510	40	8	12	20	3	Davis et al. 1988a
Chrysotile	Short	SC	10	1,170	40	1	6	7	1	Davis et al. 1988a
Chrysotile	UICC-A	UC	9.9	2,560	36	6	8	14	0	Davis et al. 1988b
Chrysotile	UICC-A (Discharged)[3]	DC	9.9	2,670	39	4	6	10	1	Davis et al. 1988b
Chrysotile	WDC Yarn[4]	WC	3.6	679	41	5	13	18	0	Davis et al. 1988b
Amosite	UICC	UA	10	550	43	2	0	2	0	Davis et al. 1978
Amosite	Long	LA	10	2,060	40	3	8	11	3	Davis et al. 1988a
Amosite	Short	SA	10	70	42	0	0	0	1	Davis et al. 1988a
Crocidolite	UICC	UR	4.9	430	43	2	0	2	1	Davis et al. 1978
Crocidolite	UICC	UR	10	860	40	1	0	1	0	Davis et al. 1978
Tremolite	Korean	KT	10	1,600	39	2	16	18	2	Davis et al. 1985
None	Control	C	0		20	0	0	0	0	Davis et al. 1978
None	Control	C	0		36	0	0	0	0	Davis et al. 1985
None	Control	C	0		61	1	1	2	0	Davis et al. 1988a
None	Control	C	0		64	1	1	2	0	Davis et al. 1988b
None	Control	C	0		47	1	1	2	0	Davis et al. 1988a

1. Source: Berman et al. 1995

2. Exposure occurred for 7 hours per day, 5 days per week for 1 year.

3. UICC-A chrysotile in this experiment was treated with mixed polarity air (produced with a source of beta radiation) following generation to reduce the surface charge on individual particles within the dust.

4. Chrysotile samples used for dust generation in this experiment were obtained from material treated by a commercial wet dispersion source.

In the statistical analysis performed in this study, the individual dose/response profiles included in the Davis et al. data (Table 5-1) were fit to a linear dose/response model:

$$P_i = 1 - EXP(- Q_o - \sum_j b_i a_j x_j) \qquad (5.1)$$

where:

"P_i" is the probability of inducing pulmonary tumors observed in the "ith" study. A probability of one is equivalent to 100% incidence among the animals dosed in study i;

"Q_o" is the correction factor for background derived from the background incidence of pulmonary tumors observed among the control populations (pooled from all studies);

"x_j" is the concentration of the "jth" size fraction of fibers in the "ith" study;

"a_j" is the coefficient of potency for the "jth" size fraction of fibers in the "ith" study; and

"b_i" is a coefficient representing a normalization factor accounting for differences between the dose/response factors found for the summed contributions of the "j" exposure indices in the "ith" study.

The "a_j"s in this analysis are constrained to be positive because it is assumed that no fiber prevents cancer. The "a_j"s are also constrained to sum to one so that contributions to overall potency from individual size fractions are normalized to the overall concentration of asbestos. Correspondingly, size fractions evaluated represent disjoint (mutually exclusive) sets.

The dose/response model was set up as indicated in Equation 5.1 to provide flexibility. The model allows separate potency coefficients to be assigned to individual size fractions in a dose/response relationship that depends on multiple size fractions. Simultaneously, the "b" coefficients allows separate potency coefficients to be assigned to different fiber types or to results from different studies performed under different experimental conditions.

Several investigators (Stanton et al. 1977; Bertrand and Pezerat 1980; Bonneau et al. 1986; and Wylie, et al. 1987 and 1993) have used a logit curve to investigate dose/response relating various measures of asbestos exposure to tumor response. The logit formula specifies that the tumor probabilities satisfy the relation:

$$\log[P/(1-P)] = a + b \cdot \log x$$

where log x is some measure of asbestos exposure, such as log of concentration of fibers in some size range. In some instances, the logit model was expanded by replacing b·log x with a term representing a linear combination of exposure indices so that multiple exposure indices could be explored simultaneously. The models were fit using standard linear regression based on normal theory.

An equivalent form for the logit model is:

$$P = e^{a}x^{b}/(1 + e^{a}x^{b})$$

Written in this form, it is clear that this model does not permit a background response (i.e. P = 0, whenever x = 0). This is not a serious limitation when there are no tumors in control animals, such as was the case in Stanton et al. (1977). However, the model will not adequately fit data in which tumors are found in control animals. This was one reason for adopting the linear model (Equation 5.1) used in the investigation of the animal data reported in the study described here.

There is no evidence from this study that the linear model is inadequate. For cases in this study in which the fit between exposure and response is shown to be inadequate, the lack of fit is typically observed to be due to an inconsistent (non-monotonic) dose/response curve so that there is no indication that a non-linear model, such as the logit, would provide a better fit.

The linear model (Equation 5.1) used in this study was fit using a maximum likelihood (Cox and Lindley 1974) approach that utilizes the actual underlying binomial probabilities. This is a more efficient estimation method model than use of regression methods based on normal theory, which was the fitting method used in the earlier studies (described above). The regression procedure indicates only whether the exposure measures that were studied are significantly correlated with tumor response.

In contrast, the statistical analyses performed in this study indicate whether exposures that are described by a particular characteristic (or combination of characteristics) satisfactorily *predict* the observed tumor incidence. To illustrate, it is apparent from Text Figure 2 of Stanton et al. (1981) that the exposure measure they identify as being most highly correlated with tumor incidence (fibers longer than 8 μm and thinner than 0.25 μm) does not provide an acceptable fit to the observed tumor incidence. Similarly, although all of the univariate exposure measures listed in Table 2 of Berman et al. (1995) are highly correlated with lung tumor incidence, none of them adequately describe (fit) the lung tumor incidence.

To test for the goodness of fit in this study, each relationship was subjected to the standard "P" test where the model was rejected if P was significant at the 5% level indicating that the true model would provide a worse fit only 5% of the time. Among models that were not rejected based on a P test, several hypotheses concerning the

relative merit of the various models were also examined according to the method of maximum likelihoods (Cox and Lindley 1974).

An example of an adequate fit to the tumor response data is provided in Figure 5-3 (Figure 3 of Berman et al. 1995). Note that Figures 2 and 3 of the original paper were inadvertently switched during publication; the correct Figure 3 is reproduced here. The exposure index plotted in Figure 5-3 is the sum:

$$\text{Exposure} = 0.0017C_1 + 0.853C_2 + 0.145C_3$$

where:

"C_1" is the concentration of structures between 5 and 40 µm in length that are thinner than 0.3 µm;

"C_2" is the concentration of structures longer than 40 µm that are thinner than 0.3 µm; and

"C_3" is the concentration of structures longer than 40 µm that are thicker than 5 µm.

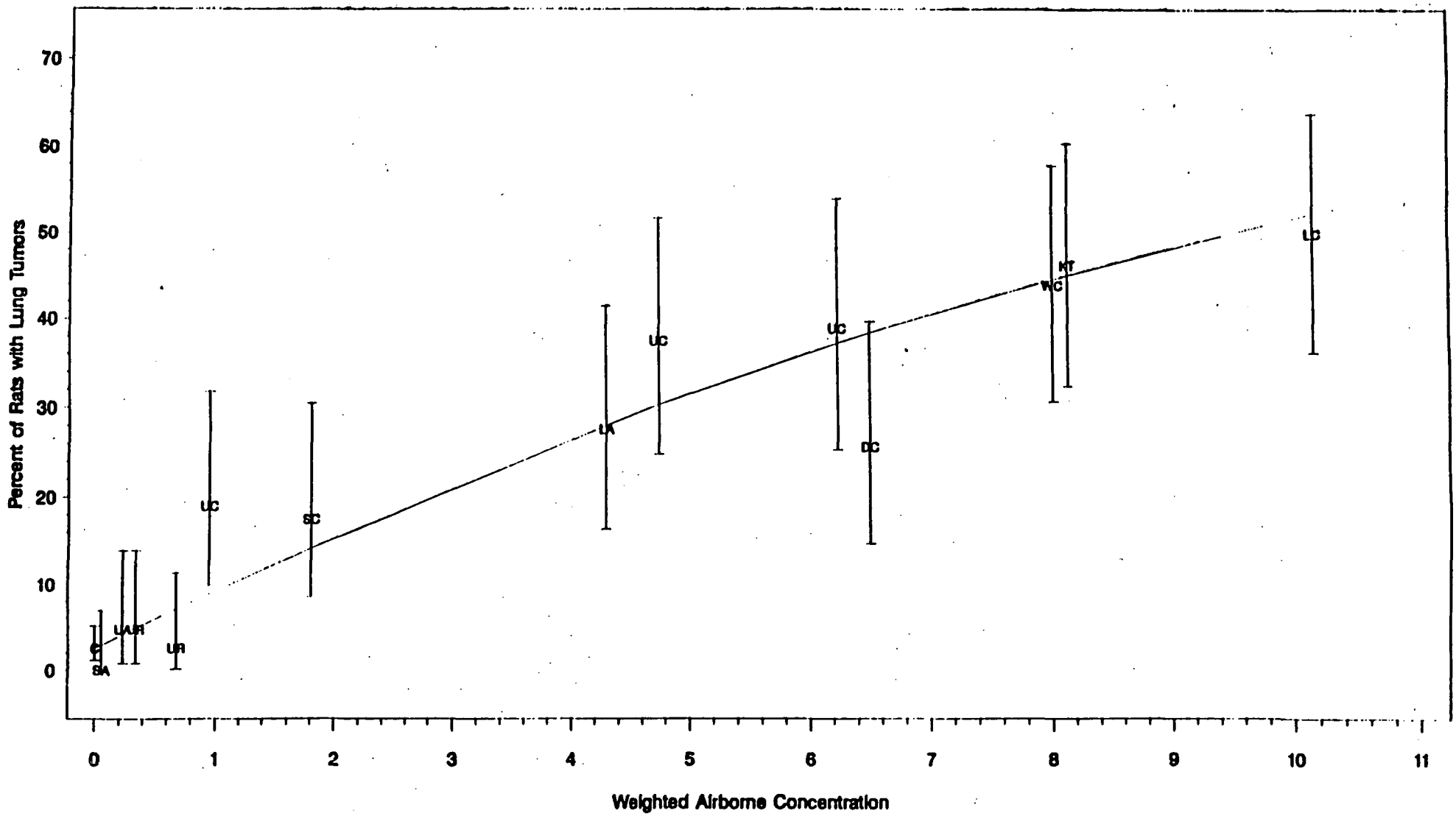
This index of exposure represents one of the optimum indices reported in Berman et al. 1995.

As is clear from the figure, when exposure is expressed in the manner described above, the tumor responses observed in the 13 separate experiments that were evaluated increase monotonically with increasing exposure. It is also apparent that the data points representing each study fall reasonably close to the line representing the optimized model for this exposure index. Thus, exposure adequately predicts response.

Results obtained from completing more than 200 statistical analyses to determine whether various measures of asbestos exposure adequately predict lung tumor response indicate that:

- neither total dust mass nor fiber concentrations determined by PCM adequately predict lung tumor incidence;
- no univariate measure of exposure (i.e. exposure represented by the concentration of a single size category of structures as measured by TEM) was found to adequately predict lung tumor incidence. Of the univariate measures of exposure examined, the concentration of total structures longer than 20 µm provides the best fit (although still inadequate); and

FIGURE 5-3
FIT OF MODEL
TUMOR INCIDENCE VERSUS STRUCTURE CONCENTRATION BY TEM
Length Categories: 5μm – 40μm, ≥ 40μm
Width Categories: < 0.3μm and ≥5μm



Vertical bars indicate 90% confidence intervals.
Abbreviations for data are explained in Table 1.
Less complex clusters and matrices replaced by components.
Original concentrations estimated by multiplying concentrations in reconstructed dusts by ratio of PCM concentrations

- lung tumor incidence can be adequately predicted with measures of exposure representing a weighted sum of size categories in which longer structures are assigned greater potency than shorter structures.

One example of an exposure measure that adequately describes lung tumor incidence is presented in Figure 5-3. Another exposure measure shown to provide an adequate fit is:

$$\text{Exposure} = 0.0024C_a + 0.9976C_b$$

where:

"C_a" is the concentration of structures between 5 and 40 μm in length that are thinner than 0.4 μm; and

"C_b" is the concentration of structures longer than 40 μm that are thinner than 0.4 μm.

In addition to the above, a series of hypotheses tests were also conducted to test such questions as: whether fiber type affects potency or whether the component fibers in complex clusters and matrices should be counted individually. Questions concerning whether mesothelioma incidence can be adequately described by the same measure(s) of exposure that describe lung tumor incidence were also addressed. Taken as a whole, the results presented in Berman et al. (1995) support the following, general conclusions:

- structures contributing to lung tumor incidence are thin (< 0.5 μm) and long (> 5 μm) with structures longer than 20 μm being the most potent;

- the best estimate is that short structures (< 5 μm) are non-potent. There is no evidence from this study that these structures contribute anything to risk;

- among long structures, those shorter than 40 μm appear individually to contribute no more than a few percent of the potency of the structures longer than 40 μm;

- lung tumor incidence is best predicted by measurements in which the component fibers and bundles of complex structures are individually counted;

- at least for lung tumor induction in rats, the best estimate is that chrysotile and the amphiboles are equipotent;

- for equivalent size and shape structures, amphiboles are more potent toward the induction of mesothelioma than chrysotile; and

- after adjusting for the relative potencies of fiber type, the size categories that contribute to lung tumor incidence appear also to adequately describe mesothelioma incidence.

A number of supplemental analyses were also conducted (after publication of the first part of the study), primarily to identify optimal procedures for performing asbestos analysis and for estimating concentrations. These analyses have not yet been published. The most important results of the supplemental analyses are that:

- tumor incidence can only be adequately fit by data derived from TEM analysis of samples prepared by a direct transfer procedure. Measurements derived from indirectly prepared samples could not be fit to lung tumor incidence in any coherent fashion; and

- it was not possible to identify an exposure measure in which potency is expressed in terms of a single, continuous function of structure length.

Regarding the last point, although we were not able to identify a continuous function of length that provides an adequate fit to the tumor incidence data, the general results from the above analysis are not inconsistent with the hypothesis that potency is a continuous function of length (i.e. the Pott hypothesis, Pott 1982). The Pott hypothesis suggests that relative potency is low for short fibers, rises rapidly over an intermediate range of lengths, and approaches a constant for the longest fibers.

5.7 CONCLUSIONS: ASBESTOS CHARACTERISTICS THAT BEST RELATE TO BIOLOGICAL ACTIVITY

By considering the studies that address the effects of deposition, clearance, degradation, and biological response (which are discussed in the previous sections of this chapter), the outstanding issues identified in Section 5.0 can now be addressed. Furthermore, an exposure index that captures the principal characteristics of asbestos that determine biological activity and, therefore, risk can now be defined (Section 5.7.2).

5.7.1 Addressing Outstanding Issues

The seven outstanding issues concerning the characteristics of asbestos that relate to biological activity identified in Section 5.0 can be addressed based on conclusions drawn from the literature review presented in this Chapter.

Short structures. Short, fibrous structures (less than 5 μm in length) do not appear to contribute to risk. This is supported both by the results of our re-analysis of the animal inhalation studies (Section 5.6.2), in which this hypothesis was tested formally, and by inference from the broad body of other literature reviewed in this document.

The results of the vast majority of injection and implantation studies that are discussed in Sections 5.4.1, many of the pathology studies discussed in Section 5.5, and the animal inhalation studies discussed in Section 5.6.1 consistently indicate that short structures do not contribute substantially to the induction of disease. In fact, there is no positive evidence from any of the studies reviewed that suggests short structures do contribute measurably to risk.

Results from several injection and implantation studies (Section 5.4.1) and other mechanism studies presented in Section 5.4.2 also suggest a reason that short structures do not contribute substantially to disease: they are efficiently cleared from lung tissue relative to longer structures. Based on the relative sizes of rat and human macrophages (Krombach et al. 1996), structures shorter than some cutoff between 5 μm and 10 μm appear to be efficiently cleared from rat lungs and structures shorter than 10 μm to 15 μm may be efficiently cleared from human lungs.

Based on formal hypothesis testing concerning short structures, the best estimate of the potency of short structures is precisely zero. Even an upper bound estimate (based on a 90% confidence interval) for the relative potency of these structures is that they are no more than 4% as potent as structures longer than 5 μm and no more than 0.009% as potent as structures longer than 40 μm. This indicates that, for virtually all of the size distributions observed to date, contributions to overall potency from short structures is inconsequential.

Given the above, the asbestos exposure index recommended in this report excludes consideration of structures shorter than 5 μm. This cutoff is selected because it is still sufficiently short to allow for the possibility that a slightly shorter set of structures contributes to the induction of mesothelioma than the set of structures that contributes to lung cancer, as some have hypothesized (e.g. Lippmann 1988).

Because the results of our re-analysis of the animal inhalation studies indicates formally that structures longer than 40 μm are even more potent than structures of intermediate length (i.e. those between 5 μm and 40 μm), the recommended exposure index incorporates a sum in which the potency of longer structures is weighted more heavily than those of intermediate length. As indicated previously (Section 5.6.2), This is entirely consistent with the Pott hypothesis (Pott et al. 1982) and other inferences that can be gleaned from the animal injection, implantation, and inhalation studies.

Thin structures. The fibrous structures that contribute to risk are apparently thin (less than 0.5 μm in diameter). This conclusion is supported by the formal hypothesis testing

performed during our re-analysis of the animal inhalation data (Section 5.6.2), by less formal analyses that have been conducted by others (e.g. Wylie et al. 1993), and by inference from the majority of injection and implantation studies reviewed in Section 5.4.1.

Dynamic models of respirability and retention (Section 5.2.3) further suggest that the respirability of fibrous structures thicker than approximately 0.7 μm is severely limited when such structures are as dense as the various asbestos minerals. Therefore, thicker structures may simply not reach the deep lung where they might otherwise be retained and potentially contribute to the induction of disease. Note that the indicated cutoff in respirability refers primarily to relatively solid structures (such as fibers or bundles). Complex structures such as clusters or matrices may contain substantial empty space so that, because of their lower density, they tend to be more respirable than their size might otherwise indicate. The importance of complex structures is addressed further below.

Importantly, the results of all of the studies cited above indicate that it is a cutoff in absolute width that defines the bounds of biological activity rather than a cutoff in aspect ratio (the ratio of length to width) that has been used to define fibrous structures heretofore. This is why the exposure index recommended in this report is defined by a maximum width rather than a minimum aspect ratio.

Based on formal hypothesis testing to evaluate the relationship between width and biological activity (Section 5.6.2), the maximum width above which fibers and bundles do not appear to contribute to risk lies somewhat below 0.5 μm; the best fits to the animal inhalation data all suggested narrower width cutoffs. Therefore, a maximum width of 0.5 μm is incorporated in the definition of the exposure index recommended in this report. Note, however, that this cutoff applies primarily to fibers and bundles. As discussed further below, this limit is not applied to complex structures (clusters and matrices), which may contain thinner components that potentially contribute to risk and are therefore included in the exposure index.

Complex structures (asbestos aggregates). The tumor incidence data from the animal inhalation studies were best fit (predicted) by exposure indices in which the component fibers and bundles of complex structures (clusters and matrices) were separately enumerated and included in the exposure index used to represent concentration (Section 5.6.2). Therefore, it is recommended in this report that those components of complex structures that exhibit the required dimensional criteria be individually enumerated and included within the exposure index defined for asbestos.

