

DRAFT REPORT– DO NOT CITE OR QUOTE

**PROPOSED APPROACH FOR ESTIMATION OF
BIN-SPECIFIC CANCER POTENCY FACTORS
FOR INHALATION EXPOSURE TO ASBESTOS**

**U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF SOLID WASTE AND EMERGENCY RESPONSE**

June 12, 2008

ACKNOWLEDGEMENTS

This report was prepared for the Office of Solid Waste and Emergency Response by Syracuse Research Corporation through Contract GS-00F-0019L, Task Orders 0803 and 0819, and FEDSIM Order GST-0005-AJ-0031. The principal author was Dr. William J. Brattin.

Drs. D. Wayne Berman and Kenneth S. Crump were instrumental in the initial development of methods for estimation of bin-specific potency factors for asbestos. This work was performed by Aeolus Inc. under various contracts with EPA.

Dr. Timothy Barry (USEPA Office of Policy, Economics, and Innovation) and Dr. Kenneth Crump (Environ Corporation) have provided invaluable technical assistance in the statistical and programming aspects of this effort. Dr. Martin Kanarek (University of Wisconsin) provided expertise in the review and evaluation of published epidemiological reports.

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LIST OF ACRONYMS AND ABBREVIATIONS

α	Relative risk of lung cancer in the absence of exposure to asbestos
C	Concentration of asbestos in air (f/cc)
CE10	Cumulative exposure (lagged by 10 years) (f/cc-yrs)
CF	Conversion factor
d	Exposure duration (yrs)
DNA	Deoxyribonucleic acid
EDS	Energy dispersive spectroscopy
EPA	Environmental Protection Agency
Im	Incidence of mesothelioma
IRIS	Integrated Risk Information System
KL	Lung cancer potency factor
KM	Mesothelioma potency factor
MCMC	Markov Chain Monte Carlo
MLE	Maximum likelihood estimation
mppcf	Million particles per cubic foot
NCEA	National Center for Environmental Assessment
OSWER	Office of Solid Waste and Emergency Response
PCM	Phase contrast microscopy
PCME	Phase contrast microscopy equivalent
PDF	Probability density function
Q	Cubic function of exposure duration and time since first exposure (yrs ³)
RMH	Relative mesothelioma hazard
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
RR	Relative risk of lung cancer
SAB	Science Advisory Board
SAED	Selected area electron diffraction
SCE	Sister chromatid exchange
SMR	Standardized mortality ratio
T	Average time since first exposure (yrs)
TEM	Transmission electron microscopy
TNF	Tumor necrosis factor
USEPA	United States Environmental Protection Agency

EXECUTIVE SUMMARY

Description of the Problem

Inhalation exposure to asbestos increases the risk of lung cancer and mesothelioma in humans. Asbestos is known to be present at a number of Superfund sites around the country, and information on the magnitude of the cancer risk posed by the asbestos is one important factor that the United States Environmental Protection Agency (EPA) considers in making risk management decisions at these sites.

However, development of quantitative risk models that may be used to predict cancer risk from asbestos is complicated by the fact that asbestos is not a single chemical species, but includes a broad family of naturally occurring silicate minerals that crystallize into long thin fibers. Moreover, asbestos fibers may occur in a wide range of different sizes with varying lengths and widths. Available data indicate that there may be differences in carcinogenic potency between different mineral types and sizes of asbestos particles.

At present, EPA uses an approach for quantifying cancer risk that is based on phase contrast microscopy (PCM) as the measure of asbestos exposure. However, PCM does not distinguish between different mineral types of asbestos, does not account for differences in particle size distribution between different exposure locations, and does not visualize thin fibers (which may contribute significantly to toxicity). Because of these potential limitations in the current methodology, EPA has been working to develop “multi-bin” cancer risk models that account for any differences in potency between differing mineral types and sizes of asbestos particles.

In the “multi-bin” approach, asbestos particles are divided into a number of different “bins” according to mineral groups or types (e.g., amphibole or chrysotile) and particle size (length, width). The asbestos risk models are then fit to available epidemiological data, expressing exposure in terms of several bin-specific concentrations rather than a single PCM concentration. The result of this fitting process is a set of bin-specific potency factors that may be used to predict the risk to people who are exposed to any specified asbestos atmosphere.

Purpose of this Document

This document summarizes an approach that EPA’s Office of Solid Waste and Emergency Response (OSWER) is proposing for selecting and parameterizing a multi-bin model that will provide an incremental improvement to the current method that EPA employs for estimating cancer risk from inhalation exposure to asbestos at Superfund sites. It is important to emphasize that this effort is intended to serve as an intermediate step in a larger Agency-wide review and

update of its asbestos risk assessment policies and practices. The approach presented in this report is focused only on the fitting of epidemiological exposure-response data to cancer risk models, and does not seek to integrate important data from other sources, including animal exposure-response data, lung burden data, *in vitro* data, mode of action data, non-cancer effects data, and differential life-stage sensitivity data. OSWER recognizes that all of these other data sources provide valuable information on asbestos toxicity and carcinogenicity, and all of these data will be considered by EPA when it updates the toxicity assessment for the Integrated Risk Information System (IRIS).

It is also important to recognize that at this time OSWER is simply proposing a draft approach for deriving bin-specific cancer potency factors for asbestos. After seeking advice from EPA’s Science Advisory Board (SAB) on the proposed draft approach, OSWER is planning to use SAB input to finalize an approach and then ask SAB to again review the revised approach. Following the SAB’s review, OSWER plans to develop a guidance document intended for use by EPA’s regional staff and other interested parties that describes how to apply these cancer potency factors in risk assessments for Superfund sites.

Summary of the OSWER Proposal

OSWER is proposing to fit the following models to the available human epidemiological data:

$$\begin{aligned} \text{Lung Cancer:} & \quad RR = \alpha (1 + \sum CE_{10_b} \cdot KL_b) \\ \text{Mesothelioma:} & \quad Im = Q \cdot \sum C_b \cdot KM_b \end{aligned}$$

where:

- RR = Relative risk of lung cancer
- α = Relative risk of lung cancer in the absence of asbestos exposure
- CE_{10_b} = Cumulative exposure (lagged by 10 years) to asbestos bin “b” (f/cc-yrs)
- KL_b = Lung cancer potency of asbestos type “b”
- Im = Incidence of mesothelioma
- Q = Cubic function of time since first exposure and exposure duration (yrs³)
- C_b = Concentration of fibers of type “b” (f/cc)
- KM_b = Mesothelioma potency of asbestos fibers of type “b”

In principle, there could be an infinite number of different asbestos bins. For the purposes of this assessment, OSWER is proposing to investigate a set of 20 different binning strategies, including seven one-bin strategies, seven two-bin strategies, and six four-bin strategies (see Table 8-2). It is expected that, if there are important differences in potency between bins, the quality of the

model fit to the data will be improved when a binning strategy is selected that adequately stratifies particles according to potency. Appropriate statistical tests will be used to determine if any multi-bin strategy results in an improvement over the current approach, and if so, which multi-bin strategy yields the largest improvement.

Fitting the risk models to the available epidemiological data is a complicated statistical undertaking. This is because the problem is multi-dimensional, and because there is substantial uncertainty (measurement error) in each of the estimates of cumulative exposure to asbestos (CE10 for lung cancer, C·Q for mesothelioma). This uncertainty arises from multiple sources, including: a) random errors in the values measured and reported by the researchers, and b) reporting of values that are not identical to the data needed for fitting, thereby requiring an extrapolation from the reported values to the needed values. In particular, one difficult problem that must be solved is the estimation of bin-specific exposures that occurred in each of the published epidemiological studies. This is because the studies published to date report exposure in terms of dust particles or PCM fibers, and none provide the data needed to estimate the levels of each of the various asbestos bins. OSWER proposes to estimate these needed values by finding published data sets based on transmission electron microscopy (TEM) that are most closely matched to the workplace exposures reported in each epidemiological study, and using these particle size data sets to extrapolate from PCM-based to bin-specific exposures.

OSWER has reviewed the literature to identify statistical techniques for fitting mathematical models to the data in cases where there is substantial measurement error in the independent variable (measures of cumulative exposure). Although there are a number of options, OSWER is proposing Bayes-Markov Chain Monte Carlo (MCMC) fitting as the most robust and most informative approach. In this approach, the uncertainty in each estimate of bin-specific cumulative exposure is characterized by one or more probability density functions (pdfs) that describe the uncertainty (measurement error, bias) in each of the data items used to calculate each bin-specific exposure value. Implementation of the Bayes-MCMC approach is expected to yield best estimate values and uncertainty distributions for each of the bin-specific potency factors, and these may be used to estimate a point estimate and the uncertainty around any risk prediction performed using the bin-specific approach.

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1.0 INTRODUCTION

1.1 Overview of the Issue

Inhalation exposure to asbestos increases the risk of lung cancer and mesothelioma in humans (USEPA 1986, USEPA 1993, ATSDR 2001). Asbestos is known to be present at a number of Superfund and other sites around the country, and information on the magnitude of the cancer risk posed by the asbestos is one important factor that the United States Environmental Protection Agency (USEPA or EPA) considers in making risk management decisions at these sites.

Development of quantitative risk models for asbestos is complicated by the fact that asbestos is not a single chemical species, but includes a broad family of naturally occurring silicate minerals that crystallize into fibers. Moreover, asbestos fibers may occur in a wide range of different sizes with varying lengths and widths. Because of these variations in type and size, there are a number of alternative methods for expressing the concentration of asbestos in air at a location of potential concern. Consequently, there are also a number of different strategies possible for development of quantitative cancer risk models for asbestos.

In 1986, EPA used existing epidemiological data from cohorts of workers exposed to asbestos in a variety of mining and manufacturing settings to select quantitative risk models and estimate potency factors for both lung cancer and mesothelioma (USEPA 1986). These potency factors were based on asbestos concentrations expressed in terms of phase contrast microscopy (PCM), which identifies fibers that are longer than 5 μm in length and have an aspect ratio (length to width) of 3:1 or greater. Since the derivation of the lung cancer and mesothelioma potency factors by USEPA (1986), evidence has accumulated that the toxicity and carcinogenicity of asbestos may depend both on mineral group or type (e.g., amphibole *vs.* chrysotile) and particle size (length, width) (e.g., Hodgson and Darnton 2000, ATSDR 2001). This is potentially significant because the PCM measurement technique does not distinguish between asbestos mineral group or type (amphibole *vs.* chrysotile), does not account for differences in particle size distribution between different exposure locations, and does not visualize thin fibers (which may contribute significantly to toxicity). Consequently, cancer risk calculations that utilize the current PCM-based potency factors may either under-predict or over-predict risk, depending on

the mineral type and size of asbestos particles that are present in the exposure setting that is being evaluated.

1.2 EPA Activities to Address the Issue

To address the potential limitations associated with the current method for quantification of cancer risk from inhalation of asbestos, EPA has been working to develop “multi-bin” cancer risk models that account for the differing potencies of differing asbestos types and sizes of asbestos particles. EPA is already encouraging the use of TEM to characterize exposure at Superfund sites. Once a methodology is finalized, these data could then be used to predict cancer risk using a multi-bin model.

In the “multi-bin” approach, asbestos particles are divided into a number of different “bins” according to mineral group or type (amphibole or chrysotile) and particle size (length, width). The asbestos risk models are then fit to available epidemiological data, expressing exposure in terms of several bin-specific concentrations rather than a single PCM concentration. The result of this fitting process is a set of bin-specific potency factors that may be used to predict the risk to people who are exposed to any specified asbestos atmosphere. Because all but one of the available epidemiological studies do not provide exposure estimates using TEM, secondary sources were used to estimate the exposures.

This general approach to development of multi-bin cancer risk models for asbestos was evaluated in 2003 using EPA’s peer consultation process, in which a panel of experts reviewed EPA’s work to date. In general, the 2003 peer consultation panel was strongly supportive of the approach, but recommended a number of areas for further evaluation and assessment (see Appendix D). This included:

- Improve the transparency and reproducibility of the approach
- Include evaluation of particles up to 1.5 um in thickness
- Consider data quality criteria for study inclusion
- Perform sensitivity analysis and goodness-of-fit evaluations
- Explore alternative risk models
- Consider alternative fitting techniques, including meta-regression and Bayes MCMC
- Consider testing different binning strategies to optimize the fit of the models to the data

1.3 Purpose and Scope of This Document

This document summarizes an approach that EPA’s Office of Solid Waste and Emergency Response (OSWER) is proposing for selecting and parameterizing a multi-bin model that will

provide an incremental improvement to the current method that EPA employs for estimating cancer risk from inhalation exposure to asbestos at Superfund sites. OSWER is seeking the advice of the Science Advisory Board's expert asbestos panel on this proposed approach for developing multi-bin cancer risk models for inhalation exposure to asbestos.

It is important to emphasize that this effort is intended to serve as an intermediate step in a larger agency-wide review and update of its asbestos risk assessment policies and practices. The approach presented in this report is focused only on the fitting of epidemiological exposure-response data to the cancer risk models. This effort does not seek to integrate important data from other sources, including animal exposure-response data, lung burden data, *in vitro* data, mode of action data, non-cancer effects data, and differential life-stage sensitivity. OSWER recognizes that all of these other data sources provide valuable information on asbestos toxicity and carcinogenicity, and all of these data will be considered by EPA when it updates the toxicity assessment for the Integrated Risk Information System (IRIS). In January 2006, EPA's National Center for Environmental Assessment (NCEA) announced its re-assessment of the carcinogenicity of asbestos that will be used to update the IRIS file for asbestos. However, it is anticipated that this may take several years to complete. In the interim, OSWER needs to complete cancer risk assessments at a number of Superfund sites where mineral type and particle size may differ widely. In this document, OSWER is proposing an approach that addresses these factors and, when finalized, can be used at Superfund sites.

After seeking advice from EPA's Science Advisory Board (SAB) on the proposed approach OSWER is planning to use their input to implement an approach and then take the results back to the SAB. Following a SAB review of the results, an updated sensitivity analysis, and accompanying report, OSWER plans to develop a guidance document. The guidance document would provide instructions to EPA's regional staff and other interested parties on how to apply these cancer potency factors in risk assessments for Superfund sites. This current draft proposal should not be construed to represent an Agency determination or policy and should not be used in its current form at Superfund sites.

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2.0 BACKGROUND INFORMATION ON ASBESTOS

2.1 Mineralogy of Asbestos

Asbestos is the generic name for the fibrous habit of a broad family of naturally occurring poly-silicate minerals. Based on crystal structure, asbestos minerals are usually divided into two groups: serpentine and amphibole.

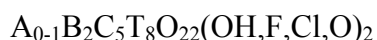
Serpentine

The general chemical composition of serpentine is $Mg_3Si_2O_5(OH)_4$. 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.

The only asbestos mineral in the serpentine group is chrysotile. Chrysotile is the most widely used form of asbestos, accounting for about 90% of the asbestos used in commercial products such as insulation, friction products, floor tiles, cement building materials, textiles, etc. (IARC 1977).

Amphiboles

Amphiboles occur as extended chains of silicate tetrahedra that are interconnected by bands of cations. The general chemical composition of amphiboles is:



where the most common cations are:

A = Na, K

B = Na, Ca

C = Mg, Fe, Mn, Ti, Al.

T = Si, Al, Ti.

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

Five asbestos minerals in the amphibole group have found limited use in commercial products (IARC 1977), including:

- asbestiform actinolite
- asbestiform cummingtonite-gruenerite (amosite)
- asbestiform anthophyllite
- asbestiform rebeckite (crocidolite)
- asbestiform tremolite

Examples of other forms of amphibole that can occur naturally in the asbestiform habit but have generally not been used in commercial products include winchite, richterite, and fluoro-edenite.

2.2 Particle Size Variability

Not all asbestos fibers are of the same size. Individual fibers may vary in length and in width. This is important because, as noted above, it is currently suspected that the cancer potency of asbestos may be influenced by the size of the fiber. In general, chrysotile fibers tend to be about 0.02 um to 0.4 um in diameter, while amphibole fibers are somewhat thicker, generally in the 0.1 to 1 um range. The length of the fibers depends on the source of the asbestos and on the degree to which the ore has been processed. Fibers may range in length from less than 0.5 um to well over 100 um. Figure 2-1 provides two examples of particle size data for asbestos particles in workplace air at factories that used chrysotile to make friction products and in factories that used amphibole (amosite) to make insulation (Dement and Harris 1979).

2.3 Measurement Techniques for Air Samples

Most methods for the analysis of asbestos are based on microscopic techniques. This requires an analyst to inspect the appearance and properties of the particles in a sample in order to identify which are asbestos. There are a range of different microscopic techniques that can be used to measure asbestos. Because this report is concerned with inhalation exposures of workers in the workplace, the following discussion is limited to methods that have been used by industrial hygienists and epidemiologists for collecting and analyzing asbestos that is present in workplace air samples. This includes the following:

- Midget impinger coupled with ordinary light microscopy
- Membrane filter coupled with phase contrast microscopy (PCM)
- Membrane filter coupled with transmission electron microscopy (TEM)

Midget Impinger

In the past, the most common technique for measuring the amount of asbestos in workplace air was the midget impinger method. Midget impingers are glass containers that draw air through

water or isopropyl alcohol, trapping airborne particles in the liquid. An aliquot of the liquid is placed in a shallow cell and the particles are allowed to settle. Examination of the settled particles is performed using an ordinary light microscope with 100x magnification (Ayer et al. 1965, Gibbs 1994). Concentrations are reported in units of million particles per cubic foot (mppcf) (Ayer et al. 1965, Gibbs 1994).

A number of limitations are associated with the use of the midget impinger technique for asbestos analysis. First, the method has poor ability to collect and detect fibers thinner than about 0.75 μm (Ayer et al. 1965, Gibbs and Lachance 1974, Lyons 1992). Second, particles are not classified based on morphology, so there is no distinction between ordinary dust particles and fibrous materials. Third, no data are collected on the properties of the particles, so it is not possible to distinguish asbestos from non-asbestos, or to distinguish between different mineral forms of asbestos. Because of these limitations, data from midget impingers provide only a crude estimate of the level of asbestos in air, with no information on type or particle size distribution.