The need to include components of complex structures in the exposure index for asbestos is further supported by inferences that such structures may degrade in vivo to their component fibers and bundles. Otherwise, studies other than our re-analysis of the animal inhalation data (Section 5.6.2) have not tended to address consideration of

complex structures. Regarding injection and implantation studies, this is largely due to the nature of the sample. Complex structures such as clusters and matrices can neither be readily identified nor easily defined within the solid matrices of the samples employed in these studies. Their consideration may also have been ignored during most of the published inhalation studies due to the wide use of SEM to characterize asbestos exposure and the limited ability to distinguish the internal details of asbestos structures with such instrumentation (Section 3.2).

Fiber mineralogy. The mineralogy (i.e. chemical composition and crystal structure) of a fibrous material is an important determinant of the potency of that material toward the induction of disease, particularly in humans. This appears due both to the dependence of in-vivo durability on mineralogy and to the dependence of the mechanisms of biological responses on mineralogy (Section 5.4).

Results from some (but not all) of the animal injection, implantation, and inhalation studies previously reviewed (Sections 5.4 and 5.6) suggest that mineralogy plays an important role in determining biological activity. However, the nature of the effects of mineralogy are not easily separated from size effects, due to the methodological limitations of the studies cited. Therefore, the evidence from these studies can be considered ambiguous. Several of the human pathology studies cited previously (Sections 5.2 and 5.5) also suggest that mineralogy is an important factor in determining risk, but these studies similarly suffer from methodological difficulties that introduce ambiguity into the inferences drawn.

Formal hypothesis testing during our re-analysis of animal inhalation studies (Section 5.6.2) indicates that, when size effects are addressed, chrysotile and the amphiboles exhibit comparable potency toward the induction of lung cancer. In contrast, amphiboles appear to be approximately three times more potent than chrysotile toward the induction of mesothelioma, once fiber size effects are addressed. Although these results suggest a modest role for mineralogy in determining risk, it is also recognized that the effects may be magnified in humans relative to animals (as discussed below).

More directly, many in-vitro studies (Section 5.4.2) indicate that mineralogy plays an important role in the mechanisms by which fibrous structures induce cancer so that mineralogy would be expected to be an important determinant of risk. Both the relationship between mineralogy and in-vivo durability and the effect of mineralogy on the rate and mechanism of production of reactive oxygen species appear to cause different mineral types to exhibit different degrees of carcinogenicity. That mineralogy may be a more important determinant of risk in humans than disease induction in rats has also been highlighted in these studies. Differences in durability between mineral types may have a greater effect in humans than rats because the time scales over which degradation occurs is long relative to the life-span of a rat but important over the time scale of a human lifetime (Section 5.2).

The strongest evidence that mineralogy is an important factor in determining risk comes from epidemiology studies. Therefore, the effects of mineralogy are addressed more fully in our review and reconciliation of the epidemiology database (Chapter 6). Formal consideration of the effects of mineralogy are incorporated into the procedures recommended in this document for assessing asbestos-related risks in the manner described in Chapter 6.

Non-asbestos fibers. There is some evidence that certain other fibrous materials may exhibit similar biological activity to that ascribed to the fibrous materials included formally under the definition of asbestos. For example, fibrous erionite has been causally associated with the mesothelioma cases that have been observed in several cities in Turkey (Baris et al. 1987).

Some have thus suggested that any refractory fibrous material be regulated in the same manner as asbestos, if the material is known both to be durable in-vivo and to occur in a distribution of sizes that includes the biologically active range. However, evidence presented in various studies reviewed in this chapter (and highlighted further in Chapter 6) indicates that mineralogy is an important determinant of potency beyond it's impact on bio-durability. Therefore, while prudence dictates that the fibrous habits of other refractory materials deserve scrutiny, potency estimates for those found to induce disease will need to be established on a case-by-case basis.

Disease end-points. At this point in time, there is no compelling evidence that the size range of fibrous structures that contribute to the induction of lung cancer and mesothelioma are substantially different. While such differences have been hypothesized by various researchers (e.g. Lippmann 1988), quantitative evidence demonstrating such differences appears to be lacking. At the same time, results of hypothesis tests conducted during the re-analysis of the animal inhalation studies (Section 5.6.2) indicates that, as long as the effects of mineralogy are adequately addressed, the same asbestos exposure index can be used to fit (predict) both the lung tumor and the mesothelioma data.

Despite the above, the size range defined by the asbestos exposure index recommended in this document is sufficiently broad to incorporate structures that contribute most strongly to both lung cancer and mesothelioma, even if small differences do exist in the range of structures that contribute to each disease.

Dose-response models. Although the validity of the dose-response models employed for lung cancer and mesothelioma in this report was not evaluated formally, there is no strong evidence to suggest that the existing models are inadequate or, if they are, at least they are not expected to lead to the underestimation of risk. This issue is discussed further in Chapter 6. Given the situation, the models recommended in the Health Effects Assessment Update (U.S. EPA 1986) were adopted without modification.

Other general considerations. Several additional considerations developed from the literature review and evaluation documented in this Chapter also contributed to the nature of the asbestos exposure index recommended in this document. These considerations include:

- it is clear both from the literature review and the re-analysis of the animal inhalation studies discussed above that asbestos risk is best described as a function of the number of structures of a specific type and size range that contribute to an individual's exposure. Estimates of exposure and dose that are based on asbestos mass cannot be used to predict risk;

- both because the structures that contribute most to risk are thin and because appropriately sized components of complex structures need to be included in the characterization of exposure, use of TEM in combination with a method that incorporates appropriate structure counting and characterization rules appears to be the only analytical procedure that is adequate for determining asbestos concentrations that can be related to risk;

- the results from our formal re-analysis of the animal inhalation data indicate clearly that samples to be prepared for TEM analysis must be prepared using a direct-transfer procedure, if the characteristics of the sample that determine risk are to be preserved. Measurements derived from samples prepared using indirect transfer cannot be related to risk. Therefore, any method employed to support asbestos risk assessment needs to incorporate sample preparation by direct transfer; and

- because longer structures (at least as long as 20 μm) have been shown to be more potent than shorter structures, it is important that the longer structures be enumerated with adequate precision when measuring asbestos concentrations. Therefore, since such structures are also rarer than shorter structures in size distributions typically encountered, long structures need to be counted exclusively in a separate scan from that employed for the more numerous, shorter structures. Any method to be employed for measuring asbestos concentrations to support risk assessment must therefore incorporate statistically balanced counting (see Table 3-2).

Section 5.7.2 Defining an Exposure Index for Asbestos

Given the results of our re-analysis of the animal inhalation studies coupled with the findings of the literature review presented in this chapter, we believe that the following

index of exposure best captures the characteristics of asbestos that determine risk:

$$C_{asbestos} = 0.003C_S + 0.997C_L \qquad 5.2$$

where:

"C_S" is the concentration of structures between 5 and 40 μm in length that are also thinner than 0.5 μm; and

"C_L" is the concentration of structures longer than 40 μm that are also thinner than 0.5 μm.

It is acknowledged that humans and rats may not respond to asbestos in precisely the same manner. However, it is believed that (due primarily to differences in the physiology of respirability) any changes in the fiber characteristics that relate to carcinogenicity in humans may shift the break point in this equation to longer fibers. Humans appear to respire and retain a greater fraction of longer fibers in the deep lung (Section 5.1.2). It is also known that human macrophages, which mediate deep lung clearance, are larger than their counterparts in the rat (Krombach et al. 1996). Thus, it is likely that the maximum length of structures effectively cleared from the lungs is greater for humans than for rats. Therefore, since the shortest fibers represent the most numerous in all asbestos dusts so far encountered, the above equation is believed to be conservative for humans relative to rats.

As indicated in the previous sections, estimates of asbestos exposure using the above defined exposure index should be derived from asbestos measurements obtained by TEM analysis of samples prepared by a direct-transfer procedure. Further, the analysis should be conducted based on a method that incorporates statistically-balanced counting and incorporates counting and characterization rules that require enumeration of appropriately sized fibers and bundles that occur either as isolated structures or as components of more complex structures. The general procedures of the current ISO Method (ISO 10312) are recommended. However, the structures recorded in the analysis can be restricted to those that satisfy the dimensional criteria defined by the recommended exposure index. This will simplify the analysis substantially.

6.0 ASBESTOS RISK COEFFICIENTS

As indicated in Section 2, the last two steps required for developing a protocol to evaluate asbestos risks are to adjust existing risk coefficients so that they can be applied to current measurements and to identify appropriate models to relate asbestos exposure to risk.

The risk coefficients and the corresponding dose-response models that are used to assess asbestos-related risks are derived from the existing epidemiology literature. An overview of the literature is provided below to highlight the considerations that need to be addressed to define a mutually-consistent set of risk coefficients. The specific risk coefficients that were selected for adjustment to support this protocol were developed from a detailed evaluation of the subset of epidemiology studies that contain sufficient information to evaluate dose-response relationships quantitatively. The evaluation is described in Appendix A.

The procedures employed for adjusting selected risk coefficients so that they can be applied to predict asbestos-related risks in exposure settings of interest are described in Section 6.2. A detailed description of the corresponding dose-response models is also provided.

6.1 OVERVIEW OF THE EPIDEMIOLOGY LITERATURE

To develop dose/response relationships (and corresponding risk coefficients) for use in risk assessment from epidemiological data, two basic types of information are necessary: information on the health response in the study population (cohort) and information on the asbestos exposure experienced by the cohort. Ideally, one would like to have complete knowledge of exposure at any period of time for each individual in the cohort and complete access to the data in order to fit different types of dose/response models to the data so that the approach can be optimized. In most instances, unfortunately, the data suffer from multiple limitations and the analyst is further constrained by less than complete access to the data.

Generally, the most severe limitations in an epidemiology study involve the exposure data. In most cases, air measurements were collected only at limited points in time and measurements may be entirely lacking from the earliest time periods, when exposures may have been heaviest. In such cases, exposures are estimated either by extrapolation from periods when measurements are available or by expert judgement based on personal accounts and records of changes in plant operations, industrial hygiene procedures, air standards, etc. The majority of analysis results used in these studies are based on area (ambient) rather than personal samples. Typically, only a few areas of a plant have been sampled so that levels in other areas must be approximated using expert judgement by persons familiar with operations at the plant.

It is difficult to judge the degree that available asbestos concentration measurements are representative of actual exposures. In some cases, it seems likely that operations were shut down or otherwise modified in preparation for sampling. Likewise, in some operations there are brief episodes of very intense exposure and it is questionable whether such episodes are adequately represented in the available data. Most of the asbestos measurements used in the published epidemiology studies were collected for insurance or compliance purposes. They were not intended to provide a representative estimate of the direct level of exposure to workers. Some of the published epidemiology studies lack any direct exposure data. For example, exposures were estimated for the cohort studied by Seidman (1984) based on conditions simulated many years later in a similar plant to the one from which Seidman studied the original cohort.

Samples collected prior to the mid-1960s were often analyzed by measuring total dust in units of millions of particles per cubic foot (MPPCF) using impingers or thermal precipitators. A description of the relative strengths and weaknesses of these techniques is provided in Section 3.2. The fibrous portion of the dust was not monitored. Impinger measurements are sometimes related to fiber counts (based on PCM) using side-by-side measurements of total dust and fiber counts collected during a relatively brief period of time (e.g., McDonald et al, 1980, Dement et al, 1983). However, the correlation between fiber counts and total dust is sometimes poor within a plant and generally poor between plants (see, for example, U.S. EPA 1986). Thus, conversions based on limited sets of paired measurements are of questionable validity. In some studies (e.g., McDonald et al, 1983b) the only available measurements are impinger measurements in MPPCF and these have been related to f/ml by PCM using conversion factors derived in other plants, which raises further questions concerning validity.

None of the published epidemiology studies incorporate TEM measurements of asbestos because such measurements are not widely available in occupational settings (Section 6.2). However, TEM is the method currently used (and recommended) to assess exposure in environmental settings. Thus, even accepting the conversions from dust counts to fiber counts, the exposure estimates that are available from existing epidemiology studies (based on PCM or impinger) do not reflect thin fibers (thinner than about 0.3 μm) and do not distinguish asbestos from non-asbestos fibers, which may also be present in the exposure settings studied (Section 3.1), because PCM is incapable of addressing such factors (Section 3.2).

In addition to problems with the actual analysis of asbestos concentrations, individual exposures are generally estimated in the existing epidemiology studies by relating ambient asbestos measurements to job descriptions and integrating the duration of exposure over the recorded time that each worker spent in each job category. However, sometimes there are no records of specific areas in which an employee worked, so that work areas must be assumed based on job title. Some types of

workers (e.g., maintenance workers) may have spent time in many different areas of a plant so their exposure varies from what might otherwise be assumed.

Although the greatest problems with the data in existing epidemiology studies likely lies within the estimates of exposure, problems with disease-response data also exist. Mesothelioma is rare and this disease may have been under-reported as a cause of death in older studies. This is probably less of a problem in more recent studies, since the association of mesothelioma with asbestos exposure is now well known. In fact, the opposite tendency (over-reporting) may now be occurring because an asbestos worker with mesothelioma is probably eligible for compensation. Some studies have re-diagnosed causes of death from all of the available data (e.g., Selikoff et al, 1979); however, this creates the problem of lack of comparability to control populations (for which such re-diagnosis is not generally performed).

The choice of an appropriate control population is also an important consideration. Local cancer rates may differ substantially from regional or national rates and the choice of an appropriate control is not always clear. A related problem is the lack of smoking data in many of the studies. Because of the interrelation between smoking and asbestos in lung cancer, errors could occur in lung cancer risk estimates if the smoking patterns of the cohort are substantially different from those of the control population.

In some of the studies, a substantial portion of the population is lost to follow-up (e.g., Armstrong 1988), and this adds additional uncertainty to the analysis. Also, the effect of exposure may be inaccurately evaluated if the follow-up of the population is too brief.

Another problem frequently associated with these studies is that available data are not reported in a form that is well-suited to risk assessment. The EPA lung cancer model, for example, requires that exposure be estimated as cumulative exposure in f/ml·years excluding the most recent 10 years (see Section 6.2.1); generally the data are not published in this form. The data are also frequently not available in a form that permits study of the shape of the lung cancer dose/response curve, so it is not possible to determine how well the EPA model describes the data. The form of the data for mesothelioma is generally even less appropriate for risk assessment. Ideally, what is needed is the incidence of mesothelioma subdivided according to exposure level, age at beginning of exposure, and duration of exposure (Section 6.2.2). Such data are almost never available and crude approximations must be made to account for this lack.

The existing asbestos epidemiology database consists of approximately 100 studies of which approximately 15 contain exposure data sufficient to derive quantitative dose/response relationships. A detailed evaluation of 15 key studies, based on the considerations presented in this overview, is provided in Appendix A.

It is important to note that the evaluation reported in Appendix A was completed in 1986 and has not been updated despite appearance in the literature of several follow-up studies to the key studies evaluated (e.g., McDonald et al.1993, Dement et al. 1994, Dement and Brown 1994, and Brown et al. 1994). Also, at least one study has been published (Sluis-Cremer et al. 1992) that addresses a new exposure setting not previously considered. Incorporation of this study would broaden the diversity of the epidemiology database. Due to the coincident exposure of amphibole asbestos with talc, it might also be helpful to add selected epidemiology studies of talc minors (Brown et al. 1979, Stille and Tabershaw 1982, Brown et al. 1983, and Gamble and Greife 1983) to the set evaluated in Appendix A.

A brief review of the new epidemiology literature suggests that there are no surprises. Thus, the risk coefficients presented in this document are unlikely to change substantially even if the newest follow-up studies are incorporated in our analysis. At the same time, if there is interest in further refining the ability to predict asbestos-related risks, it is recommended that the detailed analysis of the quantitative epidemiology studies (presented in Appendix A) be updated in the future to incorporate the newly available data, which would provide a richer database for testing hypotheses.

Even more useful: to the extent that archived samples are available from environments evaluated in the existing epidemiology studies, we highly recommend a study be completed that is similar in form to the one we completed for the animal inhalation database (Section 5.6.2). Specifically, we recommend that archived samples be re-analyzed to provide a better indication of the nature of exposure experienced by cohorts evaluated in the epidemiology studies and that a statistical analysis then be completed to better define the characteristics of asbestos that determine human risk. This would complete our effort to reconcile the published risk coefficients, the results of which are reflected in the design of the protocol that we recommend in this document (Part 1) for estimating asbestos-related risks.

6.2 ADJUSTING ASBESTOS RISK COEFFICIENTS

As indicated previously, risk coefficients derived from existing epidemiology studies must be modified to reflect the relationship between measurements by the analytical techniques used in such studies and the characteristics of asbestos that determine biological activity. Risk coefficients based on exposure indices that do not relate directly to biological activity cannot be readily applied to exposure settings different from the one in which the risk coefficients were initially derived. This is because the relationship between biological activity and any indirect measure (index) of exposure may vary between environments. Thus, risk coefficients based on indirect indices of exposure would also vary between environments, which minimizes their utility as predictive tools.

Considerations necessary to compare risk coefficients derived in different exposure settings (or to apply a coefficient to predict risk in a setting different from the one in which the coefficient was derived) have been elucidated clearly in a mathematical model (Chesson et al. 1989). The consequences of the model indicate that adjusting the existing risk coefficients so that they reflect asbestos characteristics that determine biological activity requires knowledge of the fiber size distributions of the dusts studied in the *original* epidemiology studies. To the extent they exist, such data may be used to normalize each of the published risk coefficients so that they relate to a common exposure index reflecting asbestos characteristics that determine biological activity.

Adjustment of the existing risk coefficients is necessary because they have all been derived based primarily on PCM and MI measurements and, as previously indicated, neither PCM nor MI measurements relate adequately to biological activity (Section 5.6.2). Thus, analytical techniques employed at the time these studies were conducted were not capable of providing asbestos measurements that directly reflect biological activity.

Ideally, the existing risk coefficients should be adjusted so that they are all normalized to an exposure index such as that defined by Equation 5.2, which was designed to adequately reflect the characteristics of asbestos that determine biological activity (Section 5.7). However, as indicated below, the database available for describing structure-size distributions for exposures in the original epidemiology studies do not contain sufficient information to individually characterize frequencies for structures longer than approximately 10 μm. Therefore, an ad hoc exposure index is presented, which represents a compromise between theoretical needs defined in Chapter 5 and the limitations of the available data.

In the following sections, published risk coefficients are normalized to an exposure index that better reflects biological activity using a series of published size distributions derived from TEM measurements. The distributions are defined for exposure settings that correspond to several of the settings evaluated in the epidemiology studies from which the published risk coefficients were derived. The coefficients are then combined with the asbestos risk models presented previously (U.S. EPA 1986) to complete design of a general protocol for assessing asbestos-related risks. In keeping with general risk management practices under Superfund, the approach adopted is conservative so that potential errors will not likely result in the underestimation of risk.

6.2.1 Assessing the Risk of Lung Cancer

The Airborne Health Effects Assessment Update (U.S. EPA 1986) utilizes a model for lung cancer in which the asbestos-related age-specific mortality from lung cancer at age t is proportional to cumulative asbestos exposure at time t-10 years (i.e., cumulative exposure lagged 10 years), multiplied by the age- and calendar year-specific background mortality rate of lung cancer in the absence of asbestos exposure.