Phase Contrast Microscopy (PCM)

At present, the most common technique for measuring asbestos in air is phase contrast microscopy (PCM). In this technique, air is drawn through a filter and airborne particles become deposited on the face of the filter. The filter is then examined using a phase contrast microscope. Light that passes through a particle such as an asbestos fiber becomes delayed (“out of phase”) compared to light passing next to the particle. This difference in phase between light passing through a particle and near a particle is used to increase the contrast (visibility) of the particle, which allows visualization of structures that otherwise would be very difficult to observe under ordinary light microscopy. The limit of resolution of PCM is about 0.25 μm , so particles thinner than this are generally not observable.

A key limitation of PCM is that particle discrimination is based only on size and shape. Because of this, it is not possible to classify asbestos particles by mineral type, or even to distinguish between asbestos and non-asbestos particles. Consequently, structures that are counted by PCM may include a variety of naturally occurring non-asbestos minerals that may occur in the form of long thin structures, as well as non-mineral particles such as animal hair and synthetic fibers. This tends to overestimate the true concentration of asbestos, especially in non-industrial settings. Conversely, PCM may also tend to underestimate the true asbestos content of a sample since particles that are thinner than 0.25 μm are generally too thin to be observed.

One common method for the application of PCM to the analysis of asbestos in air is NIOSH Method 7400. This method provides a full description of how samples should be collected,

prepared and examined. Under NIOSH 7400, a structure is defined as any particle more than 5 μm in length with an aspect ratio $\geq 3:1$. In general, complex particles (bundles, clusters) are counted as single particles, unless the individual components can be clearly identified (by observing both ends of each individual fiber). Results are generally reported in units of PCM structures per cubic centimeter (f/cc) of air.

Transmission Electron Microscopy (TEM)

Transmission electron microscopy (TEM) utilizes a high energy electron beam rather than a beam of light to irradiate the sample, and this allows operation at higher magnification (typically about 15,000x) and hence visualization of structures much smaller than can be seen under light microscopy. In addition, most TEM instruments are fitted with one or both of two supplemental accessories that allow a more detailed characterization of a particle than is possible under light microscopy:

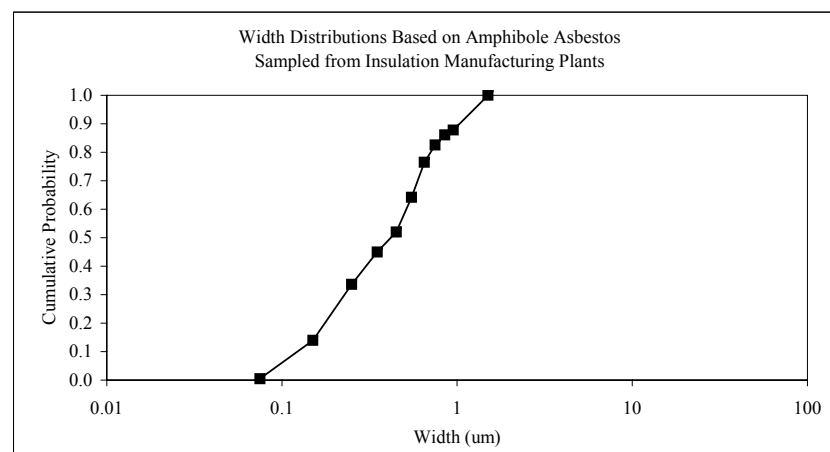
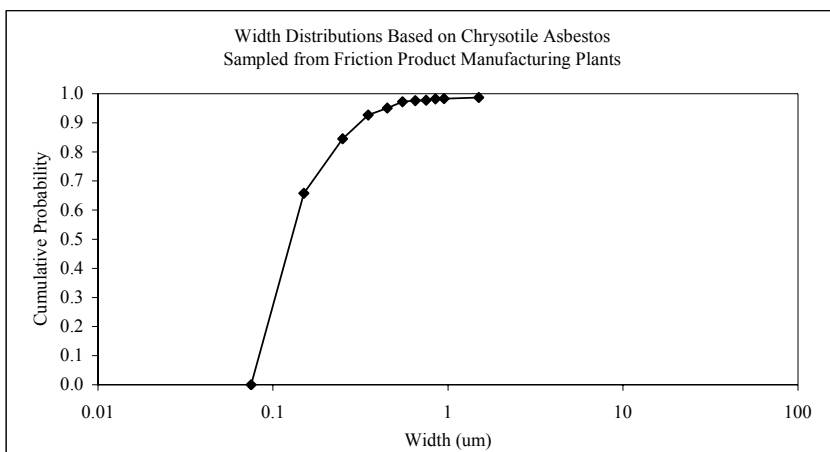
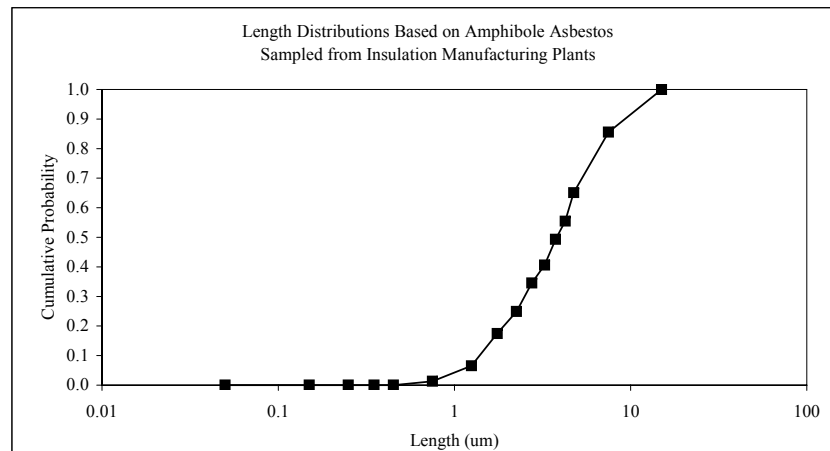
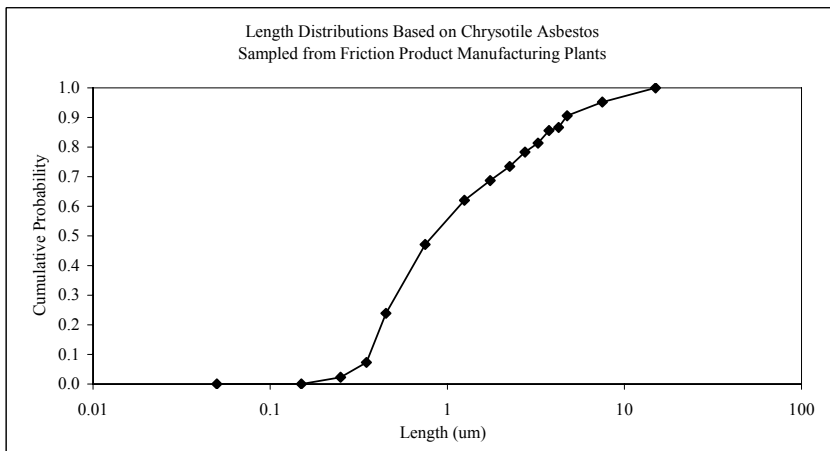
EDS (Energy dispersive spectroscopy) provides data on the elemental composition of each particle being examined. This makes it possible to distinguish organic particles from mineral particles, and also allows for distinguishing between different types of minerals.

SAED (selected area electron diffraction) provides the x-ray diffraction pattern for each particle. This information is helpful in distinguishing organic from mineral particles, and in classifying the type of asbestos (e.g. chrysotile vs. amphibole).

A variety of different methods have been developed for use of TEM to analyze asbestos, including ISO 10312 (ISO 1995), AHERA (USEPA 1987), NIOSH 7402 (NIOSH 1994) and Yamate et al. (1984). These methods differ from each other mainly in the counting rules that specify the minimum length, width and aspect ratio requirements for counting a particle, and in the strategy for dealing with complex structures (bundles, clusters, matrix particles).

When TEM is used to estimate the concentration of particles in a sample that would have been counted by PCM, these particles are referred to as PCM-equivalent (PCME).

FIGURE 2-1. EXAMPLE PARTICLE SIZE DISTRIBUTIONS



Source: Dement and Harris (1979)

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3.0 OVERVIEW OF ANIMAL STUDIES

As noted above, the approach proposed in this document for estimating bin-specific potency factors is based on data from human epidemiological studies only, and does not incorporate data from animal studies. This is because human exposure-response data are generally preferred over other types of data (e.g., animal exposure-response data) when developing quantitative risk models for use in predicting cancer risk in exposed humans (USEPA 2005), since use of human data avoid the need to extrapolate dose-response relationships between organisms (animals to human), and because uncertainty due to potential differences in toxicokinetics and pharmacodynamics between animals and humans is reduced. However, data from animals are an important component of the overall database on asbestos toxicity, and the following section provides an overview of this key area.

3.1 Study Descriptions

A large number of studies have been performed in animals to identify the effects of asbestos on the respiratory tract, and to investigate how those effects depend on the amount and type of asbestos exposure. Useful summary reports include ATSDR (2001, 2004), IARC (1977), and IPCS (1986, 1998). A brief summary of the some of the most important studies and findings is presented below.

Intrapleural Implantation and Intraperitoneal Injection Studies

Direct intrapleural implantation or intraperitoneal injection of various types of asbestos and other fibrous materials has been shown to induce increased incidences of mesothelioma-like tumors in a number of studies with rats and hamsters (for more complete reviews see ATSDR 2001, 2004; IARC 1977; IPCS 1986, 1998; Pott et al. 1987; Stanton and Wrench 1972; Stanton et al. 1977, 1981; USEPA 1986, Aeolus 2003). Results from these types of experiments provide evidence that physical dimensions are important determinants of toxicity from fibrous materials, including asbestos. For example, results from a series of 72 intrapleural application rat experiments with various types of fibrous materials (several types of amphibole asbestos and several non-asbestos fibrous materials) in hardened gelatin were used to explore correlations between carcinogenic response and particles of varying size dimensions (length and width) and mineralogical type (Stanton et al. 1981). By applying a wide range of fibers of differing types and physical dimensions at a common mass dose of the materials (40 mg), these investigators obtained a wide range in the incidences of rats that developed mesotheliomas (0-100%) and characterized the dimensions of fibrous structures in the tested materials using TEM. These results allowed statistical analyses of possible relationships between categories of fiber size and fiber types with the incidence of carcinogenic response. From this analysis, Stanton et al. (1981) concluded that

the carcinogenicity of the tested fibrous materials depended more on physical dimensions than mineralogical properties. The analysis indicated that the best correlation between cancer incidence and concentration was for structures with diameters <0.25 μm and lengths >8 μm , and that correlations diminished with size categories of increasing widths and decreasing lengths.

Berman et al. (1995) noted that there are several limitations to these studies that may limit confidence in the conclusion that mineralogy does not strongly influence the carcinogenic response to fibrous materials in animals. This includes limitations in the ability to produce samples composed of uniform fibers, limitations in the precision of the ranges of the sizes of structures in the various materials, and potential errors in the methods used to relate fiber counts to sample mass. In addition, it should be noted that implantation studies bypass any effects of particle size on lung deposition patterns, and use of hardened gelatin for implantation may have altered fiber clearance patterns. Thus, results from this type of study may not be fully applicable to inhalation exposures.

Inhalation Studies

As reviewed by ATSDR (2001) and IPCS (1986, 1998), studies from several groups of investigators have reported increased incidence of lung cancer in rats following chronic (1-2 years) inhalation exposure to chrysotile, amosite, crocidolite, anthophyllite, or tremolite. Likewise, mesotheliomas have been observed in rats following 1-2 years of inhalation exposure to tremolite, amosite, anthophyllite, crocidolite, or chrysotile, and in baboons following exposure to amosite or crocidolite for up to 4 years (see Table 3-1). These studies provide consistent evidence that chronic inhalation exposure to several types of asbestos can induce lung tumors and/or mesotheliomas in at least two different animal species.

3.2 Relative Potency Evaluations

Of the animal studies that have been reported in the literature, the most useful for investigating the relative potency of differing asbestos types is a series of experiments conducted by Davis et al. (1978, 1980, 1985, 1986a, 1986b) and Davis and Jones (1988). These studies all utilized a common protocol in which groups of about 40 male AF/HAN rats were exposed by inhalation for 7 hours per day, 5 days per week for 224 days over 1 year and then observed for at least another year. A range of different test materials were evaluated, including crocidolite, Korean tremolite, four types of chrysotile, and three types of amosite. Each type of asbestos was tested at an airborne concentration of 10 mg/m^3 ; several other concentrations were tested for some of the asbestos types. Table 3-2 summarizes the cancer findings from these studies.

The original characterization of exposure materials in the studies by Davis et al. did not include comprehensive characterization of the distribution of the length and width of the suspended structures and did not include a count of structures thinner than 0.2 μm . Because of these limitations, archived samples of the original stock samples were used to regenerate asbestos dust clouds (using the same equipment, procedures, and personnel as in the original studies) from which samples were taken and characterized more fully using TEM techniques (Berman et al., 1995). The TEM techniques provided detailed information on the mineralogy, structure type (e.g., fiber, bundle, cluster, or matrix), size (length and width) and complexity (i.e., number of identifiable components of a cluster or matrix) of the suspended material.

Using these detailed particle size and type data, Berman et al. (1995) conducted statistical analyses of the rat lung tumor incidence data in Table 3-1 to identify which size categories were best correlated with increased incidence of disease. No mathematical model with a single explanatory variable provided an adequate description of the lung tumor incidence. In contrast, multivariate models which included concentrations of particles in different size categories provided an adequate description of the lung tumor incidence data. Fitting began with a model with 5 length categories (<5, 5-10, 10-20, 20-40, > 40 μm) and five thickness categories (<0.15, 0.15-0.3, 0.3-1.0, 1.0-5.0, and > 5 μm). By eliminating bins that had potency factors that were not statistically different from zero and combining bins that were not statistically different from each other, Berman et al. (1995) developed a final model with 3 length categories (<5, 5-40, and >40 μm) and two width categories (<0.3 and > 5 μm). The relative bin-specific potency factors for this model are summarized below:

Relative Potency Estimates Based on Rat Data

Width (μm)	Length (μm)		
	< 5	5-40	> 40
≤ 0.3	0	0.0017	0.853
≥ 5.0	0	0	0.145

Adapted from Berman (1995)

As seen, fibers longer than 40 μm accounted for 99.8% of the total potency, with most of that (85%) being contributed by fibers ≤ 0.3 μm in diameter. Only a small contribution (<0.2%) was provided by fibers 5-40 μm in length, and fibers less than 5 μm did not contribute any observable potency. Further analysis of the available data in the context of the best-fitting model could not discern a difference in the lung-cancer-inducing potency of chrysotile and amphibole. Statistical analysis of the mesothelioma data indicated that amphibole potency was greater than chrysotile potency for equivalent size and shape particles (Berman et al. 1995).

3.3 Potential Limitations in Extrapolation of Animal Data to Humans

In considering the results of studies on the carcinogenicity of asbestos in animals, it is important to recognize that there are a number of anatomical and physiological differences between rodents and humans that may limit the relevance of the animal data as the basis for development of quantitative cancer risk models for humans. These differences include the following:

- Differences in the respiratory system of rats and humans may influence the depositional pattern of inhaled particles. For example, the rat lung possesses a different branching pattern than the human lung, and the bronchial tree of the rat is also physically smaller than that of man. In addition, rats are obligate nose-breathers, while humans may also breathe through the mouth. As a consequence of these differences, fibers up to 1.5 μm in diameter that are unlikely to deposit in the lungs of rodents may deposit in the lungs of humans (Hofmann et al. 1989, ATSDR 2001). Mathematical models which incorporate species differences in physiological and anatomical variables (e.g., airway volume, airway surface area, tidal volume, breathing frequency) have been developed to predict the deposition and retention of inhaled fibrous particles in rats and humans (Yu et al. 1994, 1995, 1996, 1998a, 1998b). Predictions from these models illustrate several important differences in pulmonary deposition of fibrous particles between rats and humans:
 1. the fraction of inhaled fibrous particles (with lengths between ~ 1 and $100 \mu\text{m}$ and diameters $< 1 \mu\text{m}$) deposited in the pulmonary region of the lung can be 2- to 5-fold higher in rats than humans;
 2. lung burdens can be 5-10 times higher in rats than in humans for any given exposure;
 3. lung burdens per lung surface area are higher in rats than in humans; and
 4. the mean size dimensions (length and diameter) of fibrous particles deposited in the lungs of rats are smaller than those deposited in human lungs (ATSDR 2004, Yu et al. 1995).
- The size of alveolar macrophages relates directly to their capacity to phagocytize fibrous particles (and thus clear them from the lung). Human alveolar macrophages are typically larger (mean diameter about $21 \mu\text{m}$) than alveolar macrophages from laboratory species such as the rat, Syrian Golden hamster, or cynomolgus monkey (typical diameter about $13\text{-}15 \mu\text{m}$) (Krombach et al. 1997). Consequently, human macrophages are likely able to engulf, sequester or clear some types of longer fibers more efficiently than rodent macrophages, and this may influence the magnitude of the carcinogenic effect of the inhaled particles.

- Differences in life-spans between rats and humans might result in differences in response to different mineral types. That is, fibers have a more limited time period for dissolution or other forms of clearance in rat lungs (~2 years) than in the lungs of humans with a life span of ~70 years. A longer residence time in human lung tissue may allow the less durable fiber types to dissolve and clear more completely, potentially influencing the biological responses. Conversely, more durable fiber types can have a longer residence time in human lung tissue than in rat lung tissue, allowing a greater time for the development of adverse effects. A longer residence time also allows a longer period for fiber bundles to break down into individual fibrils thus allowing a higher quantity of fibers per area (dose) in the human lungs. This does not take into account other potential species differences in response to asbestos fibers including the time-dependence requirement for cell initiation and promotion of cancer.

Because of these differences, quantitative findings on the relative potency of various sizes and types of asbestos in animals should be extrapolated to humans only with caution.

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TABLE 3-1.
SUMMARY OF ANIMAL CHRONIC INHALTION STUDIES WITH ASBESTOS

Reference	Species	Exposure	Asbestos type	Lung Cancer	Meso-thelioma
Wagner et al. 1974	Wistar rat	10 mg/m ³ , 7 hours/day, 5 days/week for 24 months	Amosite	+	-
			Anthophyllite	+	+
			Crocidolite	+	-
			Chrysotile	+	+
			Chrysotile	+	-
Davis et al. 1978	AF/HAN rat	0, 10 mg/m ³ , 7 hours/day, 5 days/week for 1 year, then observed for up to 24 months	Chrysotile UICC	+	-
			Amosite UICC	+	-
			Crocidolite UICC	+	-
Davis et al. 1985	AF/HAN rat	As per Davis et al., 1978	Korean tremolite	+	+
Davis et al. 1986a	AF/HAN rat	As per Davis et al., 1978	Amosite long	+	+
			Amosite short	-	+
Davis and Jones 1988	AF/HAN rat	As per Davis et al., 1978	Chrysotile long	+	+
			Chrysotile short	+	+
Davis et al. 1988	AF/HAN rat	As per Davis et al., 1978	Chrysotile UICC	+	-
			Chrysotile, reduced surface charge	+	+
Lee et al. 1981	Sprague-Dawley rat	0, 30 mg/m ³ , 6 hours/day for 3 months; observed until 24 months	Amosite	+	-
LeBouffant et al. 1987	Wistar rat	0, 5 mg/m ³ , 5 hours/day, 5 days/week for 24 months	Chrysotile	+	
Smith et al. 1987	Osborne-Mendel rat	0, 7 mg/m ³ , 6 hours/day, 5 days/week for 24 months	Crocidolite	+	+
Smith et al. 1987	Syrian hamster	0, 7 mg/m ³ , 6 hours/day, 5 days/week for 24 months	Crocidolite	-	-
McConnell et al. 1994a, 1994b	F344 rat	0, 10 mg/m ³ , 6 hours/day, 5 days/week, for 24 months (chrysotile) or 9-10 months (crocidolite – and observed until 24 months)	Chrysotile	+	+
			Crocidolite	+	+
Goldstein and Coetzee 1990	Baboon	15-48 months of exposure, 6 hour/day, 5 days/week, followed by post-exposure periods of 2-7 years: amosite: 7 mg (respirable)/m ³ ; crocidolite: 13.5 mg (respirable)/m ³	Amosite	-	+
			Crocidolite	-	+
Webster et al., 1993, Hiroshima et al. 1993	Baboon	6 hours/day, 5 days/week to concentrations between 1100-1200 fibers/cm ³ for 242-898 days, followed by observation until spontaneous death	Amosite	-	+

TABLE 3-2.
TUMOR INCIDENCE DATA FOR RATS EXPOSED BY INHALATION TO
SEVERAL ASBESTOS TYPES IN EXPERIMENTS CONDUCTED BY
DAVIS AND COWORKERS

Asbestos type	Concentration (mg/m ³)	Number of rats	Number of lung tumors	Number of mesotheliomas
Chrysotile UICC-A	2	42	8	1
	10	40	15	0
	9.9	36	14	0
Chrysotile UICC-A ^a	9.9	39	10	1
Chrysotile Long	10	40	20	3
Chrysotile Short	10	40	7	1
Chrysotile WDC Yarn	3.6	41	18	0
Amosite UICC	10	43	2	0
Amosite Long	10	40	11	3
Amosite Short	10	42	0	1
Crocidolite UICC	4.9	43	2	1
	10	40	1	0
Tremolite Korean	10	39	18	2
None (Control)	0	20	0	0
	0	36	0	0
	0	61	2	0
	0	64	2	0
	0	47	2	0

^a Surface charge reduced

Source: Berman et al. (1995)

4.0 OVERVIEW OF HUMAN STUDIES

The adverse effects of asbestos exposure in humans have been the subject of a large number of studies and publications. The following section is intended to provide a brief overview of the main types of adverse health effects that have been observed in humans. More detailed reviews of the literature are provided in IARC (1977), WHO (2000), and ATSDR (2001, 2004).

4.1 Noncancer Effects

Asbestosis

Asbestosis is a chronic pneumoconiosis associated with inhalation exposure to asbestos. It is characterized by the gradual formation of scar tissue in the lung parenchyma. Initially the scarring may be minor and localized within the basal areas, but as the disease develops, the lungs may develop extensive diffuse alveolar and interstitial fibrosis (American Thoracic Society 1986).

Build-up of scar tissue in the lung parenchyma results in a loss of normal elasticity in the lung which can lead to the progressive loss of lung function. The initial symptoms of asbestosis are shortness of breath, particularly during exertion. People with fully developed asbestosis tend to have increased difficulty breathing that is often accompanied by coughing or rales. In severe cases, impaired respiratory function can lead to death (American Thoracic Society 1986, 2004; ATSDR 2001).

Asbestosis is most commonly reported in populations exposed to asbestos over long periods of time and/or to high concentrations. Excess mortality attributed to asbestosis has been reported in a number of occupational cohorts (e.g., Armstrong et al. 1988, deKlerk et al. 1991, Hein et al. 2007, Peto et al. 1985, Selikoff et al. 1979, Borron et al. 1997; Coggon et al. 1995; Irwig et al. 1979; Case and Dufresne 1997), as well as several non-occupational cohorts (Luo et al. 2003, Peipens et al. 2003, Botha et al. 1986). Several studies of asbestos workers indicate that there may be a threshold fiber dose below which asbestosis will not occur (e.g., Browne 1994; Dupres et al. 1984; Sluis-Cremer et al. 1990).

Asbestosis generally takes a long time to develop, with a latency period from 10 to 20 years. Mossman and Churg (1998) suggest that latency is inversely proportional to exposure level. The disease may continue to progress long after exposure has ceased (ATSDR 2001). The progression of the disease after cessation of exposure also appears to be related to the level and duration of exposure (American Thoracic Society 2004).

Numerous studies indicate that smoking increases the development and/or progression rate for asbestosis (e.g., Browne 1994; Weiss 1984; Blanc et al. 1988; Barnhart et al. 1990; Mossman and Churg 1998).

Pleural Abnormalities

Exposure to asbestos may induce several types of abnormality in the pleura (the membrane surrounding the lungs).

- *Pleural effusions* are areas where excess fluid accumulates in the pleural space. Most pleural effusions last only several months, although they may be recurrent (Khan and Jones 2004).
- *Pleural plaques* are acellular collagenous deposits, often with calcification. Pleural plaques are the most common manifestations of asbestos exposure (ATSDR 2001, American Thoracic Society 2004).
- *Diffuse pleural thickening* is a noncircumscribed fibrous thickening of the visceral pleura with areas of adherence to the parietal pleura. Diffuse thickening may be extensive and cover a whole lobe or even an entire lung. Infolding of thickened visceral pleura may result in collapse of the intervening lung parenchyma (rounded atelectasis). Gevenois et al. (1998) and Schwartz et al. (1991) report that diffuse pleural thickening may occur as a result of pleural effusions.

Pleural effusions and plaques are generally asymptomatic, although rarely they may be associated with decreased ventilatory capacity, fever, and pain (e.g., Bourbeau et al. 1990). Diffuse pleural thickening can cause decreased ventilatory capacity (Baker et al. 1985, Churg 1986, Jarvholm and Larsson 1988). Severe effects are rare, although Miller et al. (1983) reported on severe cases of pleural thickening that lead to death.

In contrast to asbestosis (which typically develops following long-term or high exposures), changes in the pleura may occur after only low level or intermittent exposures (Peacock et al. 2000, Khan and Jones 2004). Pleural abnormalities resulting from inhalation exposure to asbestos have been documented in numerous occupational cohorts (e.g., Ehrlich et al. 1992, Amandus et al. 1987, Anton-Culver et al. 1989, Baker et al. 1985, Bresnitz et al. 1993, Jarvholm et al. 1986, McDonald et al. 1986, Ohlson and Hogstedt 1985), as well as in family members and household contacts of asbestos workers (e.g., Anderson et al. 1976, 1979) and in environmentally-exposed populations (e.g., Churg and DePaoli 1988, Jarvholm et al. 1986, Luo et al. 1992).

The latency period for pleural abnormalities is usually about 10 to 40 years (American Thoracic Society 2004), although pleural effusions may occasionally develop as early as one year after first exposure (Epler and Gaensler 1982).

Other Noncancer Effects

Chronic laryngitis

Kambic et al. (1989) and Parnes (1990) reported increased incidence of laryngitis among a group of workers with high chronic cumulative exposure to asbestos. These studies indicate that asbestos may act as an irritant on the upper airways.

Cardiovascular effects

Cor pulmonale (right-sided heart failure) may occur following decreased blood flow through the pulmonary capillary bed as a result of fibrosis of the lung (ATSDR 2001). Davies et al. (1991) reviewed a case report of a man with pleural thickening and plaques who developed acute pericarditis and a pericardial effusion, and another case report of two men who died from constrictive pericarditis associated with pleural effusions and diffuse pleural thickening.

Retroperitoneal effects

Retroperitoneal fibrosis, also referred to as Ormond's disease, is a rare condition that refers to a fibrous mass in the back of the abdomen that blocks the flow of urine from the kidneys to the bladder. Although the etiology of retroperitoneal fibrosis is unknown in most cases (Sauni et al. 1998), some cases are associated with exposure to asbestos (e.g., Boulard et al. 1995, Maguire et al. 1991). For example, in a review of 13 patients with idiopathic retroperitoneal fibrosis, Sauni et al. (1998) found that seven had previous occupational exposure to asbestos, and four had asbestos-related pleural abnormalities and lung opacities in their chest radiographs. Likewise, Uibu et al. (2004) reported a strong association between retroperitoneal fibrosis and asbestos exposure in a case-control study.

Immunological effects

Depressed cell-mediated immunity has been noted in a number of epidemiology studies of workers suffering from asbestosis (e.g. deShazo et al. 1988; Gaumer et al. 1981; Kagan et al. 1977; Lange et al. 1986). The reported immunological changes include alterations in lymphocyte and leukocyte distributions, impaired natural killer (NK) cells, and high levels of

autoantibodies (which may lead to rheumatoid arthritis) (Kubota et al. 1985; Tsang et al. 1988; deShazo et al. 1988; Gaumer et al. 1981; Kagan et al. 1977; Lange et al. 1986; Anton-Culver et al. 1988; Warwick et al. 1973; Zerva et al. 1989). In a more recent evaluation, Noonan et al. (2006) found increased risk of systemic autoimmune diseases (systemic lupus erythematosus, scleroderma, or rheumatoid arthritis) among people who had occupational or other high level exposure to asbestos-contaminated vermiculite. However, these data are not sufficient to determine if the immunological changes are a direct result of asbestos on the immune system, or if the effects are secondary to the occurrence of other asbestos-related diseases.

4.2 Cancer Effects

There are many epidemiological studies that have reported increased mortality from cancer in asbestos workers, especially from lung cancer and mesothelioma. Based on these findings, and supported by extensive carcinogenicity data from animal studies (see Section 3, above), EPA has classified asbestos as a known human carcinogen (USEPA 1993).

Lung Cancer

Exposure to asbestos is associated with increased risk of developing all major histological types of lung carcinoma (adenocarcinoma, squamous cell carcinoma, and oat-cell carcinoma) (ATSDR 2001). The latency period for lung cancer generally ranges from about 10 to 40 years (ATSDR 2001). Early stages are generally asymptomatic, but as the disease develops, patients may experience coughing, shortness of breath, fatigue, and chest pain. Most lung cancer cases result in death.

The strongest evidence for an increased risk of lung cancer as a consequence of asbestos exposure comes from studies of workers exposed to asbestos under occupational conditions (e.g., Selikoff et al. 1979; Case and Dufresne 1997; Huilan and Zhiming 1993; Armstrong et al. 1988; Dement et al. 1983b, 1994; Sluis-Cremer 1991; Wignall and Fox 1982; Meurman et al. 1974, 1994; Kleinfeld et al. 1974; Peto et al. 1985). However, increased risk of lung cancer has also been reported among household contacts and family members of asbestos workers (e.g., Magnani et al. 1993), and from environmental exposures to asbestos (e.g., Luo et al. 2003, Botha et al. 1986).

The risk of developing lung cancer from asbestos exposure is substantially higher in smokers than in non-smokers (Selikoff et al. 1968, Doll and Peto 1985, ATSDR 2001, NTP 2005). Although data are limited, it appears that the interaction between smoking and asbestos exposure is approximately multiplicative (Selikoff et al. 1968, Lee 2001, Henderson et al. 2004, ATSDR 2001, Hammond et al. 1979, Kamp et al. 1992, Mossman et al. 1996). Mossman et al. (1996)

propose that smoking may impede the clearance of asbestos from the respiratory tract or possibly influence bioreactivity and penetration of the fibers into tracheal epithelial cells.

Mesothelioma

Mesothelioma is a tumor of the thin membrane that covers and protects the internal organs of the body including the lungs and chest cavity (pleura), and the abdominal cavity (peritoneal). The latency period for mesothelioma is typically around 20-40 years (Lanphear and Buncher 1992, ATSDR 2001, Mossman et al. 1996, Weill et al. 2004). By the time symptoms appear, the disease is most often rapidly fatal (British Thoracic Society 2001).

Mesothelioma is a rare disease in the general population, but a number of studies have reported increased incidence in populations of workers exposed occupationally to asbestos (e.g., Selikoff et al. 1979; Piolatto et al. 1990; McDonald et al. 1982; Berry 1997; Selcuk et al. 1992; Tulchinsky et al. 1992, 1999). Increased incidence has also been reported in persons with no known occupational exposure to asbestos, but who lived with a person that worked with asbestos (e.g., Anderson et al. 1976; Inase et al. 1991; Magee et al. 1986; Magnani et al. 1993; McDonald and McDonald 1980; Voisin et al. 1994), and in populations with environmental exposure to asbestos (Luo et al. 2003, Hansen et al. 1998, Rees et al. 1999, Botha et al. 1986).

Other Cancers

Gastrointestinal cancer

NAS (2006) reviewed evidence regarding the role of asbestos in gastrointestinal cancers primarily following occupational exposures (these are assumed to be primarily by the inhalation route). NAS concluded that data are “suggestive but insufficient” to establish that asbestos exposure causes stomach (based on 42 occupational cohorts and five case-control studies) or colorectal cancer (based on based on 41 occupational cohorts and 11 case-control studies). Data on esophageal cancer (based on 25 cohort populations and three case-control studies) are mixed and were regarded as “inadequate to infer the presence or absence of a causal relationship to asbestos exposure”.

Data on risks of gastrointestinal cancer following ingestion-only exposure are more limited. Conforti et al. (1981) found a significant correlation ($p < 0.01$) between the presence of chrysotile asbestos in drinking water supplies in the San Francisco Bay Area and the risk of esophageal, stomach, pancreatic, and digestive tract cancers in males and females that had been exposed to the drinking water. Similarly, Kjaerheim et al. (2005) found increased risks of stomach cancer and to a lesser degree colon cancer in lighthouse keepers in Norway who drank rainwater

collected from asbestos-cement tiled rooftops. WHO (1996) concluded that data are not adequate to support the hypothesis that an increased cancer risk is associated with the ingestion of asbestos in drinking water.

Laryngeal and Pharyngeal Cancer

Goodman et al. (1999) performed a meta-analysis of data from studies of occupationally exposed workers and reported a standardized mortality ratio (SMR) for laryngeal cancer of 1.57 (95% CI 0.95-2.45). Kraus et al. (1995) and Browne and Gee (2000) reviewed the data and concluded that evidence of a causal relationship between asbestos exposure and laryngeal cancer was weak, while a more recent review by NAS (2006) concluded that the data were “sufficient to infer a causal relationship between asbestos and laryngeal cancer” based on the consistency of increased risk seen across epidemiology studies (35 cohort studies and 18 case-control studies). Pira et al. (2005) and Piolatto et al. (1990) reported increased risk of pharyngeal cancer among asbestos workers, but neither study accounted for confounding factors or reported dose-response data. NAS (2006) concluded that data are “suggestive but not sufficient to infer a causal relationship between asbestos exposure and pharyngeal cancer”.

Renal Cancer

Excess deaths from kidney and bladder cancer among persons with known exposure to asbestos have been reported by Selikoff et al. 1979, Enterline et al. 1987, and Puntoni et al. 1979. A review by Smith et al. (1989) evaluated these studies in addition to studies reporting the presence of asbestos fibers in human kidneys and urine (Patel-Mandlik 1981, Auerbach et al. 1980). Based on these data, this review concluded that asbestos should be regarded as a probable cause of human kidney cancer.

4.3 Role of Fiber Type

Increased incidence of asbestos-related diseases (both cancer and noncancer) has been reported for each of the predominate types of asbestos used in the workplace. This includes chrysotile (Liddell et al. 1997; Hein et al. 2007; Huilan and Zhiming, 1993; Albin et al. 1996), amosite (Seidman et al. 1986; Levin et al. 1998), crocidolite (deKlerk et al. 1991, 1996; Sluis-Cremer 1991; Armstrong et al. 1988), tremolite (McDonald et al. 1986, 2004; Albin et al. 1996) and anthophyllite (Sluis-Cremer 1991; Meurman et al. 1974, 1994).

While all types of asbestos have been shown to induce asbestos-related disease, there is considerable debate regarding the relative potencies of the various mineral types. In particular, the carcinogenic potential of chrysotile asbestos relative to amphibole asbestos is a controversial

issue. Based on lung burden studies, mechanistic studies, and some epidemiological data, some researchers (e.g., Hodgson and Darnton 2000, Mossman et al. 1990, McDonald and McDonald 1997) propose that amphibole fibers are more potent inducers of mesothelioma and potentially of lung cancer than chrysotile. This assertion has become known as the “amphibole hypothesis” which, in its strongest form, claims that pure chrysotile (i.e., without any associated amphibole fiber) would present little or no carcinogenic risk. However, the amphibole hypothesis is strongly disputed by other researchers. For example, Stayner et al. (1996) conducted a critical review of the supporting arguments suggesting that chrysotile asbestos has a lower carcinogenic potency than amphiboles. These authors found strong evidence from toxicological and epidemiological studies that occupational exposure to chrysotile asbestos is associated with an increased risk of both lung cancer and mesothelioma, and concluded that while chrysotile may be less potent than some amphiboles for inducing mesothelioma, the available evidence does not support a similar conclusion for lung cancer.