A linear relationship between cumulative dose and response has been assumed based on the ten epidemiology studies identified (in the 1986 EPA document) as containing sufficient information to establish a dose/response curve for asbestos induced lung cancer:

$$I_L = I_E[1+K_L \cdot PCM \cdot d_{(t-10)}] \qquad (6.1)$$

where:

"I_L" is the overall lung cancer mortality (expected lung cancer deaths per year per person) adjusted for age and calendar year;

"I_E" is the corresponding lung cancer mortality in a population not exposed to asbestos;

"PCM" is the concentration of asbestos (expressed as PCM fibers longer than 5 μm;

"t" is age;

"$d_{(t-10)}$" is the duration of exposure up to age t, excluding the most recent 10 years; and

"K_L" is the proportionality constant between dose and response. This is the risk coefficient that represents the potency of asbestos.

The above model is a relative risk model in that it assumes that the excess mortality of lung cancer from asbestos is proportional to the mortality in an unexposed population. Since smokers have a much higher mortality from lung cancer, if smoking-specific mortality rates are applied, the model predicts a higher excess mortality from asbestos-related lung cancer in smokers than in non-smokers. This is consistent with the multiplicative relationships between smoking and asbestos that have been observed in epidemiological studies. Note that the K_L in the model pertains to an occupational pattern of exposure (e.g., 8 hours per day, 240 days per year) and must be modified before application to environmental exposure patterns.

The series of unadjusted K_L values derived from the existing epidemiology study database are presented in Table 6-1. In Table 6-1, Column 1 lists the fiber types for the various studies. Column 2 lists the exposure settings (industries) studied and Column 3 lists the specific epidemiology study used to derive the K_L values listed in Columns 4, 5, and 6. The Column headed "EPA" lists K_L values reported in the Airborne Health Effects Assessment Update (U.S. EPA 1986). Columns 5 and 6 present, respectively, median level estimates and upper bound estimates derived as part of this study (see Appendix A). In general, the median levels presented in

TABLE 6-1: K_L AND K_M VALUES DERIVED FROM PUBLISHED EPIDEMIOLOGY STUDIES

Fiber Type	Exposure Setting	Epidemiology Reference	K_L			K_M ($\times 10^8$)		
				Present Study			Present Study	
			EPA 1986[a]	MLE MLE	Upper Limit	EPA 1986[a]	MLE	Upper Limit
Chrysotile	Textiles	Dement et al. 1983b	0.028	0.028	0.073		0.3	1.1
		McDonald et al. 1983a	0.025	0.012	0.017		0.051	0.19
		Representative Value:		0.02			0.2	
	Friction Products	McDonald et al. 1984	0.0001	0	0.0017		0	0.12
		Representative Value:		0.0006[b]			0.2	
	Mining and Milling	McDonald et al. 1980	0.0006	0.00045	0.0006		0.011	0.017
		Nicholson et al. 1979	0.0017					
		Rubino et al. 1979	0.00081					
		Representative Value:		0.0005			0.01	
	Asbestos Cement Manu.	Hughes et al. 1987		0.004	0.01		0.05	0.2, <0.3
		Representative Value:		0.005			0.1	
Crocidolite	Mining and Milling	Armstrong et al. 1988		0.1			14	
Amosite	Insulation Manu.	Seidman 1984	0.043			3.2		
Mixed	Textiles	McDonald et al. 1983b	0.014	0.018	0.045	1.0	0.68	1.1
		Peto 1980, 1985	0.011	0.0054[b]	0.015		1.3	
	Friction Products	Berry & Newhouse 1983	0.00058	0.0006	0.008			
	Asbestos Cement Manu. (Chrysotile and Crocidolite)	Finkelstein 1983	0.048	0.036		12	19	30
		Hughes et al. 1987		0.004	0.0098		0.3	
		Weill et al. 1979		0.0064	0.019		0.07	0.18
		Weill et al. 1979; Weill 1984	0.0053					
	Manufacturing	Henderson & Enterline 1979	0.0049					
	Insulation Application (Chrysotile and Amosite)	Selikoff et al. 1979	0.0075			1.5		

Column 5 agree closely with the values estimated by EPA. The two columns differ by less than +/- 30% except for the McDonald 1984 study of friction products, which was a negative study. The Armstrong (1988) study of crocidolite mining was published after the EPA document so that it was not evaluated by EPA. Additional columns present K_M values for mesothelioma. The representative values presented in Column 5 of Table 6-1 were used for this evaluation. Where values are not presented in Column 5, the EPA values for these studies were adopted (Column 4).

Note that the K_L values listed in Table 6-1 vary by over a factor of 200 when all fiber types are considered. Values for chrysotile alone vary by over a factor of 40 between exposure settings. As indicated previously (Chapter 4), the variation in K_L values from the different industries presented in Table 6-1 potentially derive from one or a combination of several factors including:

- fiber type;
- differences in the distribution of asbestos fiber sizes;
- the ratio of asbestos to nonasbestos in the total dust;
- the ratio of asbestos to nonasbestos in the fibrous dust;
- contributions from other etiologic agents present in specific exposure settings;
- the age of the population and period of follow-up;
- differences in the underlying cancer rates within the population under study (due to smoking habits and other factors);
- differences in the methods used for defining exposure groups and assigning exposure estimates to each group; and
- the representativeness of dust sampling in each study to the actual exposures.

The first four factors listed above involve characteristics of asbestos exposure that affect the degree with which measurements relate to biological activity and were discussed in detail in Chapter 5. It is due to these factors that we suggest the need for adjusting the existing risk coefficients so that they predict asbestos potency more consistently across exposure settings.

The last five factors listed above relate to variation in parameters not associated with exposure measurement. Although a short follow-up period should not bias the estimate

of K_L, if the model is correct and is applied correctly, it would cause K_L to be estimated with less precision. Data on smoking habits in the epidemiological populations would permit adjustment for smoking differences between this and the control population; however, such data are often not available. Except possibly for contributions from other etiologic agents, these last five factors would be unique to the set of data and epidemiological methods employed in a particular study and would not be expected to vary systematically with exposure setting.

If the variation in K_L values contributed by all of the factors *not* related to asbestos measurement could be systematically addressed, the remaining variation presumably would be due entirely to differences in the characteristics of asbestos dusts present in the various exposure settings (the first four factors listed above). As mentioned above, except for the presence of other etiologic agents, the effects of such non-measurement related factors would not be expected to correlate with exposure setting. Rather, such differences should contribute to variation "within" each exposure setting as well as "between" exposure settings.

Since the data in Table 6-1 indicates that (with one exception) K_L values "within" exposure settings vary by less than a factor of 4, the larger differences observed "between" exposure settings (over a factor of 200) can likely be attributed either to characteristics of the asbestos dusts (including fiber type) or to the presence of additional etiologic agents that are specific to each industry. Therefore, assuming that other etiologic agents are not important, it appears that factors relating to the manner in which asbestos is measured, are indeed among the major sources of variation among the observed K_L values. This is consistent with the findings reported in Chapter 5.

As for the one exception, the K_L derived from the Finkelstein study is a factor of 10 larger than other asbestos/cement values derived from other studies. The cohort followed in this study may have been exposed to higher levels of crocidolite (25%) in combination with chrysotile than the other studies, which also reported mixed exposures. Also, the Finkelstein study exhibits an unexplained non-monotonic relationship between asbestos exposure and lung cancer. Therefore, the Finkelstein study is handled separately from the other studies in this evaluation in an attempt to account for the larger contribution from crocidolite and the unusual dose/response relationship.

The potential importance of contributions from etiologic agents other than asbestos has been raised to date in association with only one of the exposure environments considered here. Some have argued that the elevated potency of chrysotile asbestos that is observed in association with textile manufacturing may be due to the spraying of asbestos fibers with oil and the consequent contributions to carcinogenicity by components of the oil (U.S. EPA 1986). However, more recent studies have tended to case doubt on this hypothesis (Dement et al. 1994b). Thus, contributions to etiologic agents other than asbestos are not considered further in this document.

Adjusted Risk Coefficients for Lung Cancer

For the lung cancer model and the associated risk coefficient, "K_L," to be applicable generally, the asbestos concentration, "f," needs to be expressed in an exposure index that incorporates the characteristics of asbestos that determine risk. Correspondingly, the risk coefficient, "K_L" needs to be normalized to a model in which "f" is properly expressed.

As indicated previously, published structure size distributions derived from TEM measurements are used to adjust the existing K_L's by normalizing them to an exposure index that better relates to biological activity than the measurements in the epidemiology studies from which the K_L's were obtained.

Assuming that the available TEM size distributions are representative of dust characteristics for the exposure settings (industries) studied, these were paired with corresponding epidemiology studies. The TEM size distributions are then used to convert the exposure measurements used in the epidemiology studies to other exposure indices that are potentially more characteristic of biological activity. Studies were paired as indicated in Table 6-2.

Only a subset of the TEM size distributions listed in Table 6-2 were actually employed in the effort to normalize K_L values. To minimize uncertainty introduced by between-study variability, it was decided to employ distributions from common studies, to the extent that this could be accomplished without reducing the number of "size-distribution – K_L" pairs available for inclusion in the analysis. Also, studies containing the best documented procedures were favored over those in which the limitations of the distributions were less clear. Ultimately, the size distributions selected for use came from only two studies, which were reported in three publications: Dement and Harris (1979), Gibbs and Hwang (1980), and Hwang and Gibbs (1981).

Table 6-3 presents bivariate fiber size distributions derived from the published TEM data that are paired with representative K_L values from the corresponding epidemiology studies. These data were used to adjust K_L values in the manner described below.

The procedure for adjusting risk coefficients is straightforward. First, note that Equation 6.1 can be rewritten as:

$$K_L(C_{PCM})(d') = RR-1 \qquad (6.2)$$

where RR is the relative risk and is equal to (I_L/I_E) and d' is the duration excluding the final 10 years before observation of total lung cancer deaths.

TABLE 6-2:
CORRELATION BETWEEN PUBLISHED QUANTITATIVE EPIDEMIOLOGY STUDIES AND AVAILABLE TEM FIBER SIZE DISTRIBUTIONS

Fiber Type	Exposure Setting	Distribution Reference	Epidemiology Reference
Chrysotile	Textiles	Dement and Harris 1979	Dement et al. 1983b
		Cherrie et al. 1979	McDonald et al. 1983a
			McDonald et al. 1983b
			Peto 1980 and 1985
	Friction Products	Dement and Harris 1979	Berry and Newhouse 1983
		Marconi et al. 1984	McDonald et al. 1984
		Winer and Cossett 1979	
		Roberts and Zumwalde 1982	
	Mining and Milling	Gibbs and Hwang 1980	McDonald et al. 1980
		Winer and Cossett 1979	Nicholson et al. 1979
			Rubino et al. 1979
	Asbestos Cement Manu.	Dement and Harris 1979	Hughs et al. 1986
		Snyder et al. 1987	
		Winer and Cossett 1979	
	Mine Environment	Sebastian et al. 1984 and 1986	
	Construction	Snyder et al. 1987	
Chrysotile and Crocidolite	Asbestos Cement Manu.	Hwang and Gibbs 1981	Finkelstein 1983
			Hughs et al. 1986
			Weill et al. 1979
			Weill et al. 1984
Crocidolite	Mining and Milling	Gibbs and Hwang 1980	Armstrong et al. 1988
		Hwang and Gibbs 1981	
Amosite	Insulation Manu.	Dement and Harris 1979	Seidman 1984
			Henderson and Enterline 1979
	Insulation Application		Selikoff et al. 1979
	Insulation Clearance	Snyder et al. 1987	
		Cherrie et al. 1979	
	Mining and Milling	Gibbs and Hwang 1980	
Tremolite	Talc Mining	Dement and Harris 1979	

TABLE 6-3:
REPRESENTATIVE K_L AND K_M VALUES PAIRED WITH AVERAGED TEM FIBER SIZE DISTRIBUTIONS FROM PUBLISHED PAPERS

Exposure Setting	Reference	K_L	K_M ($x10^8$)	Fraction of Distribution Represented by Size Categories Indicated											
				PCME	w < 0.2			w < 0.3			w < 0.4			Total		
					L < 5	5 < L < 10	10 < L	L < 5	5 < L < 10	10 < L	L < 5	5 < L < 10	10 < L	L < 5	5 < L < 10	10 < L
Chyrsotile Textile Factory	D&H 1979	0.02	0.2	0.1296	0.6563	0.0302	0.0271	0.7405	0.0433	0.0398	0.7671	0.0496	0.0488	0.8130	0.0825	0.1044
Chrysotile Friction Products	D&H 1979	0.0006	0.12	0.0724	0.7636	0.0261	0.0187	0.8280	0.0343	0.0271	0.8494	0.0390	0.0312	0.8828	0.0545	0.0627
Predominantly Chrys Pipe Manuf	D&H 1979	0.005	0.1	0.0507	0.7747	0.0228	0.0157	0.8599	0.0307	0.0204	0.8866	0.0368	0.0234	0.9107	0.0484	0.0409
Mixed Asb/Cmt Pipe Manuf	H&G 1981	0.036	19	0.0076	0.9334	0.0112	0.0016	0.9540	0.0138	0.0022	0.9746	0.0163	0.0028	0.9798	0.0168	0.0036
Chrysotile Mining	G&H 1980	0.0005	0.01	0.0140	0.9354	0.0096	0.0023	0.9540	0.0113	0.0031		0.0132[1]	0.0037[1]	0.9729	0.0205	0.0054
Amosite Ins Manuf	D&H 1979	0.043	3.2	0.3520	0.1711	0.0287	0.0072	0.3005	0.0602	0.0310	0.3774	0.0911	0.0526	0.6121	0.1948	0.1931
Amosite Ins Applic*	D&H 1979	0.0075	1.5	0.3275	0.1179	0.0218	0.0000	0.2707	0.0611	0.0044	0.3450	0.0873	0.0175	0.6507	0.2052	0.1441
Crocidolite Mining**	H&G 1981	0.1	14	0.0117	0.8902	0.0266	0.0050	0.9377	0.0330	0.0062	0.9504	0.0351	0.0063	0.9567	0.0368	0.0067
Talc Mining (actin-trem)	D&H 1979	TBD	TBD	0.0702	0.5359	0.0055	0.0012	0.7389	0.0129	0.0034	0.8184	0.0176	0.0143	0.9232	0.0451	0.0317

1. Extrapolated by averaging ratio of fractions represented by width < 0.4 µm to width < 0.3 µm for each specified length category from the listed distributions for the other exposure settings and multiplying the average by the fraction for the width of < 0.3 µm for the corresponding length category.

By multiplying Equation 6.2 by one (expressed as a product of reciprocal ratios), we obtain:

$$\left[K_L\left(\frac{C_{PCME}}{C_{Opt}}\right)\right]\left(\frac{C_{Opt}}{C_{PCME}}\right)(C_{PCM}) \qquad (6.3)$$

where:

"C_{PCME}" is the concentration of asbestos structures in the published size distribution (Table 6.3) that are typically included in PCM measurements; and

"C_{opt}" is the concentration of asbestos structures in the published size distribution that represent the optimal exposure index (i.e. the index of exposure that determines biological activity).

Note that the equation incorporates concentrations but that the ratio of concentrations of specific size categories is always equal to the ratio of the fractions of the corresponding categories within a defined size distribution. Thus, the data in Table 6-3 can be used to derive estimates of the ratios of concentrations.

Remembering that C_{PCME} is supposed to equal C_{PCM} (Section 5.6.1) and canceling terms accordingly, one is left with a new Equation for risk in which asbestos concentrations are expressed in terms of the optimal exposure index:

$$K'_L(C_{OPT})(d') = RR-1 \qquad (6.4)$$

where:

"K'_L" is the adjusted risk coefficient, defined (and derived) as:

$$K'_L = K_L\left(\frac{C_{PCME}}{C_{Opt}}\right) \qquad (6.5)$$

where all terms have been previously defined.

The adjusted risk coefficients, the "K_L's", derived from the data provided in Table 6-3 in the manner described above are presented in Table 6-4. Adjusted risk coefficients for mesothelioma, "K_M's", are also provided. K_M's and K_L's are derived in precisely the

TABLE 6-4:
COMPARISON OF ORIGINAL AND ADJUSTED K_L AND K_M VALUES

Exposure Setting	Reference	K_L	K_M ($x10^6$)	K_L'	K_M' ($x10^6$)
Chyrsotile Textile Factory	D&H 1979	0.02	0.2	0.0531	0.5313
Chrysotile Friction Products	D&H 1979	0.0006	0.12	0.0014	0.2778
Predominantly Chrys Pipe Manuf	D&H 1979	0.005	0.1	0.0108	0.2160
Mixed Asb/Cmt Pipe Manuf	H&G 1981	0.036	19	0.0974	51.4038
Chrysotile Mining	G&H 1980	0.0005	0.01	0.0019	0.0373
Amosite Ins Manuf	D&H 1979	0.043	3.2	0.2871	21.3671
Amosite Ins Applic*	D&H 1979	0.0075	1.5	0.1390	27.7915
Crocidolite Mining**	H&G 1981	0.1	14	0.1827	25.5752
Talc Mining (actin-trem)	D&H 1979	TBD	TBD		

same manner. The model adopted for mesothelioma risk is described in the next section.

Ideally, C_{opt} would be set equal to the concentration of asbestos structures defined as described in Equation 5.2. However, published size distributions cannot be used to adjust risk coefficients to be consistent with the exposure index described by Equation 5.2. This is because the longest size category individually represented in the published distributions is for all structures longer than 10 μm and the exposure index described by Equation 5.2 requires that structures longer than 40 μm be individually enumerated. Therefore, Equation 5.2 was modified in an ad hoc fashion to generate the exposure index that forms the basis of this protocol:

$$C_{opt} = 0.003C_S + 0.997C_L \qquad (6.6)$$

where:

"C_S" is the concentration of asbestos structures between 5 and 10 μm in length that are also thinner than 0.5 μm; and

"C_L" is the concentration of asbestos structures longer than 10 μm that are also thinner than 0.5 μm.

The justification for selecting the above exposure index and the potential limitations associated with its use are described in Appendix B. Until such time that a study is completed in which size distributions are generated that allows use of an exposure index incorporating consideration of longer structures (such as that defined by Equation 5.2), it is recommended that asbestos concentrations be defined in terms of the exposure index defined by Equation 6.6 when evaluating asbestos risks and that the procedures described in the companion Protocol (Part 1 of this document) be employed to assess such risks.

It is interesting to consider the effect of adjusting the asbestos risk coefficients in the manner described above. If such adjustments were truly optimal (in that they adequately reflected all of the characteristics of asbestos that determine risk), one would expect the variation observed among the adjusted risk coefficients from all exposure settings to shrink to a level no greater than that observed within each single exposure settings (approximately a factor of 4).

To examine variability, the magnitude of the ratio of the maximum and minimum values (i.e. the spread of the values) for the adjusted and the unadjusted K_L's from Table 6-4 are presented in Table 6-5. Such ratios provide a rough indication of the variability or spread in these coefficients. The same adjustment is made to K_M's (risk coefficients for mesothelioma, as described below) and these results are also presented in Table 6-5.

TABLE 6-5:
COMPARISON OF SPREAD IN RANGE OF ORIGINAL AND ADJUSTED K_L AND K_M VALUES FOR SPECIFIC FIBER TYPES

Fiber Type	Number of Values in Set	Ranges of Values			
		K_L	K_M	K_L'	K_M'
All fiber types combined	8	200	1900	207	1376
All chrysotile exposure settings	5	72	1900	70	1376
Chrysotile only (excluding mixed)	4	40	20	38	14
All amphibole exposure settings	4	13.3	12.7	2.9	2.4
Amphiboles only (excluding mixed)	3	13.3	9.3	2.1	1.3

It is apparent from Table 6-5, that the total variation (spread) in adjusted K_L values is no different than for the unadjusted values (when all fiber types and exposure settings are considered together). Although there is an apparent reduction in total variation in adjusted K_M values (compared to the unadjusted values), the improvement is relatively small. However, if one also assumes that fiber type is an important factor that affects potency (as indicated in Section 5.7), the impression changes.