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5.0 OVERVIEW OF MODE OF ACTION

The mode of action by which asbestos causes disease is not fully understood. Useful reviews include ATSDR (2001, 2004), IARC (1996), Mossman et al. (2007), and Manning et al. (2002). A brief summary of the proposed modes by which asbestos may act to induce pulmonary disease is presented below.

5.1 Noncancer Mode of Action

Alveolar macrophages are one of the key defense mechanisms employed by the lung to protect itself against injury from inhaled foreign bodies, including asbestos particles. Alveolar macrophages may have a wide range of responses to asbestos particles that are deposited in the lung, including: a) phagocytosis of the particle, b) secretion of a range of reactive oxygen species (ROS) and reactive nitrogen species (RNS) as well as antimicrobial peptides and enzymes, and c) secretion of a wide array of cytokines, chemokines, growth factors and metabolites that initiate inflammatory responses and recruit activated neutrophils into the alveolar spaces. The reactive species and the inflammatory response may then result in loss of epithelial cells and deposition of collagen by fibroblasts (Davis and Jones 1988; Davis et al. 1986a; Lasky et al. 1996). Of particular interest is tumor necrosis factor- α (TNF- α), a growth factor suggested to be an important mediator of pulmonary fibrogenesis (Mossman and Churg 1998; Churg et al. 2000; Driscoll et al. 1995). Increased levels of TNF have been found in both animals exposed to crocidolite asbestos (Zhang et al. 1993; Driscoll et al. 1995), and humans exposed to asbestos in the workplace (Zhang et al. 1993). Cell injury and the development of fibrogenesis may be mediated, at least in part, by activation of tumor suppressor gene p53 gene expression that leads to mitochondrial damage and apoptosis of alveolar epithelial cells (Panduri et al. 2006).

There are two properties of an asbestos particle that may influence the nature and severity of this response. First is the length of the particle. When the particle is too long to be fully engulfed by the alveolar macrophage, the macrophage will tend to continuously generate and release ROS and RNS as well as cytokines of inflammatory cells (Hansen and Mossman 1987; Perrett 1995; Rom et al. 1991; Kamp et al. 1992; Kinnula 1999; Quinlan et al. 1998), all of which may tend to injure nearby lung cells. Second is the amount of iron present in the asbestos particle. Iron is a normal constituent of many types of asbestos (see Section 2). Iron can catalyze the formation of the highly reactive hydroxyl radical species (HO \bullet) from less-reactive ROS such as H₂O₂ and O₂⁻ within target cells (e.g., lung cells, mesothelial cells). Studies in animals suggest that iron-catalyzed hydroxyl radicals play an important role in the development of asbestosis (Mossman and Churg 1998; Kamp and Weitzman 1997).

5.2 Mode of Carcinogenic Action

Although asbestos is a well-established carcinogen, the underlying mode of carcinogenesis is unclear. Some observations that suggest potential modes of action are summarized briefly below.

5.2.1 Genotoxicity and Mutagenicity

In Vivo Observations

An increased incidence of DNA double-strand breaks and DNA fragmentation was observed in white blood cells from workers with known occupational exposure to asbestos compared to persons with no known asbestos exposure (Marczynski et al. 1994, 2000a, 2000b). Increases in the frequency of sister chromatid exchange (SCE) in human blood lymphocytes from asbestos workers compared to control populations have been reported by several groups (e.g., Lee et al. 1999; Rom et al. 1983; Fatma et al. 1991). Fatma et al. (1991) noted that the frequency of chromosomal aberrations in human blood lymphocytes was significantly higher in smokers with previous asbestos exposure compared to non-smokers with previous asbestos exposure.

Hansteen et al. (1993) reported chromosomal aberrations in cells from a pleural effusion of an asbestos worker with malignant mesothelioma. Gene mutations have been reported in human lung cells collected from lung cancer patients with known previous exposure to asbestos (e.g., Nelson et al. 1998; Wang et al. 1995; Nuorva et al. 1994; Guinee et al. 1995). Tammilehto et al. (1992) and Tiainen et al. (1989) reported a correlation between asbestos lung burden and chromosomal abnormalities in human mesothelial cells collected from patients with confirmed malignant mesothelioma, although Segers et al. (1995) did not find chromosomal aberrations in human mesothelioma cells from 13 mesothelioma patients.

In Vitro Observations

Chromosomal aberrations have been reported in a variety of mammalian cells exposed to asbestos, including human mesothelial, lymphocyte, and amniotic fluid cells (e.g., Dopp and Schiffmann 1998; Dopp et al. 1997; Emerit et al. 1991; Korkina et al. 1992; Olofsson and Mark 1989; Pelin et al. 1995; Takeuchi et al. 1999; Valerio et al. 1980), Chinese hamster ovary and Syrian hamster embryo cells (ATSDR 2001), and rat mesothelial cells (Yegles et al. 1993). DNA strand breakage has been reported in human mesothelial cells exposed to asbestos (Ollikainen et al. 1999), and a dose-dependent increase in oxidative DNA damage in the presence of crocidolite fibers has been described in a human-hamster hybrid cell line by Xu et al. (1999).

Potential Mechanisms of Genotoxicity

The cellular and molecular mechanisms by which asbestos may cause genotoxicity are not known, but several potential mechanisms have been proposed.

Direct interaction of asbestos fibers with cellular macromolecules

A number of studies indicate that asbestos fibers may penetrate into cells and disturb the mitotic spindle, thereby interfering with cytokinesis and causing chromosomal damage. This has been reported in human mesothelioma cells or cell lines (Ault et al. 1995; Malorni et al. 1990), and Syrian hamster embryo cells (Ault et al. 1995; Broaddus 2001; Hesterberg and Barrett 1985; Jensen and Watson 1999). Barrett et al. (1989) proposed that interference with chromosome segregation may in part account for chromosome deletions seen in cell lines of human mesothelioma cells exposed to asbestos fibers.

Damage from ROS and RNS

Reactive species (ROS, RNS) have widely been implicated in the mechanism of carcinogenesis (O'Brien et al. 2005; Klaunig and Kamendulis 2004; Klaunig et al. 1998). Although detailed cellular mechanisms are not certain, ROS and RNS generated in the presence of asbestos fibers can cause mutagenic oxidative lesions that may contribute to the initiation of lung cancers or mesotheliomas (Kamp and Mossman 2002). In particular, ROS appears to play an important role in DNA damage and mutagenicity (Lund and Aust 1992; Shukla et al. 2003; Xu et al. 1999, 2007; Kamp et al. 1992). RNS may also cause nitrosylation of proteins and DNA (Kamp and Weitzman 1999; Kinnula 1999).

5.2.2 Stimulation of Cell Proliferation

Asbestos may also act as a promoter by simulating the growth of cells in the lung. Marsh and Mossman (1991) demonstrated that exposure of hamster tracheal epithelial cells to asbestos resulted in increased expression of the gene for ornithine decarboxylase, an enzyme that is essential in cell proliferation. *In vitro* data in rodent mesothelial and tracheal epithelial cells, and *in vivo* data in lung tissue of rats inhaling asbestos, suggest that asbestos fibers also activate “early response” proto-oncogenes (Heintz et al. 1993, Quinlan et al. 1994). These genes play a role in the initiation of DNA synthesis, and the ability of asbestos to induce proto-oncogenes suggest that asbestos deposition in the lung tissue or pleura may serve as a chronic source of cell proliferation (Ames and Gold 1990). Also, asbestos may alter the function of the tumor

suppressor gene p53, and this may be functionally important in the development of asbestos-induced mesothelioma (Hayashi et al. 1996; Johnson and Jaramillo 1997).

5.3 Summary

The mode of action by which asbestos induces cancer and noncancer disease in humans is not known. However, non-cancer effects appear to be related to the initiation of an inflammatory response and the release of a variety of reactive chemicals by the presence of asbestos particles in the lung. A number of studies provide evidence for a mutagenic/genotoxic mode of action for asbestos, perhaps mediated by direct interaction of fibers with cellular macromolecules and/or by damage caused by reactive chemicals that modify DNA. Asbestos may also act as a promoter to stimulate cell growth and proliferation in the lung. In summary, additional review and analysis is needed to determine a mode of action.

6.0 SUMMARY OF USEPA 1986 EVALUATION

In 1986, the USEPA used available data from published epidemiological studies of workers exposed to airborne asbestos to select risk models and derive quantitative potency factors for both lung cancer and mesothelioma (USEPA 1986). The results of this effort form the basis for the method that is currently recommended by EPA for characterization of cancer risk from inhalation exposures to asbestos (USEPA 1993). This section describes the approach that was employed by USEPA (1986).

6.1 Lung Cancer

Risk Model

For lung cancer, USEPA (1986) reviewed the available exposure-response data from epidemiological studies and determined that the data were well characterized by a relative risk model of the following form:

$$RR = \alpha (1 + KL \cdot CE_{10})$$

where:

- RR = Relative risk of lung cancer for a worker with a specified level of asbestos exposure. The value of RR measured in an epidemiological study is the ratio of the observed deaths in an exposure group divided by the expected number of deaths in that group: $RR = \text{Observed} / \text{Expected}$
- α = “Baseline” relative risk of lung cancer in unexposed members of the cohort compared to the reference population.
- KL = Lung cancer potency factor for asbestos particles (f/cc-yrs)⁻¹
- CE₁₀ = Cumulative exposure to asbestos, lagged by 10 years (f/cc-yrs).

The lag of 10-years is based both on empiric observations that the relative risk does not begin to increase for 5-10 years after exposure begins, as well as the theoretical expectation (based on the multi-stage model of carcinogenesis) that effects of an exposure require a number of years to become manifest (USEPA 1986). The value of CE₁₀ depends on the time since first exposure (T) and the duration of exposure (d) as follows:

For $T < 10$	$CE_{10} = 0$
For $10 < T < d + 10$	$CE_{10} = C \cdot (T - 10)$
For $T > d + 10$	$CE_{10} = C \cdot d$

Figure 6-1 (Panel A) shows an example of CE_{10} in an individual who is exposed to 1 f/cc beginning at age 20 and ending at age 50. As seen, CE_{10} is zero until age 30 (10 years after the start of exposure), and then increases linearly until age 60 (10 years after exposure ends). Beyond this point, CE_{10} remains constant.

Key attributes of this model are: a) the risk of lung cancer due to asbestos exposure is multiplicative with the risk of lung cancer from smoking and other causes, b) the increase in relative risk is a linear function of cumulative exposure, expressed as above, and c) the increase in relative risk does not depend on the age at first exposure.

Model Fitting

Each published epidemiological study that provided adequate data on relative risk of lung cancer as a function of cumulative exposure was fit to the linear relative risk model to derive an estimate of the lung cancer potency factor KL . All cumulative exposures were expressed in terms of PCM fibers, so the value of KL is indicated in this report as KL_{PCM} . Fitting was generally performed by weighted least squares regression, with a weight equal to the inverse of the variance of a particular data point. Figure 6-2 provides one example, based on the cohort of South Carolina textile workers studied by Dement et al. (1983). Table 6-1 summarizes the 14 study-specific KL_{PCM} values derived by USEPA 1986 using this basic approach.

Selection of a Consensus KL_{PCM} Value

As shown in Table 6-1, the study-specific KL_{PCM} values in EPA's 1986 assessment ranged from $0.01E-02$ to $6.7E-02$ (PCM f/cc-yrs)⁻¹. Geometric means were computed for different industries, as shown in Table 6-2. USEPA (1986) determined that the KL_{PCM} values associated with mining and milling were unlikely to be typical of exposures experienced in the environment, and so a value of $1.0E-02$ (PCM f/cc-yr)⁻¹ was selected as the best estimate of the KL_{PCM} for lung cancer.

6.2 Mesothelioma

Risk Model

For mesothelioma, USEPA (1986) reviewed the available data and determined that the exposure-response relationship was characterized by an absolute risk model of the following form:

$$I_m = C \cdot Q \cdot KM$$

where:

I_m = Incidence of mesothelioma in the exposed group. The value of I_m is equal to the observed number of mesothelioma deaths divided by the number of person-years of observation:

$$I_m = \text{Observed deaths} / \text{Person-years}$$

C = Concentration of asbestos in air (f/cc)

KM = Mesothelioma potency factor for asbestos particles (f/cc-yrs³)⁻¹

Q = Cumulative exposure value (yrs³), which depends on the time since first exposure (T) and the duration of exposure (d) as follows:

$$\text{For } T < 10 \quad Q = 0$$

$$\text{For } 10 < T < d + 10 \quad Q = (T-10)^3$$

$$\text{For } T > d + 10 \quad Q = (T-10)^3 - (T-10-d)^3$$

Figure 6-1 (Panel B) shows how the value of Q increases as a function of age. In this example, exposure begins at age 20 and ends at age 50. As seen, Q is zero until age 30 (10 years after the start of exposure), and then increases as a function of the cube of time. Note that the value of Q continues to increase even after exposure has ended. Also note that Q does not include the concentration term, and so is independent of exposure level.

Key attributes of this model are that incidence is a linear function of exposure concentration, and a cubic function of time since first exposure and duration of exposure. Thus, mesothelioma risk attributable to any specified level of cumulative exposure is strongly dependent on the age when exposure began. Note that the incidence of mesothelioma is assumed to be zero in the absence of asbestos exposure.

Model Fitting

The fitting approach for mesothelioma is not described in detail in USEPA (1986), but it is assumed that the approach was similar to that used for lung cancer (minimization of weighted

square errors between observed and predicted mesothelioma incidence). An example reported in USEPA (1986) is provided in Figure 6-3. As above, all cumulative exposure estimates were based on PCM, so the KM value is indicated as KM_{PCM} .

Selection of a Consensus KM_{PCM} Value

Quantitative exposure-response data that were adequate for fitting to the risk model were available for only four of the epidemiological studies. The fitted study-specific KM_{PCM} values for these 4 studies are listed below:

Index	Reference	Cohort	KM_{PCM}
1	Selikoff et al. (1979), Peto et al. (1982)	Insulation Applicators	1.5E-08
2	Peto (1980), Peto et al. (1982)	Textile Manufacturers	1.0E-08
3	Seidman (1984)	Amosite Insulation Manufacturers	3.2E-08
4	Finkelstein (1983)	Cement Manufacturers	1.2E-07

As seen, these values ranged from about 1E-08 to 1E-07 (f/cc-yrs³)⁻¹.

The author noted that all of the other ten studies that were used to estimate KL_{PCM} values (see above) reported data on the occurrence of mesothelioma cases, but did not include sufficient exposure-response data to allow fitting the risk model. In an effort to include these studies in the analysis, USEPA (1986) developed a method for extrapolating from the consensus value of KL_{PCM} to the value of KM_{PCM} :

$$KM_{PCM} = KL_{PCM} \cdot k$$

The value of k was computed using a metric called “relative mesothelioma hazard” as follows:

$$k = \left(\frac{KM_{PCM} [j]}{KL_{PCM} [j]} \right)_4 \cdot \left(\frac{RMH_{all}}{RMH_4} \right)$$

where:

$$RMH = \frac{(Mesothelioma\ deaths / Total\ deaths)}{(Cumulative\ exposure)(Study\ specific\ KL_{PCM})}$$

and:

$$\left(\frac{KM_{PCM}[j]}{KL_{PCM}[j]} \right)_4 = \text{Geometric mean of the KM/KL ratio for the four studies where KM}$$

could be calculated directly

RMH_{all} = geometric mean of RMH values for all studies except friction products (which were excluded because of uncertainty in the KL_{PCM} values)

RMH₄ = geometric mean of RMH values for the 4 studies where KM_{PCM} could be calculated directly

The values of RMH for each study are presented in Table 6-3. The geometric mean RMH for the four studies for which KM_{PCM} could be calculated was 1.59, and the geometric mean RMH for all studies excluding friction product studies was 1.07. The geometric mean of the value of KM_{PCM} / KL_{PCM} for the four studies was 1.25E-06. Based on these values, the value of k was computed as:

$$k = (1.25E-06) \cdot (1.07 / 1.59) = 0.84E-06$$

The authors noted that this value was likely to be a lower bound, and after accounting for uncertainty, a value of 1E-06 was identified as the preferred estimate of k. Thus, based on the consensus value of 1E-02 for KL_{PCM}, the value of KM_{PCM} was calculated as follows:

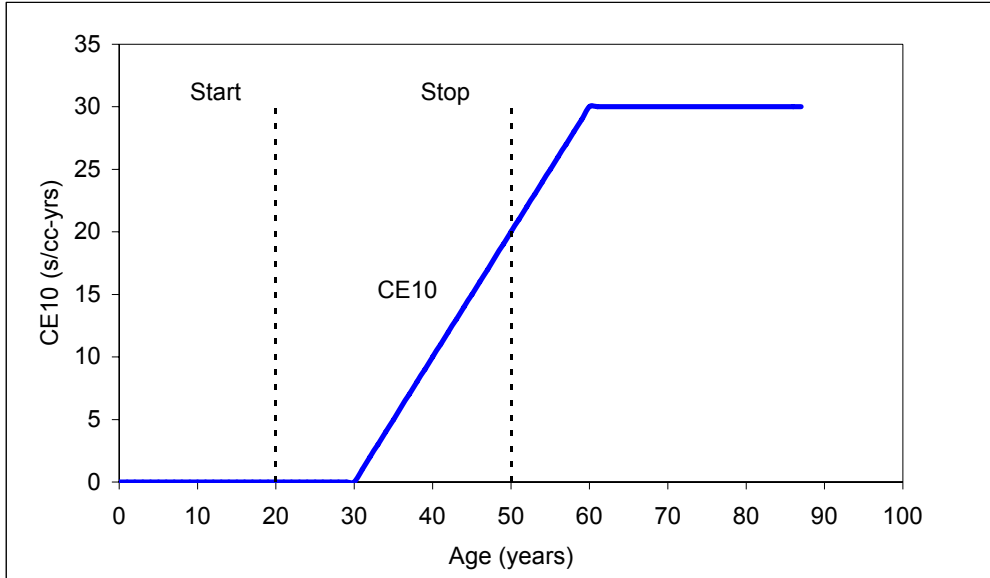
$$KM_{PCM} = 1E-02 \cdot 1E-06 = 1E-08 \text{ (f/cc-yrs}^3\text{)}^{-1}$$

6.3 Potential Limitations of the USEPA 1986 Approach

As noted above, the primary concern with regard to the potency factors derived by USEPA (1986) is that the measure of exposure is PCM fibers, which does not distinguish between different mineral classes of asbestos, and does not account for differing size distributions between different workplaces. Thus, cancer risk estimates based on the 1986 potency factors may yield reliable estimates in some cases, but might either underestimate or overestimate risks in other cases, especially when the composition of the atmosphere is dissimilar to the atmospheres upon which the potency factors are based. In addition, the number of studies available to estimate the value of KM_{PCM} was limited, and the reliability of the method used to extrapolate from KL_{PCM} to KM_{PCM} is not known.

FIGURE 6-1. MEASURES OF CUMULATIVE EXPOSURE TO ASBESTOS

Panel A: CE10 (s/cc-yrs) (assumes C = 1 s/cc)



Panel B: Q (yrs³)

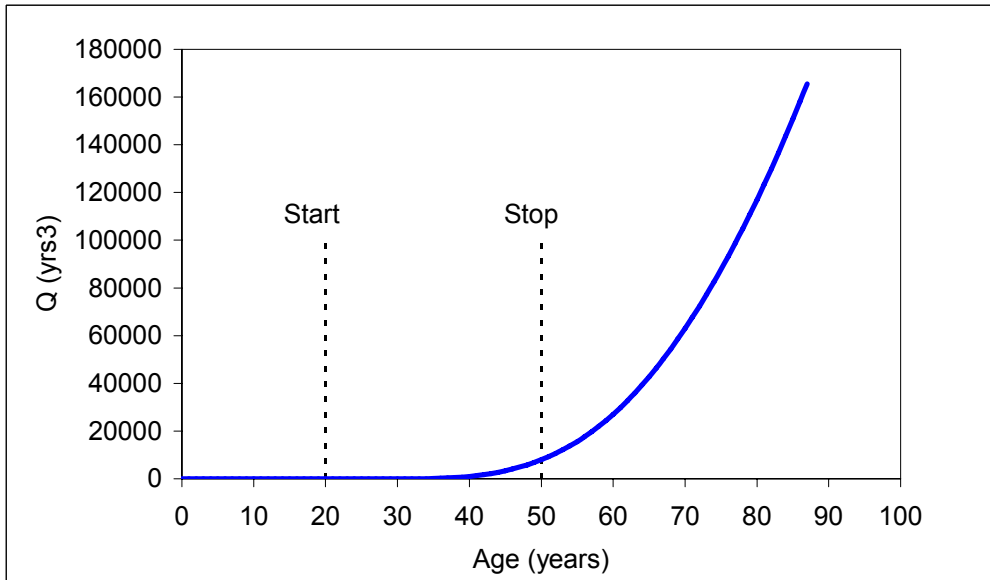
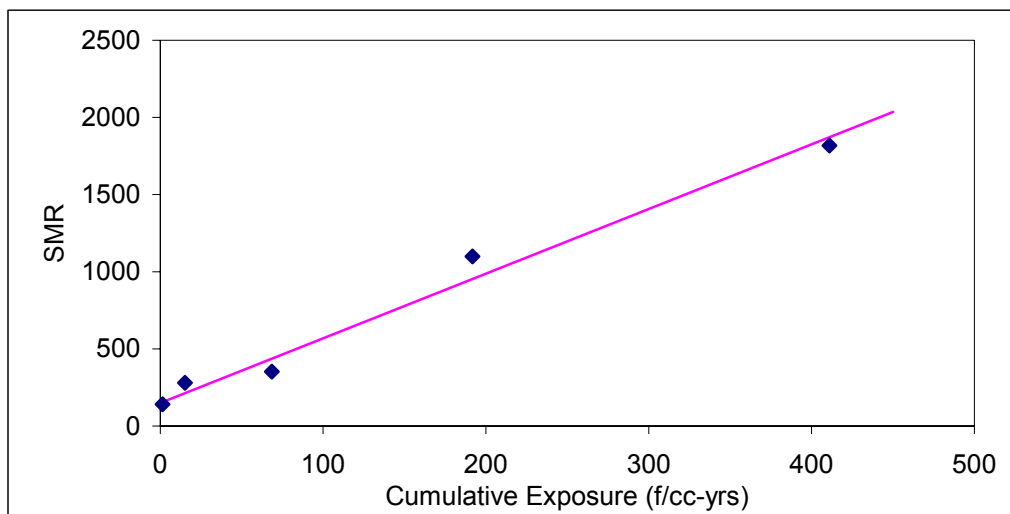


FIGURE 6-2. EXAMPLE OF FITTING A STUDY-SPECIFIC VALUE FOR KL



Data based on South Carolina textile workers (Dement et al. 1983)

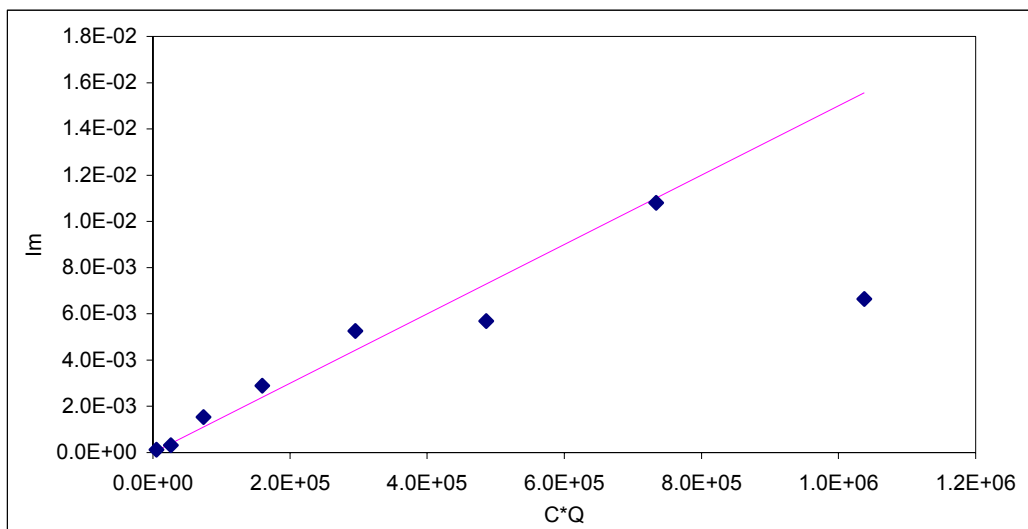
Data	
CE10	SMR
1.4	140
15.1	279
68.5	352
191.8	1099
411	1818

Weighted regression	
Intercept	150
Slope	4.19

KL	0.028
----	-------

Source: USEPA 1986

FIGURE 6-3. EXAMPLE OF FITTING A STUDY-SPECIFIC VALUE FOR KM



Data based on U.S. Insulation Workers (Selikoff et al., 1979; Peto et al., 1982)

Data	
C*Q	Im
5145	1.20E-04
25920	3.20E-04
73695	1.54E-03
159720	2.89E-03
295125	5.26E-03
486375	5.69E-03
733875	1.08E-02
1037625	6.64E-03

Fitted Value	
KM	1.50E-08

Source: USEPA 1986

TABLE 6-1. STUDY-SPECIFIC KL VALUES DERIVED BY USEPA (1986)

Index	Reference	Cohort Description	KL (x100)
1	Dement et al. (1983)	South Carolina Textile Factory	2.8
2	McDonald et al. (1983)	South Carolina Textile Factory	2.5
3	Peto (1980)	Rochedale, England Textile Factory	1.1
4	McDonald et al. (1982)	Pennsylvania Textile Factory	1.4
5	Berry and Newhouse (1983)	England Friction Product Factory	0.058
6	McDonald et al. (1984)	Connecticut Friction Product Factory	0.010
7	McDonald et al. (1980)	Quebec Mines and Mills	0.060
8	Nicholson et al. (1979)	Quebec Mines and Mills	0.17
9	Rubino et al. (1979)	Italian Mines and Mills	0.075
10	Seidman (1984)	New Jersey Insulation Factory	4.3
11	Selikoff et al. (1979)	Insulation Applicators	0.75
12	Henderson and Enterline (1979)	U.S. Retirees	0.49
13	Weill et al. (1979), Weill (1984)	New Orleans Cement Manufacturing Plant	0.53
14	Finkelstein (1983)	Ontario Cement Manufacturing Plant	6.7

TABLE 6-2. GEOMETRIC MEAN KL VALUES GROUPED BY INDUSTRY

Industry	Mineral Type	Geo. Mean KL (x 100)
Textile production	Mainly chrysotile	2.0
Friction products manufacturing	Chrysotile	0.023
Mining and milling	Chrysotile	0.098
Amosite insulation production	Amosite	4.3
Mixed manufacturing or use	Chrysotile, amosite, crocidolite	0.68
All processes	Chrysotile, amosite, crocidolite	0.65
All processes except mining and milling	Chrysotile, amosite, crocidolite	1.0
Textiles production and mixed manufacturing or use	Chrysotile, amosite, crocidolite	1.3

TABLE 6-3. STUDY-SPECIFIC RMH VALUES DERIVED BY USEPA (1986)

Index	Reference	Cohort	RMH ^a
1	Dement et al. (1983)	South Carolina Textile Factory	0.33
2	McDonald et al. (1983)	South Carolina Textile Factory	0.23
3	Peto (1980)	Rochedale, England Textile Factory	0.73
4	McDonald et al. (1982)	Pennsylvania Textile Factory	2.25
5	Berry and Newhouse (1983)	England Friction Product Factory	27.9
6	McDonald et al. (1984)	Connecticut Friction Product Factory	97
7	McDonald et al. (1980)	Quebec Mines and Mills	0.83
8	Nicholson et al. (1979)	Quebec Mines and Mills	0.29
9	Rubino et al. (1979)	Italian Mines and Mills	2.10
10	Seidman (1984)	New Jersey Insulation Factory	0.99
11	Selikoff et al. (1979)	Insulation Applicators	3.09
12	Henderson and Enterline (1979)	U.S. Retirees	0.35
13	Weill et al. (1979), Weill (1984)	New Orleans Cement Manufacturing Plant	0.98
14	Finkelstein (1983)	Ontario Cement Manufacturing Plant	2.85

^a RMH = Relative Mesothelioma Hazard

$$= \frac{(\text{Mesothelioma deaths}/\text{total deaths})}{(\text{Cumulative exposure})(\text{Study specific KL})}$$

7.0 INITIAL EPA EFFORTS TO DEVELOP BIN-SPECIFIC POTENCIES

Because of the potential limitations in the PCM-based potency factors derived in USEPA (1986), the USEPA has been working to investigate approaches for characterizing cancer risks from inhalation exposure to asbestos that take potential differences in potency between different mineral types and particle sizes into account. Initial work in this area was performed by Aeolus, Inc., working initially under contract with EPA Region 9 and later under contract with EPA Headquarters. These efforts were presented in several different draft EPA reports (Aeolus 1999, 2001, 2003), and are often associated with the names of the authors (Dr. D. Wayne Berman and Dr. Kenny S. Crump). This section describes the statistical approach developed by Aeolus.

7.1 Risk Models

Aeolus (2003) performed an evaluation of model adequacy for both lung cancer and mesothelioma. For lung cancer, this included an examination not only of the linearity of the response, but also the adequacy of the assumption that relative risk did not change as a function of time after exposure ceased. Based on a detailed analysis of unpublished raw data from the Wittenoom cohort and the South Carolina cohort, Aeolus concluded that the linear risk model was successful in describing the data, both with regard to exposure dependence and time dependence. For mesothelioma, Aeolus performed a detailed re-evaluation of the adequacy of this model based on unpublished raw data for three cohorts, including Quebec chrysotile miners, Wittenoom crocidolite miners, and South Carolina chrysotile textile workers. Based on this re-analysis, Aeolus concluded that the model did provide an adequate fit to the data, both with regard to time dependence and exposure dependence. As a result of this assessment, Aeolus (2003) retained the same basic risk models as were employed by USEPA (1986):

$$\text{Lung Cancer: } RR = \alpha (1 + KL \cdot CE_{10})$$

$$\text{Mesothelioma: } Im = C \cdot Q \cdot KM$$

7.2 Bins Evaluated

Aeolus noted the wide variability between the study-specific values of KL_{PCM} and KM_{PCM} derived in USEPA (1986), and hypothesized that this variability was attributable at least in part to differences in the composition (mineral type, particle size) of the asbestos to which workers were exposed in differing workplaces. They postulated that each observed study-specific potency value was a concentration-weighted average of the potencies of four differing asbestos bins, defined as follows:

Bins Used in Aeolus (2003) Draft Report

Bin	Mineral Type	Thickness	Length
1	Amphibole	< 0.4 um	5-10 um
2			> 10 um
3	Chrysotile	< 0.4 um	5-10 um
4			> 10 um

The choice of these bins was based primarily on data from studies in rats which suggest that toxicity is best correlated with long fibers (> 40 um) with thickness less than 0.4 um, and that fibers shorter than 5 um have very little potency (Berman et al. 1995). However, because particle size data for workplace exposures do not generally include a bin with a length cutoff of 40 um, a length cutoff of 10 um was used instead.

7.3 Approach for Lung Cancer

Basic Equation

The basic model selected by Aeolus for fitting a set of study-specific lung cancer potencies to derive estimates on the underlying bin-specific potencies is as follows:

$$KL_{PCM}[j] = \frac{KLa^* \cdot (f_{amph}[j] + rpc(1 - f_{amph}[j]))(q \cdot f_{5-10}[j] + (1 - q)f_{>10}[j])}{f_{pcme}[j]} \quad \text{Eq. 7-1}$$

where:

- $KL_{PCM}[j]$ = The study-specific potency for study “j”, expressed in terms of PCM fibers
- KLa^* = The potency of pure amphibole, based on the exposure index defined by q
- q = The relative potency of fibers thinner than 0.4 um and between 5-10 um in length relative to fibers thinner than 0.4 um and longer than 10 um
- rpc = The relative potency of chrysotile compared to amphibole
- $f_{5-10}[j]$ = Fraction of fibers with width < 0.4 um and length between 5-10 um in the atmosphere of the workplace evaluated in study “j”
- $f_{>10}[j]$ = Fraction of fibers with width < 0.4 um and length greater than 10 um in the atmosphere of the workplace evaluated in study “j”
- $f_{pcme}[j]$ = Fraction of fibers that meet PCM counting rules in the atmosphere of the workplace evaluated in study “j”

$f_{\text{amph}}[j]$ = Fraction of fibers that are amphibole in the atmosphere of the workplace evaluated in study “j”

Based on this model, the values of the four bin-specific potency factors are given by:

$$KL1 = KLa^* \cdot q$$

$$KL2 = KLa^* \cdot (1-q)$$

$$KL3 = KLa^* \cdot q \cdot rpc$$

$$KL4 = KLa^* \cdot (1-q) \cdot rpc$$

Fitting Strategy

Equation 7-1 was fit to the data using the method of maximum likelihood estimation (MLE). Each observed value of $KL_{PCM}[j]$ was assumed to be a random sample drawn from an underlying lognormal uncertainty distribution, given by:

$$KL_{PCM}[j] \sim LN(\mu[j], \sigma[j]) \quad \text{Eqn 7-2}$$

The parameter $\mu[j]$ is the log of the true (but unknown) value of KL_{PCM} for study “j”, given by Equation 7-1. The parameter $\sigma[j]$, which characterizes the magnitude of the uncertainty around the true value of $KL_{PCM}[j]$, was assumed to be a composite of study-specific uncertainty in the data and other (non-study-specific) sources of uncertainty:

$$\sigma[j]^2 = s1[j]^2 + s2^2 \quad \text{Eqn 7-3}$$

where:

$s1[j]^2$ = Variance in $KL_{PCM}[j]$ due to study-specific data uncertainties and measurement errors.

$s2^2$ = Variance due to other (non-study-specific) sources of uncertainty.

The value of $s1[j]$ was computed based on a series of uncertainty factors for classifying the relative magnitude of potential measurement error in exposure in the study, as follows:

Uncertainty Factor	Sources of Uncertainty Included	Range of values assigned
F1	<ul style="list-style-type: none"> • Uncertainty in the accuracy of the measured concentrations • Uncertainty in the relevance of measurements due to differences in times and locations of measurements vs. time and location of worker exposure 	1.5 – 4.0
F2	<ul style="list-style-type: none"> • Uncertainty in the method for conversion of concentration from original units of measure to units of PCM f/cc 	1.0 – 3.0
F3	<ul style="list-style-type: none"> • Uncertainty in the accuracy of job history (time and location of exposure) used to compute cumulative exposure 	1.0 – 2.0
F4	<ul style="list-style-type: none"> • Uncertainty in the mortality data, either because of uncertainties in the diagnosed cause of death, or because of uncertainties needed to estimate the data when they were not reported explicitly in the published studies 	1.0 – 5.0

In this system, a value of 1.0 indicates no uncertainty, with higher values indicating greater uncertainty. The value of $s1[j]$, which includes the combined effect of all of these different sources of uncertainty, was calculated for lung cancer studies as follows:

$$s1[j] = 0.5 \cdot \ln\left(\frac{UCI[j] \cdot F[j] \cdot F_{psd}[j]}{KL_{PCM}[j]}\right) \quad \text{Eqn 7-4}$$

where:

- $UCI[j]$ = 90% upper confidence interval on the observed value of $KL_{PCM}[j]$, derived using the likelihood profile method
 $F[j]$ = $\exp\{\ln^2(F1[j]) + \ln^2(F2[j]) + \ln^2(F3[j]) + \ln^2(F4[j])\}^{0.5}$
 $F_{psd}[j]$ = Judgment-based uncertainty factor assigned to account for uncertainty in particle size data used to estimate bin-specific concentrations in study j
 $KL_{PCM}[j]$ = Best estimate of the observed value of $KL_{PCM}[j]$

Based on this approach, the process of estimating bin-specific potency parameters is performed as follows:

Step 1a

The first step in deriving bin-specific potency parameters is fitting the exposure-response data from each epidemiological study to obtain a study-specific value for $KL_{PCM}[j]$. Fitting of each study is achieved using MLE, assuming that the observed number of deaths in each group

(OBS[j,k]) is a random variable characterized by a Poisson distribution. Because the true value of $KL[j]$ can not be < 0 , the parameters of the solution were constrained so that each $KL_{PCM}[j]$ was ≥ 0 . However, when the MLE value was zero, a problem arises in Equation 7-1, because the term $\ln(KL_{PCM}[j])$ is undefined when $KL_{PCM}[j]$ is zero. Therefore, studies in which the MLE estimate of $KL_{PCM}[j]$ was zero were assigned a surrogate value of $1E-11$.