Although the spread in adjusted K_L values among chrysotile-related exposures is no different than that for unadjusted values (a range of 72 versus a range of 70), the spread among K_L values for amphibole exposures is reduced substantially when the values are adjusted (a range of 13.3 versus a range of 2.9). In fact, the spread in adjusted K_L values among amphibole-related exposures is reduced to the point where it is indistinguishable from the variability that is observed within single exposure settings.

Similar effects are also observed among K_M values, when fiber type is considered. Among chrysotile associated values, the spread in adjusted K_M's is reduced marginally. Again, however, the spread in adjusted K_M values among amphibole-related values is reduced substantially so that the variability observed between exposure settings becomes indistinguishable from that observed within single exposure settings.

The apparent reconciliation in published risk coefficients described above is particularly interesting, given that the exposure index to which the adjusted values are normalized is not optimal, due to limitations in the available data (see Appendix B). One wonders whether further reconciliation might occur if the exposure index employed can be further optimized using data from a future study. However, it is also possible that the variation observed among chrysotile-related coefficients is due to factors unrelated to the manner in which asbestos exposure is characterized so that it cannot be further reduced. Such factors might include, for example, any of the last five factors that contribute to variability that were listed at the beginning of this section. Importantly, in no case do the current adjustments make the spread among risk coefficients worse.

Although the observations concerning variability discussed above are qualitative, they do tend to support the more substantive findings of the extensive literature review and the re-analysis of the animal inhalation studies presented in Chapter 5.

6.2.2 Assessing the Risk of Mesothelioma

The model used here to describe mesothelioma mortality in relation to asbestos exposure is the model proposed in the Airborne Health Assessment Update (U.S. EPA 1986). This model assumes that asbestos-induced mesothelioma mortality

is independent of age at first exposure and increases according to a power of time from onset of exposure, as described in the following relationship:

$$I_M = K_M C_{pcm}[(T-10)^3 - (T-10-d)^3] \quad \text{for } T > 10+d \qquad (6.7)$$

$$= K_M C_{pcm}(T-10)^3 \quad \text{for } 10+d > T > 10$$

$$= 0 \quad \text{for } 10 > T$$

where:

"I_M" is the mesothelioma mortality observed at "T" years from onset of exposure to asbestos for duration "d" and concentration C_{pcm} of PCM fibers;

"K_M" is the risk coefficient (proportionality constant between dose and response) for mesothelioma and represents the potency of asbestos; and

all other factors have been previously defined.

This is an absolute risk model, which means that the incidence of mesothelioma predicted by the model does not depend on the background incidence of the disease. Background mesothelioma cases are rare in the general population in any case.

This model assumes that the mesothelioma risk from exposure in any increment of time increases forever, even after exposure ceases. Information for evaluating this assumption is available in a long-term follow-up study of workers in a factory that was only open during a five year period in the 1940's (Seidman 1984). The data from this study suggest that mesothelioma risk from exposure during a given time increment peaks about 40 years after exposure and decreases thereafter (Crump et al. 1987). Data from a large study of insulation workers (Selikoff et al. 1979) also supports this point of view.

The derivation of K_M's (Appendix A) was conducted in 1986 and the model has not been revised to account for the apparent drop off in risk after 40 years that is described above. Nevertheless this model is used herein to estimate the risk from constant lifetime exposure to asbestos, which requires using the model to predict risk from a given increment of exposure 70 or more years into the future. This is far longer than the model has been shown to adequately represent the mesothelioma response to asbestos. If future mesothelioma risk does peak 40 years after exposure, as indicated by the data currently available, use of the model (Equation 6.7) will overstate mesothelioma risk.

At the time that the Health Effects Update was published (U.S. EPA 1986), four studies were found to provide suitable quantitative data for estimating a value for K_M and six additional studies provide corroborative support for the mesothelioma model applied. Five of the additional studies are considered in this evaluation to derive estimated values for K_M.

Although the characteristics of asbestos that best relate to the induction of mesothelioma were not investigated directly in the re-evaluation of the animal inhalation experiments described in Section 5.6.2, results from this study suggest that, as long as the potency of chrysotile and the amphiboles are separately considered, the exposure index found to adequately predict lung cancer was also found to adequately predict mesothelioma incidence (Berman et al. 1995).

The results from our animal inhalation study are also reinforced by the findings of the literature review reported in Chapter 5. In terms of fiber dimensions, there are no clear indications of major differences between the range of fiber sizes that lead to lung cancer and those that lead to mesothelioma, although such differences have been hypothesized (e.g., Lippmann 1988). However, several studies suggest that induction of mesothelioma is a stronger function of fiber type than the induction of lung cancer. Therefore, fiber types are treated separately in our model of risk for mesothelioma (as well as for lung cancer).

Given the above, the same two-parameter exposure index adopted for lung cancer (defined in Equation 6.6) is also assumed to reasonably represent the fiber dimensional criteria that are important to the induction of mesothelioma and K_M values are adjusted accordingly. The set of adjusted K_M values (derived as described in Section 6.2.1) is presented in Table 6-4.

That the exposure index defined in Equation 6.6 adequately represents the characteristics of asbestos that determine potency toward the induction of mesothelioma is further suggested by the data presented in Table 6-5. The spread in unadjusted K_M values associated with amphibole-related exposures decreases substantially when the K_M values are adjusted as described in Section 6.2.1. The variation in the adjusted amphibole-related K_M values appears to decrease to a level that is no greater than that observed within single exposure settings. Thus, in essence, the adjusted K_M values reported for the set of epidemiology studies considered in this evaluation converge to a single value.

Reconciliation of chrysotile-related K_M values is not as striking as observed for the amphibole-related values. However, some improvement is still apparent. The spread in adjusted K_M values for chrysotile-related environments is about 70% of the variation observed for unadjusted K_M values but remains about three times the level of variation observed within single exposure settings.

7.0 RECOMMENDATIONS FOR ASSESSING THE HUMAN HEALTH RISKS ASSOCIATED WITH EXPOSURE TO ASBESTOS

Recommended risk coefficients for lung cancer and mesothelioma (the adjusted K_L and K_M, respectively) are presented in Table 7-1:

TABLE 7-1: RECOMMENDED RISK COEFFICIENTS

Fiber Type	K_L'	K_M' ($\times 10^6$)
Chrysotile	0.05	0.5
Amphiboles	0.3	50

These risk coefficients are designed for use with exposure estimates derived from the measurement methods (based on TEM) recommended for use at Superfund sites (ISO 10312[2] and Berman and Kolk 1997) and expressed in terms of the exposure index defined by Equation 6.6. Such exposure estimates include *only* asbestos structures longer than 5 μm and thinner than 0.5 μm. Consistent with the evidence presented elsewhere in this report of a different potency for chrysotile and amphibole (which we have not been able to reconcile using the information on physical dimensions of asbestos structures presently available), separate risk coefficients are recommended for chrysotile and amphibole. The recommended values are conservative (in a health-protective sense) in that the largest of the adjusted values is recommended for each fiber type.

Estimating Cancer Risks

To assess the lifetime cancer risks using the models and procedures recommended in this document from a given exposure pattern requires knowledge of both the age-specific background lung cancer mortality rate for the population of interest and the age-specific total mortality rate for this population. These mortality rates can then be used in a lifetable analysis, along with the given exposure pattern and the appropriate values of K_L' and K_M' (from Table 7-1) to estimate the additional probability of dying of lung cancer or mesothelioma. Such a lifetable analysis is described in Appendix C.

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[2] The ISO Method (ISO 10312) is a refinement of the method originally published as a Superfund Method (Chatfield and Berman 1990). It incorporates improved rules for evaluating fiber morphology and is therefore recommended for use here. Both methods derive from a common development effort headed by Eric Chatfield.

Table 7-2 presents estimates of the additional risk of death from lung cancer and mesothelioma attributable to lifetime exposure to an asbestos concentration of 0.0005 f/ml (for fibrous structures longer than 5 μm and thinner than 0.5 μm) as determined using the TEM methods recommended for use at Superfund sites (ISO 10312 and Berman and Kolk 1997). These risk estimates are derived using the lifetable method described in Appendix C.

In Table 7-2, separate risk estimates are provided for males and females and for smokers and non-smokers. The background rates for lung cancer and total mortality used in these calculations are listed in Appendix C. Separate estimates are also presented for exposures containing varying fractions (in percent) of fibrous structures greater than 10 μm in length.

Separate estimates are presented for smokers and nonsmokers because the lifetime asbestos-induced risk of both lung cancer and mesothelioma differ between smokers and nonsmokers. The asbestos-induced risk of lung cancer is higher among smokers because the lung cancer model (Equation 6.1) assumes that the increased mortality rate from lung cancer risk due to asbestos exposure is proportional to background lung cancer mortality, which is higher among smokers.

The asbestos-induced risk of mesothelioma is smaller among smokers because the mesothelioma model (Equation 6.7) assumes that risk from constant exposure increases with the cube of age, with the result that the predicted mortality rate is highest among the elderly. Thus, since smokers have a shorter life span than non-smokers, their risk of dying from mesothelioma is also predicted to be smaller.

Separate estimates are provided for different fractions of fibrous structures longer than 10 μm because the model assumes that structures longer than 10 μm are more potent than structures between 5 and 10 μm in length (in a manner consistent with Equation 6.6).

Risks from lifetime exposures to asbestos levels other than 0.0005 may be estimated from the appropriate entry in Table 7-2 by multiplying the risk listed in the Table by the airborne asbestos concentration of interest and dividing by 0.0005 (i.e., by assuming that the additional risk is proportional to the asbestos exposure level). This procedure should provide a good approximation as long as the projected risk is no greater than 0.01 (1,000 per 100,000). Risks greater than 0.01 that are derived from the table are likely to be over-estimated.

TABLE 7-2:
ADDITIONAL RISK PER ONE HUNDRED THOUSAND PERSONS FROM LIFETIME CONTINUOUS EXPOSURE TO 0.0005 TEM f/ml LONGER THAN 5.0 µm AND THINNER THAN 0.5 µm

	Percent of Fibers Greater Than 10 µm in Length										
	0.5%	1%	2%	4%	6%	10%	15%	20%	30%	40%	50%
						CHRYSOTILE					
MALE NONSMOKERS											
Lung Cancer	0.052	0.084	0.15	0.28	0.41	0.67	0.99	1.3	2.0	2.6	3.3
Mesotheliomas	0.057	0.093	0.16	0.31	0.45	0.74	1.1	1.4	2.2	2.9	3.6
FEMALE NONSMOKERS											
Lung Cancer	0.039	0.063	0.11	0.21	0.30	0.50	0.74	0.98	1.5	1.9	2.4
Mesotheliomas	0.064	0.10	0.18	0.34	0.50	0.83	1.2	1.6	2.4	3.2	4.0
MALE SMOKERS											
Lung Cancer	0.48	0.77	1.4	2.6	3.7	6.1	9.1	12	18	24	30
Mesotheliomas	0.038	0.062	0.11	0.21	0.30	0.49	0.73	1.0	1.4	1.9	2.4
FEMALE SMOKERS											
Lung Cancer	0.32	0.52	0.93	1.7	2.5	4.2	6.2	8.2	12	16	20
Mesotheliomas	0.057	0.093	0.16	0.31	0.45	0.74	1.1	1.5	2.2	2.9	3.6
						AMPHIBOLES					
MALE NONSMOKERS											
Lung Cancer	0.51	0.82	1.5	2.7	4.0	6.5	9.7	13	19	25	32
Mesotheliomas	5.7	9.3	16	31	45	74	109	145	216	288	359
FEMALE NONSMOKERS											
Lung Cancer	0.38	0.61	1.1	2.0	3.0	4.8	7.2	9.6	14	19	24
Mesotheliomas	6.4	10	18	34	50	83	123	163	243	323	403
MALE SMOKERS											
Lung Cancer	4.7	7.6	13	25	37	60	89	118	176	235	293
Mesotheliomas	3.8	6.2	11	21	30	49	73	97	144	192	239
FEMALE SMOKERS											
Lung Cancer	3.2	5.2	9.1	17	25	41	61	81	120	160	199
Mesotheliomas	5.7	9.3	16	31	45	74	110	145	217	288	360

Other Considerations

Based on the information presented in this technical background document, the following considerations also need to be addressed when collecting data to assess asbestos-related health risks:

- samples collected for evaluating asbestos exposure need to be representative of the exposure environment;

- samples need to be prepared for analysis using a direct transfer procedure. Should indirect preparation be required (due, for example, to problems with overloading of sample filters), a sufficient number of paired samples will need to be collected and analyzed to establish a site-specific correlation and corresponding conversion factor between directly and indirectly prepared samples;

- samples need to be analyzed by TEM;

- samples should be analyzed using the counting and characterization rules defined in the ISO Method (ISO 10312) with one modification: only structures longer than 5 μm need to be enumerated. Separate scans for counts of total structures longer than 5 μm and structures longer than 10 μm are recommended to increase the precision with which the longest structures are enumerated. Importantly, ISO Method rules require separate enumeration and characterization of component fibers and bundles that are observed within more complex clusters and matrices. Such components, if they meet the dimensional criteria stated here, should be included in the structure count;

- if risks are to be estimated using the risk models described in Chapter 6, asbestos concentrations derived from the above-described measurements must be expressed as the weighted sum of structures between 5 and 10 μm in length and structures longer than 10 μm in length, per the exposure index defined in Equation 6.6. Only structures thinner than 0.5 μm are to be included in these counts. Both fibers and bundles that are isolated structures and fibers and bundles that are components of more complex structures are to be included in structure counts (as long as each structure counted satisfies the defined size criteria for the size category in which it is included); and

- if risks are to be estimated using Table 7-2, rather than deriving the weighted sum described in Equation 6.6, the concentration of asbestos structures longer than 10 μm and thinner than 0.5 μm must be derived to determine the appropriate column of the Table from which to estimate risk

and the concentration of total asbestos structures longer than 5 μm and thinner than 0.5 μm must be derived, divided by 0.0005, and multiplied by the risk estimate listed in the appropriate cell of the Table to generate the risk estimate of interest.

8.0 REFERENCES

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APPENDIX A:
REVIEW OF RELEVANT EPIDEMIOLOGY STUDIES

In this appendix, an evaluation is provided of the epidemiology studies used to derive K_L and K_M values listed in Table 16. Potency estimates derived for lung cancer and mesothelioma are based on accepted dose/response models as reported in the text and summarized here.

Risk Assessment Model for Lung Cancer

Previously, it has been assumed (EPA, 1986) that the relative risk of lung cancer risk is given by the following linear function of dose:

$$RR = 1 + K_L d, \tag{1}$$

where d is cumulative exposure to asbestos in fiber-years/ml accumulated up to ten years prior to the time of observation, and K_L is the lung cancer potency in units of (fiber-years/ml)$^{-1}$, measured by PCM. This model will extended slightly here to account for the possibility that the background rates in the studied population may be different from those of the control population used. This could occur, for example, if smoking rates in the studied population were different from those in the control population. The modified model is of the form

$$RR = a(1 + K_L d). \tag{2}$$

The parameters of this model (K_L and a) will be estimated by fitting the model to epidemiological dose response data for lung cancer. Allowing the background parameter, a, in the model allows one to adjust for differences in smoking rates between the control population and studied population without actually having data on smoking rates available for the studied population. The multiplicative form in which the background parameter appears is also consistent with the observed multiplicitive relation between smoking and asbestos (Hammond *et al.*, 1979). Whenever the model adequately describes epidemiololgical data with a=1, the corresponding K_L will be used. This K_L will be identical with the K_L that would be obtained using (1).

Risk Assessment Model for Mesothelioma

To estimate risk from mesothelioma, it will be assumed EPA (1986) that the absolute risk of death from mesothelioma in the t-th year after the beginning of exposure (assuming survival to that time) is given by

$$\begin{aligned} R_M &= K_M f[(t-10)^3 - (t-10-D)^3] && \text{for } t > 10+D \\ &= K_M f(t-10)^3 && \text{for } 10+D > t > 10 \\ &= 0 && \text{for } t < 10, \end{aligned} \tag{3}$$

where f is the average occupational fiber concentration in fibers/ml, D is the duration of exposure in years, and K_M is the mesothelioma potency in units of (fiber-years/ml)$^{-1}$ estimated by fitting the model to epidemiological data.

Application of this mesothelioma model is difficult for many studies because the data needed to apply the model were not published. In one case (Dement *et al.*, 1982) the required data were obtained from the authors in a personal communication. In other cases the needed data were reconstructed based upon reasonable assumptions. Although it would have been preferable to have had direct access

to the data, it is considered unlikely that having this data would cause the estimates to change by more than a factor of 2, which is relatively small in comparison the differences between estimates of K_L obtained from different studies.

Developing Estimates of Lifetime Risk from Estimates of K_L and K_M

The lung cancer model (2) provides estimates of the increase in the relative risk of lung cancer due to asbestos exposure. The relative risk is the instantaneous risk of death from lung cancer in the presence of asbestos exposure divided by the corresponding instantaneous risk in the absense of asbestos exposure. On the other hand, the additional lifetime risk of lung cancer death from an asbestos exposure pattern denoted by d is defined as the difference,

$$P_L(d) - P_L(0),$$

where $P_L(d)$ is the lifetime risk of death from lung cancer under exposure pattern d, and $P_L(0)$ is the lifetime risk of death from lung cancer in the absense of exposure to asbestos. To estimate the additional lifetime risk of lung cancer risk from asbestos exposure requires taking into account the backgound risk of lung cancer in the population as well as competing risks of death from causes other than lung cancer. Similarly, the mesothelioma model (3) provides estimates of the instantaneous absolute risk of mesothelioma following the the onset of exposure, and to estimate the additional lifetime risk of mesothelioma death from asbestos exposure requires data on competing causes of death.

Since death rates from lung cancer, as well as from certain other causes, are higher in smokers than in non-smokers, risks from asbestos exposure will be different in smokers and in non-smokers. Risk of lung cancer from asbestos exposure will be higher in smokers because of the multiplicative interaction between asbestos and smoking. However, risk of mesothelioma will be less in smokers because of their shorter lifespans. In order to take these differences into account, smoking-specific death rates are needed. Appendix B describes the death rates used in the calculations in this document, and how these rates are used to estimate addition lifetime risk of asbestos-related cancer death.

ANALYSIS OF INDIVIDUAL STUDIES

Production of Chrysotile Friction Products

Berry and Newhouse (1983) conducted a mortality study of 13,460 workers in a factory in Britain that manufactured brake blocks, brake a clutch linings, and other friction materials. Only chrysotile was used at the plant except for two relatively short periods before 1945 when crocidolite was used in the production of railway blocks.

The cohort studied consisted of all men or women employed at the plant between 1941 and 1977. Follow-up was to the end of 1979 and the mortality experience was examined after 10 years from first exposure. Airborne dust measurements were only available from 1967 onward and these were made using the membrane filter method. Fiber concentrations in earlier years were estimated by reproducing earlier working conditions using knowledge of when processes were changed and exhaust ventilation introduced.

Deaths from all causes were less than expected both prior to ten years from first employment (185 observed versus 195.7 expected) and afterward (432 observed versus 450.8 expected). There was no indication of an effect of employment at the plant upon lung cancer; there were 51 lung cancers more than ten years from first employment compared to 47.4 expected. A significant deficit of gastrointestinal cancers was observed after ten years from first employment (25 observed versus 35.8 expected, $p = 0.04$).

A linear dose response model between cumulative exposure and lung cancer was fit to case control data by Berry and Newhouse. The resulting potency estimate[1] was 0.00058 $(\text{fiber-y/ml})^{-1}$ and the 90% upper limit was 0.0080 $(\text{fiber-y/ml})^{-1}$.

A case control study on mesothelioma deaths showed that eight of the eleven workers had been exposed to crocidolite and another possible had intermittent exposure to crocidolite. The other two had been employed mostly outside the factory and possibly had other occupational exposures to asbestos. The case control analysis showed that the distribution of cases and controls in respect to exposure to crocidolite was unlikely assuming no association with crocidolite. The data were not presented in a form that permitted a quantitative estimate of mesothelioma risk. in a Connecticut plant that manufactured asbestos friction products.

McDonald *et al.* (1984) evaluated the mortality of workers employed. The plant began operation in 1913 and used only chrysotile until 1957, when a little anthophylite was used. Also, a small amount of crocidolite (about 400 pounds) was handled experimentally between 1964 and 1972. Brake linings and clutch facings were made beginning in the 1930s, and production of automatic transmission friction materials, friction disks and bands was begun in the 1940s.

The cohort studied was defined to include any man who had been employed at the plant for at least one month before 1959, omitting all that had worked at a nearby asbestos textile plant that closed in 1939. This cohort consisted of 3515 men, of which 36% had died by the end of follow-up (December 31, 1977). Follow-up of each worker was only begun past 20 years from first employment.

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[1] Unless otherwise qualified, "estimate" refers to maximum likelihood estimate.

Information on dust levels from impinger measurements were available for the years 1930, 1935, 1936, and 1939. There was little other information available until the 1970s. An industrial hygienist used these measurements and information on processes and jobs, environmental conditions and dust controls to estimate exposures by process and by period in units of mppcf.

Total deaths and deaths from most individual causes investigated were elevated; these elevations were due primarily to increased deaths in the group working for less than one year. This pattern holds for lung cancer in particular; the relative risk for lung cancer were highest (180) for persons exposed for less than one year. A similar pattern holds when the analysis is carried out by cumulative exposure (Table A-3). The linear relative risk lung cancer model (2) provides a very poor fit to this data ($p < 0.01$) when the Connecticut rates are assumed to be appropriate for this cohort (fixing the parameter $a = 1$); use of U.S. rates gives similar results. However, the fit is adequate ($p = 0.3$) if the background response is allowed to rise above that of Connecticut men (allowing the parameter a to vary). Although the reason for this increased response in persons that worked for a short period or have low exposures is not clear, the analysis in which the background response is allowed to vary appears to be the most appropriate. This analysis yields an estimate of $K_L = 0.0$ (mppcf-y)$^{-1}$, and a 95% upper limit of $K_L = 0.0051$ (mppcf-y)$^{-1}$. To convert estimates to units of (fiber-y/ml)$^{-1}$, a conversion from mppcf to fibers/ml is needed. Although no value was suggested by the authors, a conversion factor or between 1.4 and 6 is suggested by other studies. Assuming, as a median value, that that 3 fibers/ml is equivalent to 1 mppcf, the 95% limit is equivalent to 0.0017 (fiber-y/ml)$^{-1}$.

McDonald *et al.* did not find any mesotheliomas in this cohort. It is useful to determine the range of mesothelioma risk that is consistent with this negative finding. Although McDonald *et al.* do not furnish data in the needed form for this calculation, the needed data can be approximated from McDonald *et al.*'s Table A-1. In this table they list 511 deaths occurring after age 65. Assuming that the overall SMR of 108.5 held for persons over 65 years of age, the expected number of deaths is 511/1.085 = 471. The death rate in U.S. white males between 65 and 75 years of age is approximately 0.050 per year (from 1971 vital statistics). Therefore the number of person years observed in persons past 65 years of age is estimated as 471/0.050 = 9420.

A lower bound to the person years observed between ages 45 and 65 can be estimated by assuming that the 616 observed deaths arose in a cohort that was followed up completely. First we estimate the number of persons that would have had to have been in the cohort to experience the observed deaths. Assuming that x persons in the cohort are alive at age 45, we have the following estimates of the number entering each successive five year age interval and the corresponding number of deaths (based on death rates in 1971 white males).

Age	Number Entering Interval	Number of Deaths in Interval	Person-Years in Interval
45-50	x	0.0315x	4.921x
50-55	$x(1-.00638)^5 = .9685x$	0.0508x	4.716x
55-60	$.967x(1-.01072)^5 = .9177x$	0.0761x	4.398x
60-65	$.9167x(1-.01718)^5 = .8416x$	0.1118x	3.929x
65+	$.8406x(1-.02681)^5 = .7298x$		
Totals		0.2702x	17.964x

Given 616/1.085 = 567.7 expected deaths between ages of 45 and 60, the number of persons entering the interval is estimated as x = 567.7/0.2702 = 2101. The person years is then estimated as (2101)(17.964) = 37742.

Using the average age of beginning work of 30.95 years (McDonald *et al.*, 1984, Table A-3) yields the data in Table A-4. Moreover, the average duration of exposure in this cohort was 8.04 years and the average exposure level was 1.84 mppcf (McDonald *et al.*'s Table A-3), which is equivalent to 1.84x3 = 5.52 fibers/ml. This data yields an estimate of K_M = 0.0 (fiber-y/ml)$^{-1}$ and a 95% upper limit of $K_M = 1.2 \times 10^{-9}$ (fiber-y/ml)$^{-1}$. This upper limit is possibly too large because person-years in the 45-65 age group are probably overestimated.

Chrysotile Mining

McDonald *et al.* (1980a) followed a cohort of 11379 workers exposed almost exclusively to chrysotile in two asbestos mines and related mills in Quebec. Production at the mines began before 1900. The cohort consisted of everyone registered as working one month or more and who were born between the years of 1891 and 1920. Follow-up began for each individual after 20 years from first employment and continued the end of 1975. Smoking habits were determined for over 95% of those who died after 1950.

Estimates of dust levels were made from over 4,000 midget impinger measurements made starting in 1949. Estimates for the period prior to 1949 were based on interviews with long term employees and comparison with more recent conditions. On the basis of over six hundred side-by-side measurements made from midget impinger and PCM methods, it was estimated that 3.14 fibers/ml was, on the average, equivalent to one mppcf (McDonald *et al.*, 1980b).

Table A-5 shows the lung cancer in the cohort divided by length of employment and by exposure level. Although there is a highly significant dose response for lung cancer, the slope is smaller than for many other cohorts. The model lung cancer provides an excellent fit to this data without modification of the background rate (fixing the parameter a = 1), yielding a potency estimate of 0.00045 (fiber-y/ml)$^{-1}$ and a 95% upper limit of 0.00061 (fiber-y/ml)$^{-1}$).

McDonald *et al.*'s Table A-9 contains data on lung cancer categorized jointly by cumulative exposure to asbestos and by smoking habit. Two models were fit to these data: the multiplicative model for relative risk

$$RR = a(1 + bd)(1+cx),$$

and the additive model

$$RR = a(1 + bd + cx),$$

where d is cumulative exposure to asbestos by age 45, x is number of cigarettes smoked per day, and a,b,c are parameters estimated from the data. The multiplicative model fit the data well, but the fit of the additive model was inadequate. This corroborates the multiplicative interaction between smoking and asbestos exposure in causing lung cancer (Hammond *et al.*, 1979). The estimate of potency using the multiplicative model is 0.00051, which is very close to that of 0.00045 estimated from Table A-5, which did not utilize smoking data. This latter estimate is preferred because the the estimate which used the smoking data did not take account of asbestos exposures after age 45 and therefore would be expected to overestimate lung cancer potency somewhat.

McDonald *et al.* discovered 10 mesothelioma deaths in the cohort, all plueral. From Table A-4 of McDonald *et al.* (1980a), the average age at beginning of employment was 24.9 years, the average net employment was 10.5 years, and the average concentration was 59.5 fibers/ml. Proceeding exactly as with

the data from McDonald *et al.* (1984), the person years of observation between ages 45 and 65 and past age 65 are estimated as 127,663 and 29651, respectively. Unlike the cohort studied in McDonald *et al.* (1984), a sizeable number of deaths (754) were recorded in persons under 45 years of age. Using the average age at beginning of estimated that 40% of exposure of 24.9 years and the death rates for males ages 25-45, it is these deaths occurred between age 40 and 45. Using the death rate for males between ages 40 and 45 of 0.00408 per year, the person years of observation between ages 40 and 45 is estimated as (754)(0.40)/[(0.00408)(1.09)] = 67818, where 1.09 is the overall relative risk observed for the cohort. These calculations provide all of the data needed for the mesothelioma model except that, although we know that ten mesotheliomas occurred in all, McDonald *et al.* do not furnish the ages at which the deaths occurred (Table A-6). However, the estimate of K_M is unaffected by the age groups into which the mesothelioma death belong; the estimate is $K_M = 1.1 \times 10^{-10}$ (fiber-y/ml)$^{-1}$, no matter how the ten mesotheliomas are placed in intervals corresponding to years since first exposure.

Asbestos-Cement Products

Finkelstein (1982) studied mortality among a group of 328 employees of an Ontario asbestos-cement factory who had been hired before 1960 and who had been employed for at least nine years. Follow-up continued until October, 1980. The plant produced asbestos cement pipe from 1948, asbestos cement board from 1955 to 1970, and manufacture of asbestos insulation materials was added in 1960. Both chrysotile and crocidolite were used in each batch processed in the pipe process, but only chrysotile was used in the cement board operation. Crocidolite constituted approximately 20% of the asbestos used in the pipe process (Ontario Royal Commission, 1984).

Fiber concentrations in various work areas were estimated from membrane filter samples taken after 1969, impinger measurements taken during 1949, 1954, 1956, 1957 and regularly during the 1960s, and information on changes in dust control methods. Finkelstein judged that the resulting exposure estimates were "probably accurate to within a factor of three or five."

Finkelstein compared lung cancer mortality rates in production workers divided into three exposure groups to that of Ontario men in general (Table A-7). Mortality rates were standardized to that of Group C, the most highly exposed group. Although lung cancer rates are elevated in all three exposed groups, there is no apparent trend of increasing rates with exposure. In fact, the highest exposed group experienced the lowest lung cancer mortality. This peculiar response pattern does not appear to be due to misclassification of workers into dose groups because Finkelstein found a clear dose response trend for both mesothelioma and asbestosis (cf. Finkelstein, 1983).

These data may be put into a form roughly equivalent to the more conventional age-adjusted comparison of observed and expected lung cancer by dividing the rates in the exposed group by that of Ontario men. The results of this are shown in Table A-8, which also shows the results of fitting the lung cancer model both assuming the Ontario rates are appropriate for this cohort (fixing the parameter $a = 1$) and not making this assumption (allowing the parameter a to vary). The results are clearly inconsistent with Ontario men being the appropriate control population, with the discrepancies being due to random variation only ($p < 0.01$). On the other hand, the data are consistent with the model if the background response is allowed to rise above that of Ontario men ($p = 0.3$). However, it seems unlikely that the background lung cancer risk in this cohort was 10 times that in Ontario men in general, as suggested by the analysis ($a = 9.9$). The best explanation possibly is that the background risk was somewhat elevated in this cohort and that random variation and misclassification into exposure groups played some role, also. It seems quite likely that the estimate $K_L = 0.073$ (fiber-y/ml)$^{-1}$, obtained ignoring the lack of fit, is too large, and a more appropriate estimate is somewhere between this and the 95% upper limit $K_L = 0.011$ (fiber-y/ml)$^{-1}$ obtained by letting the background vary.

Accordingly, the estimate K_L = 0.036 (fiber-y/ml)$^{-1}$ will be used, which is one half the higher K_L and more than three times the lower value. However, the lack of a dose response for lung cancer in this cohort makes estimates derived from this study less reliable than those from other studies.

Eleven mesotheliomas were observed in this cohort (Table A-9) and, unlike the lung cancer data, mesotheliomas showed a dose response trend. The mesothelioma model describes these data adequately and provides an estimate of $K_M = 1.9 \times 10^{-7}$ (fiber-y/ml)$^{-1}$, based on an average duration of exposure of 12 years and an average exposure level of 9 fibers/ml (CPSC, 1983).

Weill *et al.* (1979) studied 5,645 men employed for at least one month before 1970 in either of two asbestos cement plants in New Orleans and who had been followed up for at least twenty years. Sixty per cent of the population were employed for less than one year and sixteen per cent for more than ten years.

This population was traced in 1975 through the Social Security Administration, and 601 persons were identified as dead. All other persons were assumed to be alive. However, only 64 per cent were known to be alive in 1974 (by consequence of having a transaction with the Social Security Administration), and consequently only 75% of the population was traced.

Both of the plants have operated since the 1920s. Chrysotile was used predominantly in both plants. The first plant used some amosite, which constituted one per cent of various products, and also used crocidolite infrequently. Chrysotile was used exclusively in the second plant, except in the pipe production area, where crocidolite constituted three per cent of the final product. Since the total percentage of asbestos fiber in most asbestos cement products ranges from fifteen to 28 per cent, it is estimated that crocidolite constituted between ten and twenty per cent of the asbestos used to make cement pipe (Ontario Royal Commission, 1984).

Estimates of airborne dust levels were made for each job by month and year from midget impinger measurements initiated in the early 1950s. Levels estimated from initial samples in the 1950s were also assumed to hold for all earlier periods because no major dust control measures had been introduced prior to that time. Based on 102 side-by-side measurements collected in various areas of one of the plants of particles using impinger methods and fibers using optical microscopy methods, Hammad *et al.* (1979) estimated an overall conversion factor of 1.4 fibers/ml per mppcf. There were substantial variations in this factor among different areas of the plant.

Lung cancers were below expected in the lowest exposure categories, and were only elevated at exposures above 100 mppcf-years (Table A-10). Although assuming non-traced individuals to be alive would have the tendency to make observed less than expected, it seems unlikely that this could cause observed cancers to fall as much below expected as was observed in this cohort. At any rate, such a tendency should not bias estimates of potency estimated by allowing the background parameter "a" to vary. The estimate of K_L = 0.0064 (fiber-y/ml)$^{-1}$ obtained allowing the background parameter to vary is therefore judged to be the most appropriate estimate of potency. Although the fit of the lung cancer model in this situation is marginal (p = 0.04), this lack of fit is due mainly to a shortfall of cancer in the 51-100 mppfc-y group and an excess in the 101-200 group; this could have been due to misassignment of persons within these groups.

Table A-11 contains the mesothelioma data from the Weill *et al.* cohort. The numbers of mesothelioma were obtained from the observation by Weill *et al.* that only two mesothelioma deaths were recorded (both pleural) one 18 years and one 19 years after initial employment. The person-years in each five-year age interval were estimated from Weill *et al.* (1979) Table A-3 by averaging the number

of workers entering the interval and the number entering the subsequent interval, and multiplying the result by 5. In the 35+ age group the number entering was multiplied by 5, assuming an average follow-up of five years. From Table A-5 of Weill *et al.* the average employment was d = 4.5 years. This same table provides an average dust concentration of 16.15 mppcf or, upon converting to fiber/ml by multiplying by 1.4, f = 22.6 fiber/ml. The resulting potency estimate is $K_M = 7.0 \times 10^{-10}$ (fiber-y/ml)$^{-1}$, which is considerably smaller than the estimate from the Finkelstein cohort. Although this value is based on only two mesotheliomas, the 95% upper limit is still only $K_M = 1.8 \times 10^{-9}$ (fiber-y/ml)$^{-1}$.

According to Table A-7 of Weill *et al.*, 77% of the workers were exposed solely to chrysotile, whereas only one of the mesotheliomas came from this group. Thus, assuming that the duration, level of exposure, and amount of followup were similar in the chrysotile and non-chrysotile exposed groups, the estimate of K_M for chrysotile exposed workers only would be $(7.0 \times 10^{-10})(0.5)/(0.77) = 4.5 \times 10^{-10}$ (fiber-y/ml)$^{-1}$.

Hughes, Weill and Hamad (1987) report on followup through 1981 of an expanded cohort of Louisiana workers from the same two asbestos cement plants studied by Weill *et al.* (1979). The study contains 6,931 workers, of whom 95% were traced. This improved trace was the result both of greater access to Social Security Administration records and greater availability of computerized secondary information sources (Dr. Hughes, personal communication).

Chrysotile was the primary type of asbestos used in both plants. Some amosite was used in Plant 1 from the early 1940s until the late 1960s and crocidolite was used occasionally for approximately 10 years beginning in 1962. Previously (Weill *et al.*, 1979) it was thought that amosite was not introduced to this plant until the late 1950s. Plant 2 utilized only chrysotile, except that pipe production, which began in 1946 and was housed in a separate building, utilized crocidolite. Thus, workers from Plant 2 that did not work in pipe production were exposed only to chrysotile.

New exposure data from Plant 2 have become available since the earlier study, and these, along with a complete review of all the exposure data, were used to revise the previous estimates of exposure. In Plant 1 the earlier and revised estimates were reasonable similar, but in Plant 2, the revised estimates tended to be about one-third of the previous estimates through the 1940s and about one-half the previous estimates thereafter. The estimate by Hammad *et al.* (1979) of 1.4 mppcf per fibers/ml will be used here.

The principal cohort studied consisted of all workers who, according to company records, were employed for at least one month prior to 1970, had a valid Social Security number, and were first employed in 1942 or later (Plant 1) or in 1937 or later (Plant 2). Mortality experience was compared with that expected based on Louisiana rates.

Hughes *et al.* found no significant difference between the dose responses for lung cancer in Plant 2 among workers exposed to chrysotile only and those who were also exposed to crocidolite in pipe production. Therefore this study does not indicate a difference in risk of lung cancer between chrysotile and crocidolite. Further, a single lung cancer dose response model dose adequately describes the lung cancer data from Plants 1 and 2 combined (Table A-12). The fit of this model is good when Louisiana men are assumed to be an appropriate control group (fixing the parameter a = 1). This fit provides an estimate of $K_L = 0.0040$ (fiber-y/ml)$^{-1}$ and a 95% upper confidence limit of 0.0070 (fiber-y/ml)$^{-1}$. These estimates are lower than those estimated from Weill *et al.* (1979) despite the fact that Hughes *et al.* (1986) estimated lower exposures in Plant 2 than were used in the earlier study. This seems to be due chiefly to the fact that the control population appears appropriate in Hughes *et al.*,

whereas there was a deficit of lung cancer in the Weill *et al.* study in the lower exposure groups. This deficit served both to make the control population appear to be inappropriate and to increase the apparent dose response slope, K_L. It is notable that the K_L estimated from Hughes *et al.* is the same as that estimated from Weill *et al.* assuming the control population used by Weill *et al.* was appropriate, although that model didn't fit the Weill *et al.* data.

Six mesotheliomas have occurred in the primary cohort studied by Hughes *et al.*, two in Plant 1 and four in Plant 2. Four other mesotheliomas are known to have occurred, one among those initially employed in Plant 2 before 1937 and three among Plant 2 workers since followup ended in 1981. A case control analysis conducted among Plant 2 workers found a relationship between mesothelioma risk and length of employment and proportion of time spent in the pipe area after controlling for length of exposure, which is consistent with a greater risk of mesothelioma from crocidolite exposure.