Step 1b

The next step is to compute the value of $s1[j]$ for each study based on the judgment-based values for each of the uncertainty factors F1 to F4 using Equation 7-4.

Step 2

Given the MLE estimates of a set of $KL_{PCM}[j]$ values from Step 1a and the study-specific value of $s1[j]$ from Step 1b, the bin-specific potency values are estimated by MLE by assuming the observed (fitted) $KL_{PCM}[j]$ value is a random draw from a lognormal distribution.

7.4 Approach for Mesothelioma

The basic approach for finding the bin-specific potency factor for mesothelioma is very similar to the approach described above for lung cancer, except that in studies where the MLE value of $KM_{PCM}[j]$ was zero, a surrogate value of $1E-17$ was assigned.

7.5 Epidemiological Studies Selected for Use

Aeolus performed a literature search to identify any updates of cohorts that had been evaluated previously by USEPA (1986) as well as to identify any studies of new cohorts that had been published since 1986. Each study was reviewed to determine if the published data were suitable for use in the model-fitting effort. In addition, unpublished data from three cohorts (South Carolina, Quebec and Wittenoom) were also available to Aeolus and were used in the fitting. The studies identified and selected for use by Aeolus are shown in Table 7-1 (lung cancer) and Table 7-2 (mesothelioma).

7.6 Estimation of Bin-Specific Concentration Values

One significant problem in developing bin-specific potency factors is that epidemiological studies published to date do not provide data on the concentrations of asbestos in each of the bins. Further, even if the raw data were available, the methods used to measure particle concentrations in air (midget impinger, PCM) lack the ability to distinguish between fiber types

and to quantify particles in some size classes. Therefore, Aeolus used published particle size data from TEM studies at a number of differing workplaces (Dement and Harris 1979, Gibbs and Hwang 1980, Hwang and Gibbs 1981) to extrapolate from exposure levels reported in terms of PCM fibers to exposures reported in terms of each of the four bins being evaluated. The basic equation is:

$$C(\text{Bin } b) = C(\text{PCM}) \cdot k(b)$$

where $k(b)$ is the ratio of the concentration of fibers in bin “b” to the concentration of PCM fibers in the workplace most similar to the epidemiological setting being evaluated.

7.7 Draft Results

Because the calculations and the data used in this approach have not been adopted by EPA, the draft results obtained by Aeolus (2003) are not reported in this document. However, the results did support the conclusion that there were differences in potency between different asbestos bins, indicating the potential usefulness of a bin-specific fitting strategy.

7.8 Potential Limitations of the Initial Approach

While the 2003 peer consultation panel generally endorsed the basic idea of a multi-bin approach (see Appendix D), there are a number of potential issues and limitations associated with the approach, as discussed below.

- 1) The approach is based on a two-step sequence in which bin-specific potency parameters are fitted to a set of fitted study-specific potency values. An alternative to this two-step approach would be to perform the fitting in one step, based on the reported raw data rather than a statistic derived from the raw data.
- 2) The assumption that uncertainty around each study-specific potency factor is lognormal was not tested or evaluated. An alternative approach would be to specify the uncertainty around each of the input data items, and then combine those uncertainty distributions to yield the uncertainty distribution around the output value.
- 3) The method for specifying the magnitude of uncertainty in a study-specific potency factor from various sources is relatively complex and, because the factors are utilized in log-space, the relative effect of choosing one uncertainty index value over another (e.g., 1.5 vs. 2.0) is difficult to assess. An alternative would be to characterize uncertainty around each uncertain input in linear space.

- 4) The method used to specify uncertainty in the study-specific potency factors includes many but probably not all of the potential contributors to uncertainty in the data. An alternative approach would be to include more potential sources of uncertainty in the assessment.
- 5) The model assumes that the relative potency of chrysotile (rpc) compared to amphibole is the same for short fibers and long fibers. While this assumption may be reasonable, it is not certain that the rpc must be equal for both size bins, and in essence this assumption reduces the number of fitting parameters from 4 to 3.
- 6) The method used to extrapolate from PCM-based exposures to bin-specific exposures in a workplace used only one TEM data set to represent the particle size distribution for that workplace, even when the atmosphere consisted of a mixture of amphibole and chrysotile particles. An alternative approach is to use different TEM data sets to compute bin-specific concentrations of amphibole and chrysotile.
- 7) Only one binning strategy was evaluated, and this was selected based mainly on observations in animals. As pointed out by the peer consultation panel (see Appendix D), the optimal binning strategy in animals may not be the optimal binning strategy for humans, due to a number of differences in respiratory physiology and anatomy.
- 8) The uncertainty around the bin-specific potency estimates was not thoroughly characterized. In addition, the findings were not accompanied with an evaluation of the sensitivity of the outcome to any of the data inputs or the assumptions employed, and there was no goodness of fit assessment.

Because of these limitations, OSWER has chosen not to implement the statistical fitting method proposed by Aeolus (2003), but to investigate an alternative statistical fitting strategy that seeks to address, to the extent possible, each of the concerns identified above. This approach is summarized in the following section.

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TABLE 7-1. LUNG CANCER STUDIES USED BY AEOLUS (2003)

Study [j]	Location	Process	Asbestos Type (a)	Fitted Parameters	
				$\alpha[j]$	$KL_{PCM}[j]$
Liddell et al. 1997	Quebec Mines	Mining and Milling	CH	1.15	2.90E-04
Piolatto et al. 1990	Italian Mines	Mining and Milling	CH	0.94	5.13E-04
McDonald et al. 1984	Connecticut Plant	Friction Products	CH	1.49	0.00E+00
Dement et al. 1994 (b)	South Carolina Plant	Textile Mfg.	CH	1.22	2.09E-02
Berry & Newhouse 1983	British Factory	Friction Products	CH	[1.00]	5.80E-04
Hughes et al. 1987	New Orleans Plants	Asbestos Cement Mfg.	CH, CR, AM	1.14	2.53E-03
Finkelstein 1984	Ontario Factory	Asbestos Cement Mfg.	CH, CR	4.26	2.87E-03
Albin et al. 1990	Swedish Plant	Asbestos Cement Mfg.	CH, CR, AM	1.82	6.69E-04
Selikoff & Seidman 1991	US Insulation Workers	Insulation Application	CH, AM	2.39	1.83E-03
McDonald et al. 1982	Pennsylvania Plant	Textile Mfg.	CH, CR, AM	0.52	1.81E-02
Peto et al. 1985	Rochdale, England Factory	Textile Mfg.	CH, CR	1.10	4.15E-03
de Klerk et al. 1994 (c)	Australian Mines	Mining and Milling	CR	2.13	4.74E-03
Seidman et al. 1986	Patterson, NJ Factory	Insulation Mfg.	AM	3.32	1.09E-02
Levin et al. 1998	Tyler, TX Factory	Insulation Mfg.	AM	2.48	1.34E-03
Amandus & Wheeler 1987a,b	Libby, MT Mines	Mining and Milling	TR, AC	1.11	5.13E-03

(a) Asbestos type abbreviations: CH = chrysotile; CR = crocidolite; AM = amosite; TR = tremolite; AC = actinolite.

(b) Based on unpublished supplemental data provided to Aeolus (2003) from NIOSH.

(c) Based on unpublished supplemental data from Dr. de Klerk with follow-up through 2001.

TABLE 7-2. MESOTHELIOMA STUDIES USED BY AEOLUS (2003)

Study [j]	Location	Process	Asbestos Type (a)	Fitted Parameter
				KM _{PCM} [j]
Liddell et al. 1997 (b)	Quebec Mines	Mining and Milling	CH	1.64E-10
McDonald et al. 1984	Connecticut Plant	Friction Products	CH	0.00E+00
Dement et al. 1994 (c)	South Carolina Plant	Textile Mfg.	CH	2.48E-09
Hughes et al. 1987	New Orleans Plants	Asbestos Cement Mfg.	CH	2.00E-09
Hughes et al. 1987	New Orleans Plants	Asbestos Cement Mfg.	CH, CR, AM	3.00E-09
Finkelstein 1984	Ontario Factory	Asbestos Cement Mfg.	CH, CR	1.80E-07
Selikoff and Seidman 1991	US Insulation Workers	Insulation Application	CH, AM	1.28E-08
McDonald et al. 1982	Pennsylvania Plant	Textile Mfg.	CH, CR, AM	1.10E-08
Peto et al. 1985	Rochdale, England Factory	Textile Mfg.	CH, CR	1.31E-08
Seidman et al. 1986	Patterson, NJ Factory	Insulation Mfg.	AM	3.95E-08
de Klerk et al. 1994 (d)	Australian Mines	Mining and Milling	CR	7.95E-08

a) Asbestos type abbreviations: CH = chrysotile; CR = crocidolite; AM = amosite; TR = tremolite; AC = actinolite.

b) Based on unpublished supplemental data provided to Aeolus (2003) from Dr. McDonald and Professor Liddell.

c) Based on unpublished supplemental data provided to Aeolus (2003) from NIOSH.

d) Based on unpublished supplemental data provided to Aeolus (2003) from Dr. deKlerk.

8.0 CURRENT APPROACH PROPOSED BY OSWER

OSWER has been working for several years to extend the work of USEPA (1986) and Aeolus (1999, 2001, 2003) in order to develop bin-specific cancer potency values for asbestos. This section describes the approaches that OSWER has considered, and identifies the approach that OSWER is proposing for use.

8.1 Nomenclature and Notation

Table 8-1 provides the nomenclature and mathematical notations used in this section.

8.2 Risk Models

Conceptually, there are a wide variety of risk models other than those used by USEPA (1986) and Aeolus (2003) that could be considered for use in fitting available epidemiological data on lung cancer or mesothelioma risk from asbestos exposure. For lung cancer, this might include use of a model in which a) the interaction between asbestos and other causes of lung cancer (e.g., smoking) is additive or intermediate between additive and multiplicative, b) the increase in relative risk is a non-linear function of cumulative exposure, potentially including a threshold below which exposure does not increase relative risk, and c) the lag time is different than 10 years, or is dependent upon the type of asbestos exposure. For mesothelioma, this might include use of a cumulative exposure index in which the dependency of risk on time since first exposure and exposure duration is some power other than cubic.

In order to determine which risk models to follow, OSWER reviewed evaluations that have been performed by others, as described below.

Lung Cancer

As noted above, USEPA (1986) performed a thorough evaluation of the exposure-response pattern for lung cancer in exposed workers. The author noted that there was a very good linear relationship between relative risk and cumulative exposure over the entire range of exposure for most of the available studies, and determined that a linear model was strongly indicated. The increase in relative risk was observed to occur within about 5-10 years of first exposure, and that the increase is proportional to the cumulative exposure and is independent of age at which exposure begins. Data on the interaction between smoking and asbestos exposure were also reviewed, and were found to be generally consistent with a multiplicative interaction.

Aeolus (2003) also performed a detailed evaluation of the adequacy of the lung cancer model. This included an examination not only of the linearity of the response, but also the adequacy of the assumption that relative risk did not change as a function of time after exposure ceased. Based on a detailed analysis of raw data from the Wittenoom cohort and the South Carolina cohort, Aeolus concluded that the linear risk model was successful in describing the data, both with regard to exposure dependence and time dependence.

Stayner et al. (1997) performed a detailed evaluation of the ability of a variety of linear and non-linear models, including threshold models, for describing the dose-response relationship for lung cancer in the South Carolina cohort, and concluded that a simple linear no-threshold model was adequate and that no improvement in model fit occurred with the other model forms.

The interaction of asbestos with smoking on risk of lung cancer has been investigated by a number of researchers (Hammond et al. 1979, Berry et al. 1985, Vainio and Boffetta 1994, Liddell and Armstrong 2002, Aeolus 2003). Most assessments conclude that available data on the interaction of smoking and asbestos are too limited to perform a truly robust analysis, but that, based on the data that are available, the interaction, while variable, appears to be more nearly multiplicative than additive.

Finally, EPA cancer guidelines (USEPA 2005) recommend that “When the weight of evidence evaluation of all available data are insufficient to establish the mode of action for a tumor site and when scientifically plausible based on the available data, linear extrapolation is used as a default approach, because linear extrapolation generally is considered to be a health-protective approach. Nonlinear approaches generally should not be used in cases where the mode of action has not been ascertained.”

Based on these considerations, OSWER is proposing the linear multiplicative non-threshold relative risk model for lung cancer for use in this analysis. However, in order to account for differing potency of asbestos as a function of mineral type and particle size, the “one-bin” form of the risk model is revised to account for multiple asbestos “bins”, as follows:

One-bin PCM Model: $RR = \alpha (1 + CE10_{PCM} \cdot KL_{PCM})$

Multi-bin Model: $RR = \alpha (1 + \sum_{b=1}^{nb} CE10_b \cdot KL_b)$

where:

- α = Relative risk of lung cancer in the cohort in the absence of exposure
- KL_{PCM} = Lung cancer potency factor based on PCM asbestos
- KL_b = Lung cancer potency factor for asbestos bin “b” (f/cc-yrs)⁻¹

CE10_{PCM} = Cumulative exposure (lagged by 10 years) to PCM asbestos (f/cc-yrs)
 CE10_b = Cumulative exposure (lagged by 10 years) to asbestos bin “b” (f/cc-yrs)

Mesothelioma

The risk model for mesothelioma selected by USEPA (1986) was based on the multistage model. At the time, only four studies were available on the exposure-response patterns in exposed workers (Jones et al. 1980, Seidman 1984, Hobbs et al. 1980, Finkelstein 1983). The authors noted that three of the studies (Jones et al. 1980, Hobbs et al. 1980, Finkelstein 1983) indicated a linear relationship between exposure duration (a surrogate for cumulative exposure), while the fourth (Seidman 1984) was not linear. USEPA (1986) attributed this apparent non-linearity to statistical uncertainties associated with small numbers of cases. Polynomial models of degree one and two were fitted to the data of Jones et al. 1980, Hobbs et al. 1980, and Finkelstein 1983, and in no case was the quadratic term required. A lag of 10 years was assumed based on extrapolation from the lung cancer studies, and the power of the model that best fit the data was found to be 3 (USEPA 1986).

Aeolus (2003) performed a re-evaluation of the adequacy of this model based on the raw data for three cohorts, including Quebec chrysotile miners, Wittenoom crocidolite miners, and South Carolina chrysotile textile workers. Based on this re-analysis, Aeolus concluded that the model did provide an adequate fit to the data, both with regard to time dependence and exposure dependence.

Based on the evaluations by USEPA (1986) and by Aeolus (2003), OSWER is proposing the linear non-threshold cubic absolute risk model for mesothelioma for use in this analysis. However, in order to account for the differing potency of asbestos as a function of mineral type and particle size, the “one-bin” form of the model is revised to account for multiple asbestos “bins”, as follows:

One-bin PCM Model: $I_m = Q \cdot C_{PCM} \cdot KM_{PCM}$

Multi-bin Model: $I_m = Q \cdot \sum_{b=1}^{nb} C_b \cdot KM_b$

where:

Q = Cubic function of duration and time since first exposure (yrs³)
 KM_{PCM} = Mesothelioma potency factor based on PCM asbestos
 KM_b = Mesothelioma potency factor for asbestos bin “b”
 C_{PCM} = Concentration of PCM asbestos (f/cc)

C_b = Concentration of asbestos bin “b” (f/cc)

8.3 Fitting Metric

OSWER considered two basic alternative strategies for fitting the data to the models. The first strategy is to perform the fitting based on observed and predicted study-specific potency values, similar to the strategy followed by Aeolus (2003). The second approach is to perform the fitting based on the observed and predicted number of cancer cases in each group of each study. As noted previously, one concern with optimization at the level of study-specific potency values is that it requires a two-step approach, in which fitting of bin-specific potency factors is based on fitted study-specific KL or KM values. In addition, it is not certain what approach is best for characterizing the uncertainty around each fitted study-specific potency value and for performing the optimization. For these reasons, OSWER is proposing that fitting occur at the level of observed cases for each group of each study. This approach allows fitting to occur in one step, is based on measured data (number of cancer cases) rather than derived statistics (KL or KM values), and is more readily amenable to specification of uncertainty in the data (see below).

In this approach, the observed number of cancer cases observed in an exposure group is assumed to be a random value from a Poisson distribution whose true (but unknown) rate (λ) is a function of the nature and level of cumulative exposure for the person-years of observation in the group:

Observed cases = random value from Poisson (λ)

$$\text{Lung cancer: } \lambda = \alpha \cdot \text{Expected} \cdot \left(1 + \sum_{b=1}^{nb} KL_b \cdot CE10_b \right)$$

$$\text{Mesothelioma: } \lambda = Q \cdot PY \cdot \sum_{nb=1}^{nb} KM_b \cdot C_b$$

The choice of a Poisson distribution is based on the recognition that the basic unit of observation in these studies is a person-year of observation, and that the observed outcome in each person-year (either death or not death from cancer) is characterized by a Bernoulli distribution with a parameter p. The number of deaths observed in each group of binned person-years is thus the sum of values from a large number of Bernoulli distributions, each with a small value of p, which is expected to approach a Poisson distribution for large N.

Given the measure of cumulative exposure for each asbestos bin and the set of bin-specific potency values, the probability (p) of observing the reported number of cases (OBS) in a specified group is given by:

$$P = \frac{e^{-\lambda} \cdot \lambda^{OBS}}{OBS!}$$

and the overall likelihood (L) of observing the combined data set across all groups is the product of the group-specific probability values:

$$L = \prod_{g=1}^{ng} \frac{e^{-\lambda_g} \cdot \lambda^{OBSg}}{OBS_g!}$$

8.4 Characterizing Uncertainty in the Exposure Data

It is often assumed that the only errors that occur in the data are in the dependent variable (i.e., Poisson error in the observed number of cases), and that there are no errors in the independent variable (cumulative exposure). However, in this effort, it is very clear that there are errors in the cumulative exposure values (CE10 and C·Q), and that these errors may be substantial.

Based on a review of how the exposure data are collected and utilized in epidemiological studies, OSWER has identified the following main sources of uncertainty in the reported measures of cumulative exposure:

- sampling and analytical error in asbestos or dust concentrations in workplace settings
- extrapolation of dust measurements to PCM-based measurements
- use of measures from stationary rather than personal air samplers
- use of data collected during one time period to estimate values in another time period
- use of CE (not lagged by 10 years) rather than CE10 to quantify exposure in lung cancer studies
- use of group average values of time since first exposure and/or exposure duration as surrogates for computing cumulative exposure measures for individual person-year values in mesothelioma studies
- use of bin midpoints to represent average exposure
- estimation of group average exposure for unbounded bins
- extrapolation from values based on PCM to values based on bin-specific concentrations

The general approach that OSWER is proposing for characterizing these multiple sources of uncertainty in the data is the specification of probability density functions (pdfs) that describe the relative probability of a range of alternative values for each uncertain data item. If there is no suspected bias in the method used to collect the data, the measured value will generally be located in the central portion of the density, which may be either symmetrical or skewed. If there is a known or suspected bias in the method used to collect the data, the measured value is likely to be located either in the lower or upper part of the distribution (depending on the direction of the bias).

Note that some data items have multiple sources of uncertainty, so the overall uncertainty is estimated by combining each of the source-specific densities that apply to that data item. Also note that some sources of uncertainty apply at the level of a study and impact cumulative exposure estimates for all of the groups of that study, while other densities apply at the level of individual groups in a study. Thus, there is some degree of correlation between the densities that specify cumulative exposure for different groups within (but not between) studies.

Specification of a density for a data input term has two elements: the mathematical form of the distribution (e.g., normal, lognormal, uniform, triangular, etc.), and the parameters of the distribution (e.g., mean, standard deviation, minimum, maximum, mode, etc.). Appendix C describes the mathematical forms and parameters used to specify the distributions for each of the major sources of uncertainty and bias in the data proposed for use in this effort. In general, OSWER is proposing an approach for specifying uncertainty densities in which the magnitude of the uncertainty is proportional to the measured value, and the errors combine in a multiplicative fashion.

8.5 Fitting Approach

Overview

Despite the simple linear algebraic structure of the proposed risk models for mesothelioma,

$$deaths = Q \cdot PY \cdot \sum_{b=1}^{nb} C_b \cdot KM_b$$

and lung cancer,

$$deaths = \alpha \cdot E \cdot \left(1 + \sum_{b=1}^{nb} CEI0_b \cdot KL_b \right)$$

the presence of significant uncertainties (see Section 8.3) in the explanatory variables (the bin-specific exposures, $CEI\theta_b$ and C_b) leads to serious statistical challenges for the estimation of the bin-specific potencies (\mathbf{KM} , \mathbf{KL}), as well as for characterizing their uncertainties.

A number of alternative statistical approaches have been developed for fitting models to data in which there are measurement errors in the explanatory variables (e.g., see Fuller 1987, Cheng and Van Ness 1999, Carroll, Ruppert, and Stefanski 1995, Gustafson 2004). OSWER reviewed the literature on this subject in order to identify the approach that seems most appropriate in the case of asbestos. Based on this review, OSWER concluded that a likelihood-based approach would be best. Two alternatives were considered, as discussed below.

Maximum Likelihood

In the absence of measurement error, the method of maximum likelihood (ML) requires specifying a probability model, $f(x, \theta)$ and then maximizing the sample likelihood (usually log-likelihood) over the parameter space,

$$\hat{\theta} = \underset{\text{over } \theta}{\text{MAX}} \left\{ L(\mathbf{Y} | \mathbf{C}, \theta) = \prod_{g=1}^{NG} f(y_g | c_g, \theta_1, \theta_2, \dots, \theta_k) \right\}$$

Here, $\theta = \mathbf{KM}$ for mesothelioma, and $\theta = (\alpha, \mathbf{KL})$ for lung cancer. Uncertainty in the estimated parameter $\hat{\theta}$ is commonly estimated using likelihood profiles or based on likelihood ratios (Pawitan 2001).

However, when the asbestos exposures are measured with error, the marginal likelihood is:

$$L(\mathbf{Y} | \theta) = \int L(\mathbf{Y} | \mathbf{C}, \theta) dF(\mathbf{C})$$

where $F(\mathbf{C})$ is the uncertainty distribution characterizing the uncertainties in asbestos exposures. Maximizing $L(\mathbf{Y} | \theta)$ with respect to θ yields ML estimates weighted by the uncertainty in exposures.

While ML is an efficient estimator, it has three primary drawbacks. First, maximum likelihood can be sensitive to misspecification of the probability models, potentially leading to biased or inconsistent estimates and a loss of efficiency (Pawitan 2001). However, in the asbestos analysis, misspecification is not expected to be a serious problem since there is a firm foundation for the probability model. Second, maximum likelihood estimation is often numerically

challenging. The integral in the asbestos analysis is highly-dimensional necessitating the use of an efficient numerical quadrature technique to approximate the integral. For example, adaptive quasi-Monte Carlo routines based on importance sampling and stratified sampling might be used (e.g., VEGAS and MISER algorithms). Alternatively, Markov Chain Monte Carlo (MCMC) could also be used to more efficiently estimate the joint density. Lastly, ML estimation requires a robust numerical optimization routine since the distributional parameters must be simultaneously estimated from a typically very flat log-likelihood surface.

Bayes-MCMC

Bayesian analysis is based on Bayes theorem which states that the posterior distribution of the parameters, conditional on the observed data, is proportional to the likelihood times the prior distribution of the parameter. That is:

$$f(\boldsymbol{\theta}, \mathbf{C} | \mathbf{OBS}) = \frac{L(\mathbf{OBS} | \boldsymbol{\theta}, \mathbf{C})f(\boldsymbol{\theta}, \mathbf{C})}{P(\mathbf{OBS})} \propto L(\mathbf{OBS} | \boldsymbol{\theta}, \mathbf{C})f(\boldsymbol{\theta}, \mathbf{C})$$

Markov Chain Monte Carlo (MCMC) methods, based on the Metropolis-Hastings algorithm and its special case, the Gibbs sampler, are commonly used to generate an empirical estimate of the posterior density (Gilks et. al.1996).

A Bayesian framework seems particularly relevant to the asbestos error measurement problem for a number of reasons: (1) there is a natural, defensible probability model for the observations, which would tend to minimize any concerns about model misspecification, (2) the exposure-response models for lung cancer and mesothelioma are well accepted by the risk assessment community, (3) the extreme high dimensionality of the likelihood integral necessitates very efficient integration algorithms, (4) Bayesian analysis provides the joint posterior parameter density directly, allowing statistical inferences to be made about the parameters (e.g., credible intervals, covariance, etc.), and (5) user-friendly Bayes-MCMC software is publicly available and widely used.

OSWER Proposal

Based on a consideration of the issues described above, OSWER is proposing Bayes-MCMC as the statistical approach for fitting the risk models to the available epidemiological data.

8.6 Bayesian Framework for Asbestos

8.6.1 Basic Mathematics

In the asbestos model, the Poisson parameter λ is differentiated across s studies and g dose groups as follows:

$$OBS_{s,g} \sim Poisson(\lambda_{s,g})$$

in which the Poisson parameter λ is given by

$$\text{Lung Cancer: } \lambda_{s,g} = \alpha_s \cdot E_{s,g} \cdot \left(1 + \sum_{b=1}^{nb} CE10_{s,g,b} \cdot KL_b \right)$$

$$\text{Mesothelioma: } \lambda_{s,g} = Q_{s,g} \cdot PY_{s,g} \cdot \sum_{b=1}^{nb} C_{s,g} \cdot KM_b$$

The sample likelihood is then the product of Poisson probabilities over studies and exposure groups within studies:

$$L(OBS) = \prod_{s=1}^{ns} \prod_{g=1}^{ng(s)} Poisson(OBS_{s,g} | \lambda_{s,g})$$

In the above likelihood, the double product over studies and exposure groups within a study is necessary since $\alpha = \{\alpha_1, \alpha_2, \dots, \alpha_{ns}\}$ is a study dependent parameter and because there are correlations among asbestos exposures at the study level. Using Bayes Theorem, the joint posterior densities are then,

$$f(KM, C | OBS) \propto L(OBS | KM, C) f(KM) f(C)$$

$$f(KL, \alpha, CE10 | OBS) \propto L(OBS | KL, \alpha, CE10) f(KL) f(\alpha) f(CE10)$$

Parameters of interest in the lung model are $\{KL, \alpha\}$ and KM in the mesothelioma analysis.

8.6.2 Specification of Priors

In the Bayes approach, it is necessary to specify the state of knowledge about the potential values of a fitting parameter before the Bayesian analysis is begun. This specification, typically in the

form of a probability density function, is referred to as the prior density. Assuming that the Bayes-MCMC approach is to be implemented, one of the first steps is to select prior densities for each of the bin-specific potency factors. In addition, in the case of lung cancer, it is necessary to specify priors for each of the study-specific $\alpha[s]$ terms. Prior distributions for $\{CE10, C\}$ are derived from a multiplicative error model based on multiple factors as discussed in Appendix C. Prior densities for $\{KM, KL, \alpha\}$ are generally selected to be very wide and flat, i.e., uniform distributions with very wide bounds. These bounds are chosen to be maximum limits which define an interval certain to contain the parameter. Tentative priors for $\{KM, KL, \alpha\}$ are discussed below.

Priors for Alpha

In the lung cancer model, the study-specific parameter $\alpha[j]$ reflects the ratio of the baseline risk of lung cancer in the exposed cohort compared to that in the reference population. The expected value of each α_s term is about 1, but higher or lower values may occur, especially when the reference population is not well matched to the cohort. However, true values of α_s may not be ≤ 0 . Based on general epidemiological experience that the majority of α_s values are likely to fall between about 0.5 and 2, the prior that OSWER proposes for each α_s is UNIFORM(0.1, 10). Because these bounds are substantially wider than expected values, this prior is considered to be weakly informed and is intended to constrain values within credible bounds.

Priors for Bin-Specific Potency Factors

Specifying the priors for the bin-specific potency factors is more complicated than for $\alpha[j]$, since the “expected” value of each bin-specific value is not known, and may vary substantially between different binning strategies. Based on the work of USEPA (1986) and Aeolus (2003), OSWER is proposing the following generalized priors:

$$\begin{aligned} \text{Lung cancer:} & \quad KL_b \sim \text{uniform}(0,1) \\ \text{Mesothelioma:} & \quad KM_b \sim \text{uniform}(0,0.001) \end{aligned}$$

The lower bound of zero is based on the recognition that the true value for a bin-specific potency may not be < 0 (although it may be zero). The upper bounds are based on the observation that values of the most potent KL_b values are likely to be in the 1E-02 range and the most potent KM_b values are likely to be in the 1E-07 range, although the actual values will depend on the binning strategy being evaluated.

8.7 Comparing Results for Different Binning Strategies

One of the most important objectives of this effort is to compare the model fit results for a number of alternative binning strategies in order to determine if an improvement in model fit to the data can be achieved by moving from the current one-bin strategy to a new multi-bin strategy, and, if so, to determine which multi-bin strategy is “best”. This approach is based on the expectation that if there are significant differences in potencies between different bins, then if a binning strategy is selected that effectively groups fibers of similar potency, the quality of the model fit based on that binning strategy will be better than for a strategy that does not effectively group fibers of similar potency.

Conceptually, there could be hundreds of different strategies investigated, differing in the size cutoffs used as well as the extent to which fibers are separated according to mineral type (chrysotile, amosite, crocidolite, tremolite, etc). However, the number of bins that can be fit to the data is limited by the number of individual studies that are available. For example, in order to fit a 4-bin model, the absolute minimum number of independent data sets required is 4, and a reliable fit requires many more. Because the number of data sets available is only 23 for lung cancer and 8 for mesothelioma, OSWER believes that any attempt to fit more than 4 bins would result in over-parameterization of the model. In addition, the choice of the size cutoffs used in bin definition is in part constrained by the size cutoffs used in the available TEM particle size distribution studies. For example, nearly all TEM data sets do not stratify fibers longer than 10 μm , so it is not possible to specify bins above this limit (e.g., 10-20 μm vs > 20 μm). Based on these constraints and considerations, OSWER is proposing a set of 20 differing binning strategies for evaluation in this effort. These are listed in Table 8-2. As seen, a number of 1-bin, 2-bin and 4-bin options are suggested. The 1-bin options do not distinguish between mineral form (i.e., amphibole and chrysotile are grouped together as a function of size). The 2-bin approaches are the same as the 1-bin approaches, except that amphibole and chrysotile are separated. The 4-bin approaches also separate chrysotile from amphibole, but allow for two size bins in each mineral type rather than just one. For example, Strategy 4F has the following 4 bins:

Bin	Mineral Type	Length (μm)	Width (μm)
1	Amphibole	0 - 10	< 1.5
2	Amphibole	> 10	< 1.5
3	Chrysotile	0 - 10	< 1.5
4	Chrysotile	> 10	< 1.5

As indicated above, OSWER is not proposing to split amphibole asbestos into separate bins (e.g., amosite, crocidolite, tremolite), because this would very likely result in over-parameterization of

the model. The proposed length and width cutoffs are based mainly on the strategies selected by previous investigators (USEPA 1986, Aeolus 2003), as well as the constraints imposed by the available TEM data (see Section 10, below). Depending on the results, other binning strategies may be evaluated as well. Note that Strategy 1P is the same as used by USEPA (1986) (i.e., the bin definition is that for PCME fibers), and Strategy 4B is the same as has been used by Aeolus (1999, 2001, 2003).

OSWER is proposing the use of Bayes Factor Analysis as the primary means for comparing between different binning strategies. Given two alternative binning strategies, designated here as S_1 and S_2 , the Bayes factor is the ratio of the posterior odds:

$$S_{1,2} = \frac{P(\text{OBS} | S_1)}{P(\text{OBS} | S_2)} = \frac{\int P(\text{OBS} | S_1, \hat{\Theta}_1) P(\hat{\Theta}_1 | S_1) d\hat{\Theta}_1}{\int P(\text{OBS} | S_2, \hat{\Theta}_2) P(\hat{\Theta}_2 | S_2) d\hat{\Theta}_2}$$

where $\hat{\Theta}$ includes the exposure concentrations **C**, **CE10** and the parameters of interest (**KM** for mesothelioma and **KL** and **α** for lung cancer). Note that integration over $\hat{\Theta}$ is expected to be numerically challenging.

Kass and Raftery (1995) suggest the following scheme for interpretation of Bayes factors:

Bayes Factor ($S_{1,2}$)	Evidence Against S_2
< 3.2	Negligible
3.2 to 10	Substantial
10 to 100	Strong
> 100	Decisive

8.8 Other Methods for Characterizing Goodness of Fit

Once binning strategies have been compared and a sub-set of "preferred" strategies are identified, OSWER believes it is appropriate to perform a more detailed characterization of goodness of fit for each preferred strategy in order to help determine if the differences between binning strategies are meaningful. In this regard, OSWER has investigated a number of alternative approaches, as described below.

- Scatter Plot of Observed vs. Predicted Cases. One obvious approach is a comparison of observed vs. predicted cases in each group, since the bin-specific potency factors are selected to optimize this agreement. A refinement to this is to compare observed vs. predicted excess cases. For example, if for some group the expected number of cases is

100, the observed number of cases is 110, and the predicted number of cases is 120, a comparison of observed vs. predicted (110 vs. 120) may appear favorable, but a comparison of observed vs. predicted excess cases (10 vs. 20) is a more meaningful indicator of actual agreement.

- Residual Plots. Another approach for assessing goodness of fit is to create residual plots that display the difference between observed and predicted cases on a group-by-group basis. These may be graphed as a function of study, industry, or other potentially relevant variables (e.g., exposure level, duration, length of follow-up, etc.) in order to help identify the conditions under which the model is predicting accurately and where it is not.
- Observed vs. Predicted Study-Specific Potency Factors. A third approach for assessing goodness of fit is to compare observed and predicted study-specific potency factors. This is done by finding the "observed" study-specific potency factor (typically based on PCM fibers) by fitting the data from a study to the model using Poisson MLE, then computing what the expected study-specific potency would be based on the fitted bin-specific potency factors and the bin-specific concentrations in the workplace.

Figure 8-1 shows example graphical formats (using strictly hypothetical data) for these alternative metrics. OSWER has considered and evaluated these options, and believes that all of them are potentially useful in characterizing and contrasting goodness of fit between different binning strategies. Because each metric is based on a different criterion, it should be understood that different methods might not always be in agreement regarding the quality of fit, and final decisions should take the strengths and limitations of each method into account.