Data were not presented in the paper in the form required for estimating K_M. However, Hughes and Weill (1986) present estimates of mesothelioma potency from several data sets, including the cohort studied in Hughes *et al.* and containing six mesotheliomas, but using a model slightly different from (3). Estimating K_M by multiplying the potency estimated by Hughes and Weill model by the ratio of the potency values estimated for another study using (3) and the Hughes-Weill model yielded the following estimates of K_M for the Hughes *et al.* data: 0.25×10^{-8} (fiber-y/ml)$^{-1}$ (Selikoff *et al.*, 1979); 0.21×10^{-8} (fiber-y/ml)$^{-1}$ (Dement *et al.*, 1983b); 0.27×10^{-8} (fiber-y/ml)$^{-1}$ (Seidman, *et al.*, 1979); and 0.43×10^{-8} (fiber-y/ml)$^{-1}$ (Finkelstein, 1983). Based on these calculations, $K_M = 0.30 \times 10^{-8}$ (fiber-y/ml)$^{-1}$ is a reasonable estimate for the Hughes *et al.* cohort.

Three additional mesotheliomas have occurred in this cohort since followup ended in 1981. It would be worthwhile to estimate mesothelioma risk using additional followup that included these cases. However, we can be assured that such an estimate would be no larger than $K_M = 0.45 \times 10^{-8}$ (fiber-y/ml)$^{-1}$. This is because, since there were six mesotheliomas in the cohort studied by Hughes *et al.*, even if the additional person years of followup past 1981 is not taken into account, the three additional mesotheliomas would increase the estimate of $K_M = 0.30 \times 10^{-8}$ (fiber-y/ml)$^{-1}$ obtained from followup through 1981 by only 50%.

Hughes *et al.*'s finding of an association with crocidolite exposure implies that a smaller K_M would correspond to the chrysotile-only exposed group in Plant 2. Although Hughes *et al.* didn't furnish the data needed for precise estimation of K_M from this cohort, it is possible to make some reasonable approximations to this K_M. Since none of the six mesotheliomas occurred among workers exposed only to chrysotile, $K_M = 0$ would be the point estimate derived from the data used by Hughes *et al.*

However, one mesothelioma was discovered in a person whose employment began in 1927 and thus was not eligible for inclusion in the cohort. This person was employed continuously for 43 years in the shingle production area, indicating exposure only to chrysotile. In addition, three more mesotheliomas have occurred in former workers in the pipe department since followup ended in 1982. Considering these additional four mesotheliomas, there have been eight mesotheliomas in Plant 2 workers, seven of whom were exposed to crocidolite. Since the cohort from Plant 2 is about 1.8 times as large as that of Plant 1 (based either on number of men or number of deaths) and twice as many mesotheliomas were discovered in the Plant 2 as in the Plant 1 cohort, it is reasonable to estimate that Hughes and Weill (1986) would have obtained about the same estimate of mesothelioma potency had they used only data from Plant 2. Since only 37% of Plant 2 were exposed to crocidolite and these workers worked an average of four times as long, a reasonable adjustment of the earlier estimate of K_M

to apply only to chrysotile exposed workers would be $K_M = 0.3 \times 10^{-8} \times (1/8) \times (0.37) \times (4) = 0.05 \times 10^{-8}$ (fiber-y/ml)$^{-1}$.

As a third approach to estimating K_M from the non-crocidolite exposed group, it was observed that the duration of observation of the Hughes *et al.* cohort was roughly equivalent to that of the Dement *et al.* (1983b) cohort. Using the person years in the Dement *et al.* cohort, adjusted by the ratio of the sizes of Dement *et al.* and the Hughes *et al.* non-crocidolite-exposed cohort from Plant 2, and applying the average duration of exposure (2.5 years) and fiber level (11.2 fibers/ml) appropriate for the Hughes *et al.* cohort yields $K_M = 0.2 \times 10^{-8}$ (fiber-y/ml)$^{-1}$.

Each of these approaches imply that the K_M for chrysotile exposure in asbestos cement production should be less than the value of 0.3×10^{-8} (fiber-y/ml)$^{-1}$ estimated for the Hughes *et al.* cohort as a whole.

Chrysotile Textile Products

Dement *et al.* (1982, 1983a, 1983b) conducted a retrospective cohort study of 1261 white male employees of a chrysotile textile plant in South Carolina who worked for one or more months between 1940 and 1965. Followup was through 1975, thus insuring at least a ten year latency.

A considerable excess of lung cancers which exhibited a dose response relationship were observed in this population (Table A-14). Dement *et al.* used U.S. rates for calculating expected deaths even though local are 75% higher. Dement *et al.* argues that local were probably influenced by a World War II shipyard and also by this plant; however, these sources of elevated lung cancer risk seem unlikely to have influenced local rates greatly. Furthermore, if the background is not held fixed when fitting the model, the estimated background is 56% higher than that derived from U.S. rates (Table A-14). Thus the most accurate potency estimate from this cohort is considered to be $K_L = 0.0285$ (fibers-y/ml)$^{-1}$ estimated from the analysis in which the background is allowed to vary.

Only one mesothelioma was detected in this cohort (Table A-15). The person-years in this table, as well as the details of the mesothelioma case (20+ years of employment and a latency of about 40 years) were furnished through the courtesy of Dr. Dement. Table IV of Dement *et al.* (1983b) indicates that the average duration of employment was about ten years. Dement *et al.* do not furnish data that are particularly appropriate for determining average exposure. However, in a study of the same mill McDonald *et al.* (1983a) estimated the average exposure to be 1.8 mppcf. Using the conversion factor of three fibers/ml per mppcf estimated by Dement for this mill, the average exposure in fiber/ml is estimated as 5.4. Based on this data the estimate is $K_M = 3.0 \times 10^{-9}$ (fiber-y/ml)$^{-1}$ and the 95% upper limit is $K_M = 1.1 \times 10^{-8}$ (fiber-y/ml)$^{-1}$.

McDonald *et al.* (1983a) conducted a cohort mortality study in the same South Carolina textile plant that was studied by Dement *et al.* (1983b). Their cohort consisted of all men employed for at least one month before 1959 and for whom a valid social security record existed. This cohort consisted of 2410 men, of whom 36% had died by the end of followup (December 31, 1977). Followup of each worker was only begun past 20 years from first employment.

McDonald *et al.* had available the same exposure measurements as Dement *et al.* (1983b) and used these to estimate cumulative exposures for each man in mppcf-y. In their review of the environmental measurements in which both dust and fiber concentrations were assessed, they found a particle to fiber conversion range of from 1.3 to 10.0 with an average of about 6 fibers/ml per mppcf.

This value, which is intermediate between the values of 3 and 8 found by Dement *et al.* for different areas of the same plant, will be used in the calculations involving the McDonald *et al.* (1983a) study.

McDonald *et al.* describe two practices at the plant that entailed very high exposures and which were not reflected in either their's or Dement *et al.*'s estimates: cleaning of burlap bags used in the air filtration system by beating them with buggy whips during the years 1937-53, and the mixing of fibers, which was carried out between 1945 and 1964 by men with pitch forks and no dust suppression equipment.

A strong dose response for lung cancer was observed (Table A-16), which parallels the results of Dement *et al.* Unlike Dement *et al.*, McDonald *et al.* used South Carolina men as the control group rather than U.S. men. Use of this control group provides an adequate description of the data and lung cancer potency values estimated both assuming that the control population is appropriate (fixing the parameter a = 1) and not making this assumption (allowing the parameter a to vary) yield practically identical results (K_L = 0.012 (fiber-y/ml)$^{-1}$ in the former case and 0.010 (fiber-y/ml)$^{-1}$ in the latter). These results are reasonably consistent with the potency estimated from the Dement *et al.* study with a allowed to vary [K_L = 0.028 (fiber-y/ml)$^{-1}$], but not with the results with a = 1 [K_L = 0.050 (fiber-y/ml)$^{-1}$].

McDonald *et al.* found one case of mesothelioma in this cohort, apparently the same one discovered by Dement *et al.*: a man born in 1904 who died in 1967 and worked at the plant for over 30 years. Since this study was conducted exactly as McDonald *et al.* (1984), the same method used there to reconstruct person-years by years from first exposure can be applied to this cohort as well. The reconstructed data are listed in Table A-17. The estimated potency is $K_M = 5.1 \times 10^{-10}$ (fiber-y/ml)$^{-1}$, with a 95% upper limit of 1.9×10^{-9} (fiber-y/ml)$^{-1}$. This estimate is about six-fold smaller than than estimated from the Dement cohort. However, McDonald *et al.* found the same number of mesotheliomas as Dement despite observing almost three times as many deaths (857 versus 308), and used a larger particle-to-fiber conversion factor overall than that used by Dement *et al.* Also, since Dement *et al.* restricted their cohort to persons working after 1940, the McDonald *et al.* cohort should contain considerably more person-years observed more than 30 years from first exposure, when mesothelioma risk is estimated by the EPA model to be greatest.

Peto *et al.* (1985): A textile factory in Rochdale, England has been the subject of a number of investigations (Doll, 1955; Knox *et al.*, 1965; Knox *et al.*, 1968; Peto *et al.*, 1977; Peto, 1978, 1980a and 1980b; and Peto *et al.*, 1985). This analysis will be based on the latter study, which has the most complete follow-up (through 1983) and emphasizes assessment of risk. The factory, which began working with asbestos in 1879, used principally chrysotile, but approximately five per cent crocidolite was used between 1932 and 1968.

Quantitative estimates of risk will be based on a subgroup of Peto *et al.*'s "principal cohort" consisting of all men first employed in 1933 or later who had worked in scheduled areas or on maintenance and had completed five years of service by the end of 1974. In the analyses of interest relating to lung cancer, follow-up only begins 20 years after the beginning of employment and exposure during the last five years of follow-up is not counted.

Routine sampling using a thermal precipitator began at 23 fixed sampling points in 1951. Comparisons of particle counts and fiber counts taken in 1960 and 1961 were used to convert between particles/ml and fibers/ml. Dust levels prior to 1951 were assumed to be the same as those observed during 1951-1955 for departments for which no major changes had been made. In departments in which conditions had improved, higher levels were assigned to periods prior to 1951. These levels and work histories were used to assign individual exposure estimates. A conversion factor of 34 particles/ml per

fibers/ml was determined by comparing average results obtained by the Casella thermal precipitator (particles/ml) with Ottway long running thermal precipitator (fibers/ml) at the same sampling point during 1960 and 1961. However, a conversion factor of 35.3 was used by Peto *et al.* for the sake of consistency with earlier work, and this factor will be used here as well.

After 20 years from first employment, there were 93 lung cancer deaths with only 64.6 expected. Using a lung cancer model essentially the same as (1), Peto *et al.* estimated $K_L = 0.0054$ (fiber-y/ml)$^{-1}$ for the entire cohort, and $K_L = 0.015$ (fiber-y/ml)$^{-1}$ when the analysis is restricted to men first employed in 1951 or later. Peto *et al.* felt that the most plausible explanation for this difference is that it was largely due to chance and also possibly to the chance that exposure to the most carcinogenic fibers was not reduced as much as changes in particle counts from 1951 and 1960 would suggest.

Ten mesotheliomas were observed in the cohort used by Peto *et al.* for quantitative analysis (an eleventh case who was exposed for four months and died four years later was omitted because the short latency made it unlikely that this case was related to exposure at the factory). Observed mesotheliomas and corresponding person years of observation by duration of service and years since first employment are shown in Table A-18 (person years were not provided in Peto *et al.* (1985) and were obtained from Table A-20 in Doll and Peto, 1985). Table A-18 also shows the mesotheliomas predicted using a "cubic residence time" model of mesothelioma, which is different from the mesothelioma model defined by (3). However, all the data needed for application of (3) are contained in the table except for average exposure. An overall average exposure was estimated by applying the Peto model to the data in Table A-18 with a single exposure estimate, and selecting the value that gave the smallest least squares fit of this model to the mesothelioma data. The fitting was carried out both unweighted and by weighting by the person years, with resulting estimates of 360 and 322 particles/ml, respectively; the latter value was the one selected. Using this estimate of average dust level, the mesothelioma model (3) was fit to the data, utilizing the different estimates of duration of work. The resulting estimate of mesothelioma potency was $K_M = 3.7 \times 10^{-10}$ (particle-y/ml)$^{-1}$ or, using the conversion factor of 35.3 particles/ml per fibers/ml, $K_M = 1.3 \times 10^{-8}$ (fiber-y/ml)$^{-1}$. The predicted mesotheliomas derived using this approach are also shown in Table A-18. This fitting approach, although crude in that individual particle levels were not available for each entry in the table, yields a better fit than the model used by Peto *et al.* (goodness of fit p-value > 0.25 based on (3) and = 0.05 for Peto *et al.* model).

McDonald *et al.* (1983b) report on mortality in an asbestos plant located near Lancaster, Pennsylvania that produced mainly textiles, but also some friction materials. About 3,000 to 6,000 tons of chrysotile were processed annually at the plant, which began operation in the early 1900s. Crocidolite and amosite were used from 1924 onward; about three to five tons of raw crocidolite were processed annually and the use of amosite reached a peak of 600 tons during World War II.

The cohort reported on in McDonald *et al.* (1983b) consisted of all men employed for at least one month prior to 1959 and who had a valid record with the Social Security Administration. This group consisted of 4022 men, of whom 35% had died by the end of follow-up (December 31, 1977). Follow-up of each worker was only begun past 20 years from first employment.

To estimate exposures, McDonald *et al.* had available reports of surveys conducted by the Metropolitan Life Insurance Company during the period 1930-1939, Public Health Service surveys conducted during 1967 and 1970, and company measurements made routinely from 1956 onward. These data were used to estimate exposures by department and year in units of mppcf.

The lung cancer mortality in this cohort exhibited a significant dose response trend (Table A-19), which was partially due to a deficit of cancers in the group exposed to <10 mppcf-y (21

with 31.4 expected). A survey of those employed in the plant in 1978 revealed a larger per cent of nonsmokers (25%) than were found in the other plants studied by these researchers (McDonald *et al.*, 1983a and 1984); however this finding is based on a sample of only 36 workers. Regardless of the reason for this shortfall in the number of lung cancers, it appears that the most appropriate analysis is that in which the background is allowed to vary; this analysis describes the data well ($p > 0.7$), whereas the analysis which assumes the Pennsylvania rates are appropriate provides a marginal fit ($p = 0.1$). Consequently, the former analysis is judged to be the most appropriate (allowing the parameter a to vary). Assuming that 3 fiber/ml is equivalent to one mppcf, the resulting estimate of lung cancer potency is $K_L = 0.018$ (fiber-y/ml)$^{-1}$ and the 95% upper limit is $K_L = 0.045$ (fiber-y/ml)$^{-1}$.

A diagnosis of mesothelioma was specified on fourteen death certificates (ten pleural and four peritoneal). Seventeen other deaths were given the ICD code 199 (malignant neoplasms of other and unspecified sites) and the diagnosis given in many of these cases was said to be consistent with an unrecognized mesothelioma. McDonald *et al.*'s Table A-3 lists the average age at beginning of employment as 28.92 and the average duration of employment as 9.18 years, and their Table A-1 lists 191, 667, and 534 deaths as occurring before age 45, between 45 and 65, and after 65 years of age, respectively. Assuming that 1/2 of the deaths given the ICD code 199 might have been due to mesotheliomas, the total number of mesotheliomas in this cohort is estimate to be between 14 and 23. Proceeding exactly as in the mesothelioma analysis carried out for the McDonald *et al.* (1980a) data, the data in Table A-20 are generated. Noting again that the age since first exposure categories in which the mesotheliomas occurred is irrelevant as far as estimating K_M is concerned, the estimates are $K_M = 6.7 \times 10^{-9}$ (fiber-y/ml)$^{-1}$ (assuming 14 mesotheliomas) and $K_M = 1.1 \times 10^{-8}$ (fiber-y/ml)$^{-1}$ (assuming 23 mesotheliomas).

Armstrong *et al.* (1988) studied a cohort consisting of 6505 men and 411 women who were employed in the mining and milling of crocidolite in Western Australia between 1943 and 1966. Followup was through 1980. Vital status at this point in time was known for 73% of the men and 58% of the women. Expected deaths were calculated in two ways: assuming all subjects lost to followup were alive at the close of 1980 (SMR1) and followup of individuals only until the last date known to be alive (SMR2), which was generally the last date of employment for those lost to followup. Ascertainment of deaths were considered to be relatively complete, and if so, SMR1 would be the most accurate. Measurements of airborne dust concentrations were made periodically between 1948 and 1958 using a koniometer. Concentrations of airborne respirable fibers longer than five microns were measured in various workplaces in 1966 using thermal precipators. Based on these data, fiber concentrations were estimated for different job/workplace combinations. Each subject's cumulative exposure was calculated from these data and work histories.

The total number of deaths observed was 820, which corresponded to standardized mortality ratios of SMR1 = 0.96 and SMR2 = 1.53. The corresponding standardized mortality ratios for neoplasms of trachea, bronchus and lung were SMR1 = 1.60 and SMR2 = 2.64, based on 91 observed deaths.

There are no dose response data reported that are suitable for developing a risk assessment, so K_L and K_M will be estimated from summary data from the entire cohort. Although the median duration of exposure was four months, and the median exposure was six f/ml-years, data from Table A-1 of Armstrong *et al.* indicate that average duration of employment was about 7.5 months and average cumulative exposure was 10 f/ml-years. This suggests an average exposure of 10 f/ml-years/(7.5/12 years) = 16 f/ml. Using this average cumulative exposure and SMR1 = 1.6, the estimate obtained is $K_L = (1.60\text{-}1)/10 = 0.06$ (f/ml-years)$^{-1}$. If SMR2 is used, the estimate is $K_L = (2.62\text{-}1)/10 = 0.16$.

There were 32 deaths from mesothelioma in this cohort. The figure in Armstrong *et al.* indicates that, based on all exposure groups combined, the incidence of mesothemioma increased monotonically to a value of approximately 90 per 100,000 man-years 25 years since beginning of exposure. Using an average exposure of 16 f/ml and an average duration of 7.5 months, the estimated potency for mesothelioma is

$(90/10^5)/[(25\text{-}10)^3 - (25\text{-}10\text{-}7.5/12)^3]/16 = 14 \times 10^{-8}$ (f/ml-years)$^{-1}$.

Selection of Representative Potency Values for Specific Fiber Types and Operations

Table A-21 summarizes K_L and K_M values computed from various studies and compares them with corresponding values calculated in the EPA Health Effects Update for Asbestos (EPA, 1986). Values obtained herein agree generally with those in EPA (1986). However, a number of potency values calculated here were not calcualated in EPA (1986). E.g., the Armstrong *et al.* (1988) was not published in in 1986. Also, K_M have been calculated for a number of studies which were not used for this purpose in EPA (1986).

Table xxx21 categorizes studies according to process (e.g., mining, textiles, friction product manufacture, etc.) and also according to fiber type. We note that, with the exception of exposure to mixture of chrysotile and crocidolite in asbestos cement manufacture, potency values calculated for similar operations and fiber types are in general agreement, whereas there are large differences in potencies obtained for different operations (e.g., exposure to chrysotile in textile mills or mines) and for different fiber types in the same type of operation (e.g., exposure to chrysotile or crocidolite in mines). One goal of this analysis is to develop potency estimates specific for operation and fiber type to match with fiber size distributions obtained by TEM from similar settings. Accordingly, representative values for potencies will be derived for each of the processes and fiber types.

Chrysotile Textile Manufacturing

The K_Ls from four textile studies are quite similar, regardless of whether they involve exposure to chrysotile alone or to mixed fiber types, as they range from 0.0054 to 0.028 (f/ml)$^{-1}$. As a representative value the value of 0.2 (f/ml)$^{-1}$ will be used, which is about the average of the values obtained from the individual studies.

Unlike lung cancer, it appears that there may be an effect of fiber type within textiles in producing mesothelioma. K_Ms are larger in cohorts exposed to mixed fiber types over those exposed to chrysotile only by factors ranging from 2.3 to 25. For a representative value for chrysotile exposure, $K_M = 1 \times 10^{-9}$ will be used. This value is between the K_M estimated from the McDonald *et al.* and Dement *et al.* studies, and is below the upper confidence limit obtained from either of these studies.

Chrysotile Friction Products

Although McDonald *et al.* (1984) is classifed as chrysotile exposure and and Berry *et al.* (1983) as mixed exposure, in fact, both studies involved exposure to some amounts of amphiboles, although the amount in the former study was apparently minimal. Neither of these studies demonstrate a clear relationship between asbestos and lung cancer; the former study shows no dose response trend ($K_L = 0$) while the latter study shows a small but nonsignificant positive trend. As a representative value for friction products, the value of $K_L = 0.0006$ obtained in Berry *et al.* will be used. This value is within the range consistent with the McDonald *et al.* study, and there is no evidence of a fiber type effect upon lung cancer rates in these studies.

In contrast, Berry *et al.* found an association between mesothelioma and crocidolite, so only the McDonald *et al.* study will be used to derive an estimate for K_M based on chrysotile exposure. The value of 0.1 f/ml^{-1} will be used, which is somewhat less than the upper limit calcululated for this study. This value should be used with caution and considered an upper bound, since no mesotheliomas were found in this cohort.

Chrysotile Mining

For chrysotile mining, the point estimates from the McDonald *et al.* (1980a) will be used as representative values: $K_L = 0.0005$ and $K_M = 1 \times 10^{-10}$.

Asbestos Cement

The lung cancer data for asbestos cement do not show a consistent relationship among studies. The K_L from the Finkelstein (1983) study is six to nine times larger than those from the studies of Weill and Hughes. Among eight studies of asbestos cement workers surveyed by Hughes *et al.* (1986), including several for which K_Ls could not be estimated, the relative risk for lung cancer was considerably higher for the Finkelstein study than for any of the other seven; thus the Finkelstein study is an outlier. Further, as as discussed earlier, the dose response for lung cancer from this study was not consistent with an asbestos effect; the most highly exposed group had the lowest lung cancer rate. As a representative value for chrysotile exposure, the value of 0.005 $(f/ml)^{-1}$ will be used, based on study by Hughes *et al.* (1987), recalling that no difference was found in this study in lung cancer dose responses between workers exposed only to chrysotile and workers also exposed to crocidolite. As a representative value for K_M from exposure to chrysotile, the value of $K_M = 1.0 \times 10^{-9}$, which is based on the Hughes *et al.* (1986) study.

Representative values selected for crocidolite mining and milling and for amosite insulation manufacture will be those obtained from the Armstrong *et al.* (1988) and Seidman (1984) studies, respectively.

Seidman et al. (1979) and Seidman et al. (1986) studied the mortality experience of 820 men employed in a plant in Patterson, New Jersey that manufacture insulation for ships during World War II. Only amosite asbestos was used in the plant, which operated from 1941 to 1954. Seidman (1986) reports on follow-up through 1982, at which time 72% of the cohort was deceased. Exposure estimates for particular jobs were estimated based on PCM air measurements obtained in similar plants in Tyler, Texas and Port Alleghers, Pennsylvania in the late 1960's and the 1970's. Estimates of K_L=0.043 and $K_M = 3.2 \times 10^{-8}$ will be used for this cohort; these were developed by EPA (1986) from a draft report of Seidman et al. (1986).

Selikoff et al. (1979) reported on the mortality experience of 17,800 insulators on the roles of the asbestos workers union in the United States and Canada. Information available included date of birth, date of first insulation work, employment status on January 1, 1967, respirator use, smoking habits and work practices. This cohort was followed by Selikoff et al. from 1967 through 1976. Exposure were to chrysotile and amosite insulation. Assuming an average exposure of 15 f/ml for this cohort, based on limited surveys of exposure to insulation workers, EPA (1986) estimated risk factors of K_L=0.0075 and $K_M = 1.5 \times 10^{-8}$.

Table A-3

Lung Cancer by Exposure Level in a
Connecticut Chrysotile Friction Plant
(McDonald *et al.*, 1984)

Conn. rates	Observed (a=1)[a]	Expected based on (a allowed to vary)[b]	Expected from lung cancer model mppcf-y	Cancers
5 (<10)	55	32.9	33.8	49.0
15 (10-20)	6	5.9	6.4	8.8
30 (20-40)	5	4.7	5.5	7.0
60 (40-80)	6	3.7	4.9	5.5
110 (>80)	1	1.8	2.9	2.7
Goodness of fit p-value		<0.01	<0.01	>0.2

[a] Assumes Connecticut men are appropriate control group.
[b] Assumes Connecticut men are not necessarily appropriate control group.

Estimates with background estimated (a variable)
Maximum likelihood estimates
a = 1.49 K_L = 0.0 $(mppcf\text{-}y)^{-1}$ = 0.0 $(fiber\text{-}y/ml)^{-1}$
Chisquare = 3.3
95% upper confidence limit on K_L = 0.00507 $(mppcf\text{-}y)^{-1}$ =
0.00169 $(fiber\text{-}y/ml)^{-1}$ (a = 1.37)

Estimates with background fixed (a = 1)
Maximum likelihood estimates
K_L = 0.00564 $(mppcf\text{-}y)^{-1}$ = 0.00188 $(fiber\text{-}y/ml)^{-1}$
Chisquare = 15
95% upper confidence limit on K_L = 0.0183 $(mppcf\text{-}y)^{-1}$ =
0.00610 $(fiber\text{-}y/ml)^{-1}$

Table A-4

Reconstructed Mesothelioma Data from a
Connecticut Chrysotile Friction Plant
(McDonald *et al.*, 1984)

Years since First Exposure		Person Years of Observation	Observed Mesothe-liomas	Mesotheliomas per 1000 Person Years	Expected Mesotheliomas Under Model
22	(14-34)	37742	0	0	0
39	(34+)	9420	0	0	0

Maximum likelihood estimate: $K_M = 0.0$ (fiber-y/ml)$^{-1}$
Chisquare = 0.0
95% upper confidence limit on $K_M = 1.19 \times 10^{-9}$ (fiber-y/ml)$^{-1}$

Table A-5

Lung Cancer by Length of Service and by Exposure Level in Workers in Quebec Chrysotile Mines and Mills (McDonald *et al.*, 1980a)

Years of Service	mppcf-y	Observed Cancers	Expected based on Quebec rates	Expected from lung cancer model (a=1)[a]	Expected from lung cancer model (a allowed to vary)[b]
<1					
	0.5	19	16.2	16.3	15.3
	1.7	12	13.2	13.2	12.4
	5.8	9	10.2	10.3	9.7
	39	7	8.75	9.23	8.8
1-5					
	3.3	5	7.58	7.61	7.17
	13.6	13	13.68	13.9	13.2
	59	6	7.32	7.93	7.54
	231.3	5	6.41	8.50	8.28
5-20					
	16	13	9.22	9.43	8.90
	58.2	14	11.48	12.4	11.8
	178.5	7	8.43	10.6	10.2
	704	16	7.37	14.7	14.8
>20					
	104.6	28	23.1	26.6	25.5
	261.3	20	18.5	25.4	24.8
	549.1	24	10.9	19.4	19.4
	1141.4	32	12.1	31.5	32.3
Goodness of fit p-value			<0.01	>0.8	>0.8

[a] Assumes control group is appropriate.
[b] Assumes control group is not necessarily appropriate.

Estimates with background estimated (a variable)
Maximum likelihood estimates
a = 0.941 K_L = 0.00161 (mppcf-y)$^{-1}$ = 0.000513 (fiber-y/ml)$^{-1}$
Chisquare = 9.28
95% upper confidence limit on K_L = 0.00247 (mppcf-y)$^{-1}$ = 0.000787 (fiber-y/ml)$^{-1}$ (a = 0.833)

Estimates with background fixed (a = 1)
Maximum likelihood estimates
K_L = 0.00141 (mppcf)$^{-1}$ = 0.000449 (fiber-y/ml)$^{-1}$
Chisquare = 9.34
95% upper confidence limit on K_L = 0.00192 (mppcf-y)$^{-1}$ = 0.000611 (fiber-y/ml)Ca

Table A-6

Reconstructed Mesothelioma Data from
Cohort of Quebec Chrysotile Miners
(McDonald *et al.*, 1980a)

Years Since First Exposure	Person Years of Observation	Observed Mesotheliomas
17.5 (15-20)	67818	?
28 (20-40)	127663	?
45 (45+)	29651	?

Total: 10

Maximum likelihood estimate: $K_M = 1.08 \times 10^{-10}$ (fiber-y/ml)$^{-1}$

95% upper confidence limit on $K_M = 1.73 \times 10^{-10}$ (fiber-y/ml)$^{-1}$

Table A-7

Lung Cancer Rates in Production Workers
at an Ontario Asbestos-Cement Plant
(Finkelstein, 1983)

Fiber-y/ml	Observed Cancers	Rates Per 1000 Man-Years
44	5	13.6
92	7	26.1
181	6	11.9
	Ontario men	1.6

Table A-8

Observed and Expected Lung Cancer Rates in Production Workers at an Ontario Asbestos-Cement Plant (Finkelstein, 1983)

Fiber-y/ml	Observed Cancers	Expected Based on Ontario Men	Expected from lung cancer model (a=1)[a]	(a allowed to vary)[b]
44	5	.588	2.5	5.8
92	7	.429	3.3	4.2
181	6	.807	11.5	8.0
Goodness of fit p-value		<0.001	<0.01	0.3

[a] Assumes Ontario men are appropriate control group.
[b] Assumes Ontario men are not necessarily appropriate control group.

Estimates with background estimated (a variable)
Maximum likelihood estimates
a = 9.87 K_L = 0.0 (fiber-y/ml)$^{-1}$
Chisquare = 2.4
95% upper confidence limit on K_L = 0.0110 (fiber-y/ml)$^{-1}$ (a = 4.34)

Estimates with background fixed (a = 1)
Maximum likelihood estimates
K_L = 0.0733 (fiber-y/ml)$^{-1}$
Chisquare = 9.26
95% upper confidence limit on K_L = 0.111 (fiber-y/ml)$^{-1}$

Table A-9

Mesothelioma in Production Workers at
an Ontario Asbestos-Cement Plant
(Finkelstein, 1983)

Years Since First Exposure	Person Years of Observation	Observed Mesothe-liomas	Mesotheliomas per 1000 Person Years	Expected Mesotheliomas Under Model
17.5 (15-20)	1182	1	0.85	.84
22.5 (20-25)	1061	4	3.77	3.50
27.5 (25-30)	555	5	9.01	4.86
32.5 (30-35)	104	1	9.62	1.80
Goodness of fit p-value				>0.3

Maximum likelihood estimate: $K_M = 1.87 \times 10^{-7}$ (fiber-y/ml)$^{-1}$
Chisquare = 0.46
95% upper confidence limit on $K_M = 2.97 \times 10^{-7}$ (fiber-y/ml)$^{-1}$

Table A-10

Lung Cancer by Exposure Level in Two
Louisiana Asbestos-Cement Plants
(Weill *et al.*, 1979)

Total dust within 20 yr. of first exp. Louisiana Rates	Observed	Expected Based on (a=1)[a]	Expected from lung cancer model (mppcf-y) (a allowed to vary)[b]		Cancers
5 (0-10)	19	24.7	25.2	17.2	30
11.4	12.8	9.6			
75 (51-100)	1	3.8	5.0	4.2	8
150 (101-200)	9	3.1	5.0	4.8	14
6.2	13.9	15.1			
300 (>200)					
Goodness of fit p-value		<0.001	0.08	0.04	

[a] Assumes Louisiana men are appropriate control group.
[b] Assumes Louisiana men are not necessarily appropriate control group.

Estimates with background estimated (a variable)
Maximum likelihood estimates
a = 0.666 K_L = 0.00889 (mppcf-y)$^{-1}$ = 0.00635 (fiber-y/ml)$^{-1}$. Chisquare = 6.6
95% upper confidence limit on K_L = 0.0185 (mppcf-y)$^{-1}$ =
0.0132 (fiber-y/ml)$^{-1}$ (a = 0.480)

Estimates with background fixed (a = 1)
Maximum likelihood estimates
K_L = 0.00412 (mppcf-y)$^{-1}$ = 0.00294 (fiber-y/ml)$^{-1}$
Chisquare = 9.7
95% upper confidence limit on K_L = 0.00728 (mppcf-yr)$^{-1}$ =
0.00520 (fiber-y/ml)$^{-1}$

Table A-11

Mesothelioma in Two Louisiana Asbestos-Cement Plants
(Weill *et al.*, 1979)

Years Since First Mesotheliomas	Person Years of Person Years	Observed Mesotheliomas	Mesotheliomas per 1000 Under Model	Expected Mesotheliomas	Exposure	Observation
12.5 (10-15)	31180	0	0	0.0076		
17.5 (15-20)	29473	2	0.068	0.18		
22.5 (20-25)	25080	0	0	0.57		
27.5 (25-30)	14018	0	0	0.70		
32.5 (30-35)	3832	0	0	0.33		
37.5 (35+)	1565	0	0	0.21		

Maximum likelihood estimate: $K_M = 6.95 \times 10^{-10}$ (fiber-y/ml)$^{-1}$
Chisquare = 20
95% upper confidence limit on $K_M = 1.84 \times 10^{-9}$ (fiber-y/ml)$^{-1}$

Table A-12

Lung Cancer by Exposure Level in Two Louisiana Asbestos Cement Plants After 20 Years from Initial Exposure (Hughes *et al.*, 1987)

Total Dust to Within 10 Yrs. of Observation		Expected		
			Expected from lung cancer model (mppcf-y)	
Cancers	Observed Louisiana Rates	Based on (a=1)[a]	(a allowed to vary)[b]	
		Plant 1		
4	3	2.9	2.96	3.36
13	9	8	8.58	9.57
35	2	3.7	4.42	4.75
74	3	3.8	5.36	5.48
183	5	4.1	8.25	7.72
		Plant 2		
3	20	18.9	19.2	21.84
12	19	14.5	15.5	17.28
36	12	6	7.19	7.73
71	10	5.5	7.66	7.87
164	12	5.2	9.92	9.39
Goodness of fit p-value			>0.25	0.25

[a] Assumes Louisiana men are appropriate control group.
[b] Assumes Louisiana men are not necessarily appropriate control group.

Estimates with background estimated (a variable)
Maximum likelihood estimates
a = 1.14 K_L = 0.00354 (mppcf-y)$^{-1}$ = 0.00253 (fiber-y/ml)$^{-1}$.
Chisquare = 7.7
95% upper confidence limit on K_L = 0.00927 (mppcf-y)$^{-1}$ = 0.00662 (fiber-y/ml)$^{-1}$
(a = 0.949)

Estimates with background fixed (a = 1)
Maximum likelihood estimates
K_L = 0.00553 (mppcf-y)$^{-1}$ = 0.00395 (fiber-y/ml)$^{-1}$
Chisquare = 8.9
95% upper confidence limit on K_L = 0.00978 (mppcf-y)$^{-1}$ = 0.00699 (fiber-y/ml)$^{-1}$

Table A-14

Lung Cancer by Exposure Level in a
South Carolina Chrysotile Textile Plant
(Dement *et al.*, 1983b)

	Observed	Expected Based on U.S. rates (a=1)[a]	Expected from lung cancer model (a allowed to vary)[b]	Fiber-y/ml	Cancers
1.4 (<2.74)	5	3.58	3.83	5.81	
15.1 (2.74-27.4)	9	3.23	5.68	7.15	
68.5 (27.4-110)	7	1.99	8.84	8.98	
192 (110-274)	10	0.91	9.70	8.94	
411 (>274)	2	0.11	2.38	2.12	
Goodness of fit p-value		<0.001	>0.5	>0.5	

[a] Assumes U.S. men are appropriate control group.
[b] Assumes U.S. men are not necessarily appropriate control group.

Estimates with background estimated (a variable)
Maximum likelihood estimates
a = 1.56 K_L = 0.0275 (fiber-y/ml)$^{-1}$
Chisquare = 1.2
95% upper confidence limit on K_L = 0.0730 (fiber-y/ml)$^{-1}$ (a = 0.830)

Estimates with background fixed (a = 1)
Maximum likelihood estimate
K_L = 0.0503 (fiber-y/ml)$^{-1}$
Chisquare = 2.7
95% upper confidence limit on K_L = 0.0734 (fiber-y/ml)$^{-1}$

Table A-15

Mesothelioma in a South Carolina Chrysotile Textile Plant
(Dement *et al.*, 1983b)

Years Since First Exposure	Person Years of Observation	Observed Mesotheliomas	Mesotheliomas per 1000 Person Years	Expected Mesotheliomas Under Model
5 (<10)	11390	0	0	0.0
15 (10-20)	10921	0	0	0.022
25 (20-30)	8055	0	0	0.43
35 (30+)	2775	1	0.36	0.55
Goodness of fit p-value				>0.5

Maximum likelihood estimate: $K_M = 3.01 \times 10^{-9}$ (fiber-y/ml)$^{-1}$
Chisquare = 0.81
95% upper confidence limit on $K_M = 1.10 \times 10^{-8}$ (fiber-y/ml)$^{-1}$

Table A-16

Lung Cancer by Exposure Level in a
South Carolina Chrysotile Textile Plant
(McDonald *et al.*, 1983a)

S.C. rates	Observed (a=1)[a]	Expected based on (a allowed to vary)[b]	Expected from lung cancer model	mppcf-y	Cancers
5 (<10)	31	21.7	29.2	30.4	
15 (10-20)	5	2.7	5.6	5.7	
30 (20-40)	8	2.6	8.1	8.0	
60 (40-80)	7	1.7	8.6	8.4	
110 (>80)	8	0.78	6.7	6.5	
Goodness of fit p-value		<0.01	>0.9	>0.8	

[a] Assumes South Carolina men are appropriate control group.
[b] Assumes South Carolina men are not necessarily appropriate control group.

Estimates with background estimated (a variable)
Maximum likelihood estimates
a = 1.07 K_L = 0.0618 (mppcf-y)$^{-1}$ = 0.0103 (fiber-y/ml)$^{-1}$
Chisquare = 0.69
95% upper confidence limit on K_L = 0.147 (mppcf-y)$^{-1}$
= 0.0245 (fiber-y/ml)$^{-1}$ (a = 0.653)

Estimates with background fixed (a = 1)
Maximum likelihood estimates
K_L = 0.0692 (mppcf-y)$^{-1}$ = 0.0115 (fiber-y/ml)$^{-1}$
Chisquare = 0.74
95% upper confidence limit on K_L = 0.0987 (mppcf-y)$^{-1}$
= 0.0165 (fiber-y/ml)$^{-1}$

Table A-17

Reconstructed Mesothelioma Data from a
South Carolina Chrysotile Textile Plant
(McDonald *et al.*, 1983a)

Years Since First Mesotheliomas	Person Years of Person Years	Observed Mesotheliomas	Mesotheliomas per 1000 Under Model	Expected Mesotheliomas	Exposure	Observation
28 (19-39)	26280	0	0	0.68		
44 (39+)	2787	1	0.36	0.32		

Maximum likelihood estimate: $K_M = 5.09 \times 10^{-10}$ (fiber-y/ml)$^{-1}$

Chisquare = 2.1

95% upper confidence limit on $K_M = \cdot 1.86 \times 10^{-9}$ (fiber-y/ml)$^{-1}$

Table A-18

Observed and Predicted Numbers of Mesotheliomas
(Peto *et al.*, 1985)

Duration of Service (Yr.)	Years Since First Employment: Less Than 20 (11.5)	20-24 (22.5)	25-29 (27.5)	30-34 (32.5)	35-49 (37.5)	40 or More (42)	Total
Less than 1	Obs. 0	0	0	0	0	0	0 (0.5)
	P-Yr.[a] 28015	4668.2	3469.8	2041.2	840.4	402.3	39437
	P_3[b]	0.10	0.13	0.19	0.19	0.11	0.12
	0.84						
	P_{EPA}[c]	0.0080	0.13	0.19	0.18	0.11	0.07
1-4	Obs. 0	0	0	0	0	1	1 (3)
	P-Yr. 4785.6	877.4	631.7	421.3	237.7	148.4	7102
	P_3	0.07	0.09	0.12	0.12	0.09	0.08
	0.57						
	P_{EPA}	0.0019	0.11	0.17	0.20	0.17	0.15
5-9	Obs. 0	0	0	0	0	0	0 (7.5)
	P-Yr. 8520.5	1416.8	1103.5	707.2	383.3	249.1	12380
	P_3	0.29	0.37	0.55	0.63	0.51	0.51
	2.86						
	P_{EPA}	0.0034	0.31	0.57	0.68	0.58	0.54
10-19	Obs. 0	0	0	3	0	1	1 (15)
	P-Yr. 4814.1	1423.3	869.7	469.7	204	102.3	7883
	P_3	0.40	0.40	0.49	0.47	0.31	0.21
	2.28						
	P_{EPA}	0.0019	0.33	0.55	0.62	0.46	0.34
20-29	Obs.	1	1	2	1	0	5 (25)
	P-Yr.	848.3	935.3	599.7	257.1	121.7	2762
	P_3	0.31	0.70	0.76	0.48	0.34	2.59
	P_{EPA}	0.20	0.60	0.82	0.64	0.47	
30 or more	Obs.			0	0	0	0 (35)
	P-Yr.	86.2	106.9	103.4	297		
	P_3				0.16	0.31	0.43
	0.90						
	P_{EPA}				0.12	0.27	0.40
Total	Obs. 0	1	1	5	1	2	10
	P-Yr. 46135.2	9234	7010	4325.3	2029.4	1127.2	69861
	P_3	0.86	1.30	2.04	2.32	1.80	1.69
	10.01						
	P_{EPA}	0.016	1.08	2.09	2.61	2.23	1.98
	10.01						

[a]Person-years.
[b]Predicted numbers based upon Peto *et al.*'s cubic residence time model. [c]Predicted numbers based upon mesothelioma model employed herein (equation (3)).

Table A-19

Lung Cancer by Exposure Level in a Pennsylvania Asbestos Plant
(McDonald *et al.*1983b)

Penn. Rates	Observed (a=1)[a]	Expected Based on (a allowed to vary)[b]	Expected from lung cancer model mppcf-y	Cancers
5 (<10)	21	31.4	34.1	20.7
15 (10-20)	5	5.98	7.51	5.64
30 (20-40)	10	6.41	9.68	8.76
60 (40-80)	6	3.75	7.58	8.30
110 (>80)	11	2.64	7.58	9.57
Goodness of fit p-value		<0.01	0.10	>0.7

[a] Assumes control group is appropriate.
[b] Assumes control group is not necessarily appropriate.

Estimates with background estimated (a variable)
Maximum likelihood estimates
a = 0.519 K_L = 0.0544 (mppcf-y)$^{-1}$ = 0.0181 (fiber-y/ml)$^{-1}$
Chisquare = 1.1
95% upper confidence limit on K_L = 0.135 (mppcf-y)$^{-1}$ = 0.0450 (fiber-y/ml)$^{-1}$ (a = 0.296)

Estimates with background fixed (a = 1)
Maximum likelihood estimates
K_L = 0.0170 (mppcf-y)$^{-1}$ = 0.00567 (fiber-y/ml)$^{-1}$
Chisquare = 7.7
95% upper confidence limit on K_L = 0.0282 (mppcf-y)$^{-1}$ = 0.0940 (fiber-y/ml)$^{-1}$

Table A-20

Reconstructed Mesothelioma Data from Pennsylvania Asbestos Plant
(McDonald *et al.*, 1983b)

Years Since First Exposure	Person Years of Observation	Observed Mesotheliomas
15.5 (15-16)	17179	?
24 (16-38)	40868	?
41 (36+)	9840	?

Total mesotheliomas: between 14 and 23

Maximum likelihood estimate:

$K_M = 6.70 \times 10^{-9}$ (fiber-y/ml)$^{-1}$ (assuming 14 mesotheliomas)

$K_M = 1.1 \times 10^{-8}$ (fiber-y/ml)$^{-1}$ (assuming 23 mesotheliomas)

APPENDIX B:
BACKGROUND FOR DEVELOPMENT OF
AN AD HOC EXPOSURE INDEX FOR ASBESTOS

BACKGROUND FOR DEVELOPMENT OF AN AD HOC EXPOSURE INDEX FOR ASBESTOS

The asbestos exposure index recommended for supporting risk assessment in this report (C_{opt}, as defined by Equation 6.6) represents a compromise. The index preserves most of the important features (including the maximum structure width, the minimum structure length, and the analytical requirements for obtaining the required counts) of the optimum exposure index (Equation 5.2), which is recommended based on the results of our literature review combined with our formal statistical re-analysis of the animal inhalation studies conducted by Davis et al. (Section 5.6.2 of the main text). However, due to the limitations in the published size distributions available for re-evaluating the human epidemiology studies, the longest category of structures had to be shortened from that incorporated in Equation 5.2 (Section 6.2).

Nevertheless, we expect C_{opt} to provide somewhat conservative (in a health protective sense) estimates of asbestos exposure because we believe that:

- the minimum length for the structures included in C_{opt} (5 μm) is sufficiently short to capture the bulk of the range of structures that contribute both to lung cancer and to mesothelioma in humans;

- the maximum width for the structures included in C_{opt} (0.5 μm) is greater than the greatest width observed to contribute in our formal analysis of the Davis et al. studies and is expected to be sufficiently wide to capture the bulk of the range of structures that contribute both to lung cancer and to mesothelioma. Importantly, contributions from thicker, complex structures are also included because the counting rules adopted to provide measurements for generating estimates of C_{opt} require that the thinner components of these complex structures be individually enumerated and included in the overall count of structures; and

- the weighting factors incorporated in Equation 6.6 are conservative (in a health protective sense) in that they are adopted directly from the optimum exposure index (Equation 5.2) but they are applied so that a greater number of structures (i.e. those between 10 and 40 um in addition to those greater than 40 um) are included within the concentration that is assigned the greater potency value.

Despite the compromises adopted to define and apply C_{opt}, the analysis reported in Chapter 6 of this document indicates that it indeed represents an improved index of exposure (over traditional indices), which better captures the characteristics of asbestos that determine biological activity. The analysis presented demonstrates that, when published risk coefficients are adjusted to account for exposure expressed as C_{opt}, the variation observed in the published values across studies is substantially reduced. In fact, the between-environment variation in published risk coefficients for the amphiboles is completely eliminated by adapting the coefficients to C_{opt}.

Remarkably, the improved across-study agreement observed when risk coefficients are adapted to C_{opt} is achieved despite the limitations of the manner in which the coefficients are adjusted, including:

- that the definition of C_{opt} itself is a compromise that does not fully account for the effects of structure size. The specific exposure index recommended in Chapter 5 of this document could not be applied to the epidemiology studies because available TEM size distributions would not support it. Therefore, the length dimensions of the longest size category incorporated into C_{opt} is substantially shorter than what is considered optimal (see Section 6.2);

- that the size distributions employed to adapt risk coefficients to C_{opt} were obtained from analyses performed in separate studies than those from which the corresponding risk coefficients were derived. Thus, the size distributions employed for the adjustments were typically derived under time-frames and conditions that differed from those that obtained during the studies from which the risk coefficients were derived, even if such studies were conducted in the same facility;

- that the same size adjustment was applied to each of the multiple risk coefficients representing a particular fiber type in a particular type of industrial setting (e.g. chrysotile in textile production) even when such risk coefficients were derived from studies at different facilities, which would typically exhibit varying conditions; and

- that each risk coefficient was subjected to a single, average adjustment for fiber size despite the fact that each such coefficient was derived from a long-term study during which exposure conditions (potentially including fiber size distribution) typically changed substantially over the course of the study.

Due to the limitations described above, a small number of follow-on studies are recommended in the text of this document, which would establish the relative importance of these limitations and, in some cases, control for their effects. By completing such studies, it is possible that the remaining variation still observed among published risk coefficients for chrysotile would be further reduced. In any case, such studies would add substantially to the understanding of the relationship between asbestos exposure and risk.

APPENDIX C:
DERIVATION OF LIFETIME RISKS FOR LUNG CANCER AND MESOTHELIOMA FROM MODELS USING K_L AND K_M ESTIMATES FOR POTENCY

This appendix shows how additional lifetime risk of lung cancer or mesothelioma are calculated from the models from which K_L, the potency for lung cancer, and K_M, the potency for mesotheliomas, are derived. First a general model is developed that allows a variable exposure pattern, and the lung cancer and mesothelioma models are shown to be special cases of the more general expression. Next the procedure used to implement these models based on human mortality rates is explained. Finally, the mortality rates used in these calculations are derived.

Let $D = \{D(t);\ t > \geq 0\}$ represent exposure to asbestos (i.e., exposure at age t is D(t) f/ml), let $S_D(t \mid x)$ be the probability of surviving to age t given survival to age $x < t$. Let $M_D(t)$ be the mortality rate for a given cause at age t. The probability of dying of the given cause during a small age interval Δt at age t is the probability of surviving to age t times the probability of dying from the given cause given survival to age t, or

$$S_D(t \mid x)M_D(t)\Delta t.$$

The probability of dying of the given cause is given survival to age x therefore given by the integral

$$P_D(x) = \int_x^\infty S_D(t \mid x)M_D(t)dt. \qquad (B1)$$

The corresponding probability of dying of the given cause without any exposure to asbestos is given by

$$P_O(x) = \int_x^\infty S_O(t)M_O(t)dt, \qquad (B2)$$

where the subscript O indicates no exposure, and the additional probability of dying from the given cause as a result of exposure pattern D is

$$P_D(x) - P_O(x). \qquad (B3)$$

The lung cancer and mesothelioma models in Section 6.2 basically model the mortality rate $M_D(t)$. It is shown below how expressions (B1), (B2), and (B3) are used to convert estimates from the models in Section 6.2 into estimates of additional risk.

It will be assumed that the increase in the mortality rate at age t from an exposure of D(v) between ages v and $v+\Delta v$, $v<t$, is given by

$$D(v)g(t-v,t)\Delta v.$$

Thus g(u,t) is an intensity function that relates an exposure u years prior to age t to the resulting mortality rate at age t. It is further assumed that the total mortality rate at age t is the sum of the contributions from all doses prior to age t, plus the background mortality rate $M_O(t)$; i.e.,

$$M_D(t) = M_O(t) + \int_0^t D(v)g(t-v,t)dv.^1 \tag{B4}$$

To obtain the relative risk model for lung cancer in Section 6.2.1, let

$$g(u,t) = \begin{cases} M_O(t)K_L & u > 10 \\ 0 & u < 10. \end{cases} \tag{B5}$$

By applying (B5) to (B4) and performing the integration, it follows that

$$M_D(t) = M_O(t)\,[1+K_L \int_0^{t-10} D(v)dv]. \tag{B6}$$

Thus, the relative risk at age t, $M_D(t)/M_O(t)$, is given by

$$1 + K_L * [\text{total exposure up to 10 years prior to age t}], \tag{B7}$$

which agrees with expression (E.4) in Section 6.2.1. However (B7) holds generally for any exposure pattern D(v), whereas (E.4) is more specialized in that it presupposes a constant exposure.

To obtain the absolute risk model for mesothelioma in Section 6.2.2 from (B4), define the intensity function

$$g(u,t) = \begin{cases} 3K_M\,(u-10)^2 & u > 10 \\ 0 & u < 10 \end{cases} \tag{B8}$$

Thus the intensity function is proportional to the square of elapsed time since exposure less 10 years. It then follows that

$$M_D(t) = M_O(t) + 3K_M \int_0^{t-10} D(v)(t-v-10)^2dv. \tag{B9}$$

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[1]This expression assumes a linear dose response. For a non-linear response, replace D(v) by H(D(v)) where H is a non=linear function (e.g. $H(v)=v^2$).

If a constant exposure rate is assumed over a fixed age interval,

$$D(v) = \begin{cases} f & t_1 < v < t_2 \\ 0 & \text{otherwise,} \end{cases} \tag{B10}$$

then

$$M_D(t) = \begin{cases} M_O(t) + K_M f(t-t_1-10)^3 & \text{for } t_1+10<t<t_2+10 \\ M_O(t) + K_M f[(t-t_1-10)^3 - (t-t_2-10)^3] & \text{for } t>t_2+10, \end{cases} \tag{B11}$$

which agrees with the mesothelioma model (E.5) in Section 6.2.2.

To implement these models the integral (B1) must be evaluated using the appropriate expression for the mortality rate $M_D(t)$ (expression (B6) for lung cancer and (B11) for mesothelioma). Let b_1, b_2,..., b_{18} be the mortality rates (expected number of deaths) for all causes per year per 100,000 persons for the age intervals 0-5, 5-10,...,80-85, and 85+ years, respectively, and let $a_1...a_{18}$ be the corresponding rates for lung cancer. Given survival to age x=5k, the probability of survival to t=5i years is estimated as

$$S_O(t,x) = \prod_{j=k+1}^{i} [1-5b_j/100,000]. \tag{B12}$$

Given survival to age 5(i-1), the probability of dying of lung cancer by age 5i is estimated as

$$5a_i/100,000. \tag{B13}$$

The probability of dying of lung cancer given survival to age 85 is estimated as a_{18}/b_{18}. Therefore, the probability of dying of lung cancer in the absence of asbestos exposure, given survival to age x=5k is estimated as

$$P_O(x) = \sum_{i=k+1}^{17} [(5a_i/100,000) \prod_{j=k+1}^{i-1}(1-5b_j/100,000)] + (a_{18}/b_{18}) \prod_{j=k+1}^{17} (1-5b_j/100,000), \tag{B14}$$

which represents a discrete approximation to the integral (B2).

To estimate the probability $P_O(x)$ of dying of lung cancer when exposed to a particular pattern D of asbestos exposure, expression (B14) is again used, but a_i and b_i are replaced by $a_i + E_i$ and $b_i + E_i$, where, following (B7),

$$E_i = a_i K_L \cdot [\text{total exposure up to 10 years prior to mid-point of ith age interval}], \quad \text{(B15)}$$

where K_L is the potency parameter (risk factor) for lung cancer. (Here a_i+E_i is playing the role of $M_D(t)$ in equation (B6).) The additional lifetime risk of lung cancer is estimated by the difference $P_D(x)-P_O(x)$. For example, to estimate the future risk to a person presently 20 years of age, we would use x=20 (i.e., k=4) in (B14).

The additional lifetime risk of death from mesothelioma is estimated using the same formulas, except a_i is replaced by zero (background rate of mesothelioma is so small as to be unimportant), and (following equation B9) E_i is replaced by a discrete approximation to

$$3K_M \int_0^{t_i-10} D(v)(t_i-v-10)^2 dv,$$

where t_i is the mid-point of the ith age interval. Appropriate modifications are made to these expressions when x is not a multiple of 5.

Sex- and smoking-specific estimates are used for the mortality rates required in the above calculations (a_i and b_i). Lung cancer mortality rates for nonsmokers are obtained by averaging rates for nonsmokers are obtained by averaging rates for three different time periods calculated from the American Cancer Society prospective study (Garfinkel 1981). Lung cancer mortality rates in smokers, [P(LCF | S)], are calculated using the equation

$$P(LCD) = P(LCF|S)P(S) + P(LCD|NS)[1-P(S)], \quad \text{(B16)}$$

where P(LCD) is a 1980 age- and sex-specific death rate from lung cancer in the general U.S. population, P(S) is the fraction of smokers in the population, P(LCD | NS) is an age- and sex-specific death rate from lung cancer in nonsmokers computed from Garfinkel (1981), and P(LCD | S) is a corresponding rate in smokers. The proportion of smokers, P(S) is assumed to be 0.67 for males and 0.33 for females, which is consistent with the U.S. EPA (1986) approach. Smoking-specific rates for all causes are calculated from 1980 U.S. rates for all causes assuming that the mortality rate in smokers is a factor, f, times the mortality rate in nonsmokers. An age-specific mortality rate, P(AC | NS), in nonsmokers is then calculated using the formula

$$P(AC) = fP(AC|NS)P(S) + P(AC|NS)[1-P(S)],$$

where P(AC) is a 1980 age- and sex-specific death rate from all causes in the general U.S. population. Following Hammond (1966), the factor f is taken as 1.83 for males and 1.26 for females. This procedure is followed for all age groups despite the fact that smokers generally do not begin smoking until teenage years and the effects upon mortality will not occur until still later. This makes little difference in the risk calculations because mortality rates are relatively low at early ages.

The resulting mortality rates are listed in Table B1.

Table B1

Smoking- and Sex-Specific Mortality Rates Per Year Per 100,000 Population for Respiratory Cancer and Total Mortality

Age	Total Mortality		Respiratory Cancer	
	Smokers	Nonsmokers	Smokers	Nonsmokers
		Males		
0-1	1679.0	918.0	.4	0
1-5	85.4	46.7	.0	0
5-10	41.2	22.5	.0	0
10-15	45.0	24.6	.0	0
15-20	166.3	90.9	.1	0
20-25	239.3	130.8	.4	0
25-30	230.7	126.1	.7	0
30-35	230.5	126.0	2.2	0
35-40	288.4	157.6	9.3	0
40-45	428.3	234.0	26.2	8.3
45-50	686.8	375.3	76.1	3.1
50-55	1109.0	606.0	155.1	7.9
55-60	1717.8	938.7	263.2	10.2
60-65	2623.7	1433.7	402.8	17.3
65-70	3991.2	2181.0	556.7	28.2
70-75	5972.2	3263.5	698.5	25.2
75-80	8796.8	4807.0	750.6	44.9
80-85	13218.0	7222.9	711.0	72.5
85+	22110.4	12082.2	527.1	100.5
		Females		
0-1	1324.9	1051.5	.3	0
1-5	63.5	50.4	.3	0
5-10	29.7	23.6	.3	0
10-15	26.6	21.1	.0	0
15-20	61.6	48.9	.0	0
20-25	71.8	57.0	.3	0
25-30	79.1	62.8	.9	0
30-35	98.1	77.8	2.7	0
35-40	144.4	114.6	10.6	0
40-45	233.0	184.9	27.9	2.4
45-50	372.8	295.9	67.4	3.5
50-55	578.7	459.3	124.0	5.2
55-60	869.2	689.8	178.8	7.0
60-65	1327.5	1053.6	234.8	13.6
65-70	1993.3	1582.0	282.6	16.2
70-75	3101.6	2461.6	286.4	20.9
75-80	4939.5	3920.2	240.8	34.7
80-85	8424.9	6686.4	182.2	45.5
85+	17112.8	13581.6	184.8	52.7