8.9 Sensitivity Analysis

As discussed above, it is apparent that there are a number of statistical options for fitting available data to the risk models in order to estimate bin-specific potency factors. In addition, as discussed above, it is important to emphasize that the selection of the data to be used may, in some cases, be subject to debate. One procedure that is helpful in understanding the degree to which the methods and/or the data may influence the results is to perform a series of "what if" calculations. That is, fitting is performed to determine how the results (i.e., the values of the bin-specific potencies) would change if:

- individual groups, studies, or groups of studies were excluded
- the parameters or distributional form of one or more PDFs were changed
- different fitting strategies were employed

In general, if the results tend to be relatively insensitive to the statistical choices or the inclusion/exclusion of specific data, confidence in the results is increased. Conversely, if the results vary substantially when different methods are used or when selected data are included or excluded, confidence in the results is decreased.

An example of this approach, using purely hypothetical data, is shown in Figure 8-2. In this case, the uncertainty distribution for KM1 is relatively unchanged by omission of studies 1, 2, 4, 5, or 7, but is increased by omission of study 3, and decreased by omission of study 6. In this case, it would be concluded that the results are significantly influenced by these two studies.

OSWER intends to employ this general technique primarily as a tool for determining which data items and which PDFs are and are not critical in determining the values and uncertainty in bin-specific potency factors.

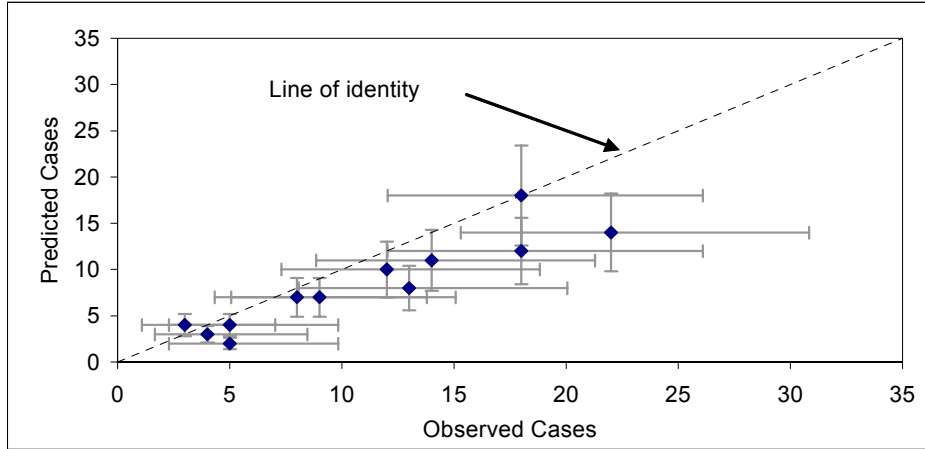
8.10 Summary of Proposed Statistical Approach

In summary, the statistical approach that OSWER is proposing for selecting and parameterizing a multi-bin model for predicting cancer risk from inhalation exposure to asbestos is as follows:

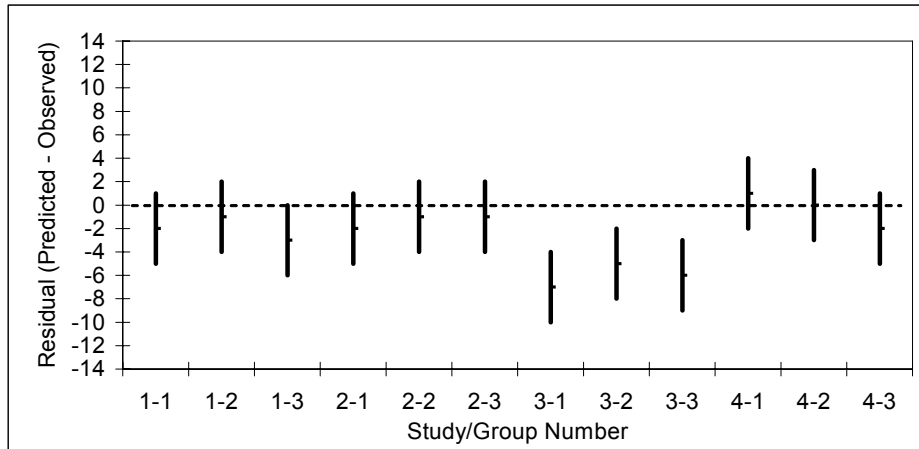
1. The basic risk models to be used are the same as employed by USEPA (1986), except that the models are modified to allow for differing potencies between differing asbestos bins.
2. Fitting will be done at the group level based on maximizing the agreement between observed and predicted number of cases, using Poisson MLE.
3. Uncertainty in reported values of cumulative exposure will be accounted for by specifying PDFs to characterize the uncertainty in each data item.
4. Fitting will be achieved by Bayes-MCMC, using uniformed priors.
5. A number of alternative binning strategies will be evaluated. Binning strategies will be compared using the Bayes Factor analysis, using the interpretational framework suggested by Kass and Raftery (1995).
6. A variety of other goodness of fit techniques, especially residual plots, will be employed to help compare between binning strategies and to assess the significance of the differences.
7. A sensitivity analysis will be performed by deletion of selected groups, studies, or sets of studies, and by revising the parameters or form of selected PDFs, in order to determine which inputs are and are not critical in determining the output.
8. The end result of the effort will be a recommended set of bin-specific potency factors for use in computing excess cancer risk from inhalation exposure to asbestos, along with an approach for characterizing the uncertainty in any risk predictions.

FIGURE 8-1
EXAMPLE GRAPHICAL FORMATS FOR EVALUATING GOODNESS OF FIT

Panel A: Observed vs Predicted Cases



Panel B: Residual Plot



Panel C: Observed vs Predicted Study-Specific KL Values

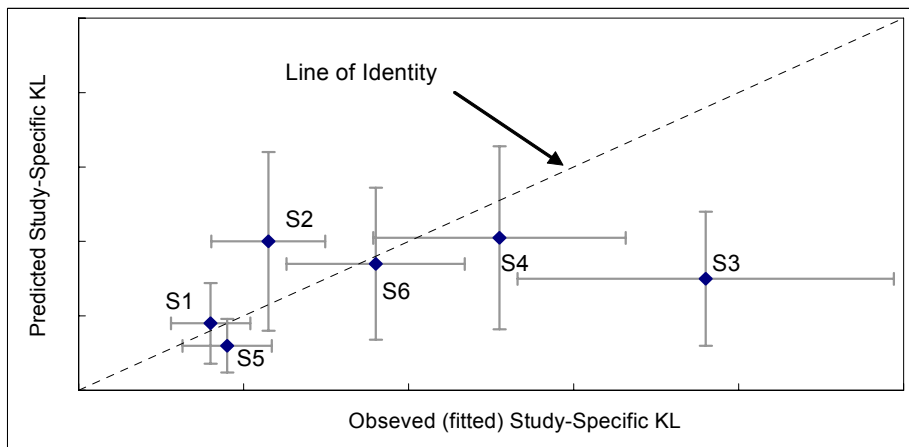


FIGURE 8-2. EXAMPLE SENSITIVITY ANALYSIS

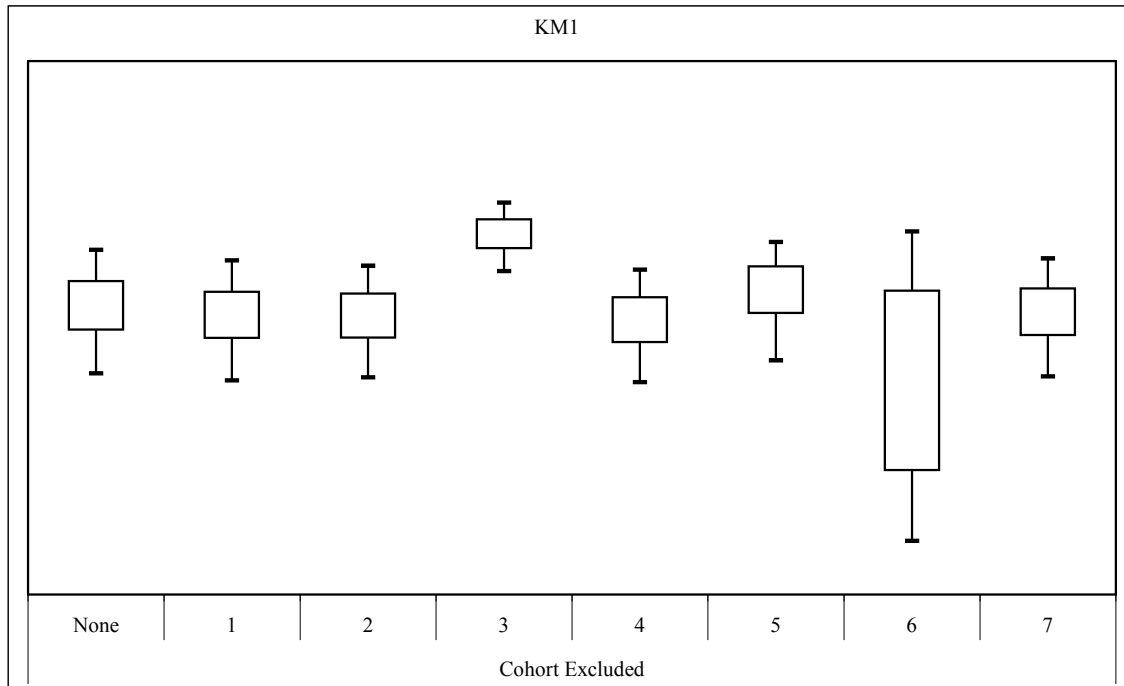


TABLE 8-1. NOMENCLATURE AND CONVENTIONS

Indices	
s	= an index indicating study number
g	= an index indicating group number within study s
b	= an index indicating bin number
ng	= number of exposure groups
nb	= number of asbestos bins
For lung cancer:	
$OBS_{s,g}$	= Observed number of lung cancer cases in group g of study s
$PRED_{s,g}$	= Predicted number of lung cancer cases in group g of study s , based on the fitted model
$E_{s,g}$	= Expected number of lung cancer cases in group g of study s
α_s	= Study-specific value of α
$CE10_{b,s,g}$	= Cumulative exposure to bin b in group g of study s
KL_b	= Lung cancer potency of bin b
For mesothelioma:	
$OBS_{s,g}$	= Observed number of mesothelioma cases in group g of study s
$PRED_{s,g}$	= Predicted number of mesothelioma cases in group g of study s , based on the fitted model
$PY_{s,g}$	= Person-years of observation for group g of study s
$C_{b,s,g}$	= Concentration of asbestos bin b for group g of study s
$Q_{s,g}$	= Cubic function of average exposure duration and time since first exposure for group s of study g
KM_b	= Mesothelioma potency of bin b
Bolded characters are vectors, e.g. \mathbf{C}	
The vectors \mathbf{KM} and \mathbf{KL} have implicit sizes set by the binning strategy under consideration. That is, $\mathbf{KM} = \{KM_1, KM_2, \dots, KM_b\}$ where b is the number of asbestos type-size bins in a specific strategy. Likewise, the vector \mathbf{C} has an implicit dimension of $nb \cdot ng$.	

TABLE 8-2. LIST OF BINNING STRATEGIES PROPOSED FOR EVALUATION

Number of Bins	Designation	Mineral Type	Length (um)	Width (um)
1	1P	Amphibole and chrysotile are considered together	> 5	≥ 0.25
	1A		All	< 0.4
	1B		> 5	< 0.4
	1C		> 10	< 0.4
	1D		All	< 1.5
	1E		> 5	< 1.5
	1F		> 10	< 1.5
2	2P	Amphibole and chrysotile are considered separately	> 5	≥ 0.25
	2A		All	< 0.4
	2B		> 5	< 0.4
	2C		> 10	< 0.4
	2D		All	< 1.5
	2E		> 5	< 1.5
	2F		> 10	< 1.5
4	4A	Amphibole and Chrysotile are considered separately	0-5 > 5	< 0.4
	4B		5-10 > 10	< 0.4
	4C		0-10 > 10	< 0.4
	4D		0-5 > 5	< 1.5
	4E		5-10 > 10	< 1.5
	4F		0-10 > 10	< 1.5

9.0 EPIDEMIOLOGICAL DATA PROPOSED FOR USE

As noted above, the approach proposed in this report is based on fitting mathematical equations (risk models) to the data from epidemiological studies to characterize the quantitative relationship between inhalation exposure to asbestos and the relative risk of lung cancer and/or the incidence of mesothelioma in exposed humans. This section summarizes the data requirements that must be satisfied for a study to be used in the model fitting effort, and provides a summary of the studies that are proposed for use in the fitting effort. Detailed descriptions of these studies are presented in Appendix A.

9.1 Criteria for Study Selection

A large number of studies have been published that provide information on the adverse effects of inhalation exposure to asbestos on human health (IPCS 1986, 1998, WHO 1998, ATSDR 2001). In order to be retained for use in the fitting effort, OSWER is recommending that a study must meet the following conditions:

- The study must be published in a refereed journal
- The study must provide data that can be expressed in terms of the quantitative risk models for lung cancer and/or mesothelioma
- The study cohort must consist of individuals who were exposed to approximately the same atmospheric composition of asbestos

OSWER is proposing that all studies that meet these criteria be retained for use, and that studies that do not provide sufficient data to establish quantitative estimates of exposure or cancer response, or that combine data for sub-cohorts exposed to different types of asbestos atmospheres, should be excluded. As noted previously, studies that are not used in the fitting effort may still be considered by EPA as part of the IRIS update.

An important part of this strategy is that studies that meet the inclusion requirements above are not further restricted to studies that meet some specified level of data quality. This is in contrast to suggestions from some of the peer consultation panel members that reviewed the approach of Aeolus (1999, 2001) (see Appendix D). OSWER carefully considered the recommendation of the peer consultation panel, but has concluded that imposing a more stringent set of data quality requirements is impracticable for the following reasons:

1. Because of the wide range in the sources and magnitudes of the errors that may occur in the cumulative exposure estimates for the groups, both within and between studies, it is

very difficult to articulate a simple set of acceptance rules. For example, if such an approach were to be implemented, it would seem that data quality requirements would be needed to address variables such as: size of the cohort, length and completeness of follow-up, quality of data on smoking and other confounding factors, accuracy of methods used to obtain vital status and cause of death data, accuracy and representativeness over both space and time of workplace measures of asbestos in air, accuracy of the job-exposure matrix, accuracy of data on the relative amounts of various types of asbestos used, etc.

2. Even if it were possible to establish such rules, studies that are retained for use would still have a wide range of data quality, and it would still be necessary to find a way to account for these differences in data quality.

OSWER believes that the assignment of PDFs around each input data item in each study that is retained can serve as an adequate means for accounting for the differing levels of data quality between groups and studies. This is consistent with the recommendations of some members of the 2003 peer consultation panel (see Appendix D).

In this approach, a study with relatively poor data in one or more data categories will have relatively wide uncertainty PDFs around those data items, and this will tend to diminish the effect of the data from that study on the resulting bin-specific potency factor solutions. Conversely, studies that are generally of higher quality will have PDFs that are relatively narrow around most of the data items, and this will tend to increase the effect of that study on the bin-specific potency factor solutions.

9.1.1 Specific Data Requirements for Lung Cancer Studies

As discussed above (see Section 8.1.1), data required to evaluate the exposure-response relationship for asbestos-induced lung cancer include the following:

Observed and Expected Lung Cancer Deaths

For lung cancer, the effect of asbestos exposure is characterized by the increase in relative risk attributable to the exposure. In an epidemiological study, the measure of relative risk is the ratio of the observed number of lung cancer deaths in a group divided by the expected number of lung cancer deaths in that group:

$$RR = \text{Observed Cases} / \text{Expected Cases}$$

Consequently, in order to be considered for inclusion in this analysis, each lung cancer study must provide both the observed and expected number of lung cancer cases for each exposure group, or provide data from which these values can be derived.

Cumulative Exposure

In order to be considered for inclusion in this analysis, a lung cancer study must provide estimates of the average cumulative exposure (f/cc-yrs) for each exposure group, or sufficient data to allow estimation of the cumulative exposure for each group. Typically the cumulative exposure will be expressed in terms of PCM f/cc-yrs, or else in terms of dust measurements (mppcf-yrs).

Number of Exposure Groups

Each lung cancer study is associated with a study-specific value of α , which is the relative risk of lung cancer in unexposed members of the cohort compared to the reference population. Because of this extra parameter in the lung cancer model, lung cancer studies require that there be at least two exposure groups per study, otherwise there is no constraint on the value of α for that study.

In the lung cancer data set proposed for use by OSWER, there is one exception to this rule. This is the study of U.S retirees by Henderson and Enterline (1979) and Enterline et al. (1987). In this case, it is clear that the cohort consists of several sub-cohorts who were exposed to differing asbestos mixtures. Henderson and Enterline (1979) provide data on the SMR for lung cancer stratified according to asbestos mixture, but the data are provided only as single groups (i.e., not stratified into two or more exposure bins for each asbestos mixture) (see Appendix A, Figures A3-1 to A3-3). However, Enterline et al. (1987) provide data that allow calculation of the value of α for the combined cohort (see Appendix A, Figure A3-4). Assuming that there are no substantial differences in the baseline risk of lung cancer as a function of the type of asbestos exposure that occurred, this value of α can be applied to each of the sub-cohorts, allowing the retention of the data from this study for use in the fitting effort for lung cancer.

9.1.2 Specific Data Requirements for Mesothelioma Studies

As discussed above (see Section 8.1.2), data required to evaluate the exposure-response relationship for asbestos-induced mesothelioma include the following:

Incidence of Mesothelioma

For mesothelioma, the effect of asbestos exposure is characterized by the probability that mesothelioma will occur as a consequence of the exposure. In an epidemiological study, the measure of this probability is the incidence of mesothelioma (I_m) in an exposure group, which is defined as the number of mesothelioma cases in the group divided by the total number of person-years of observation for the group:

$$I_m = \text{Observed Cases} / \text{Person-Years}$$

Consequently, in order to be considered for inclusion in this analysis, each mesothelioma study must provide both the observed number of cases and the person-years of observation for each group, or sufficient data such that these values may be estimated.

Cumulative Exposure

As discussed in Section 8.1.2, the metric of cumulative exposure used in the risk model for mesothelioma is a linear function of the exposure concentration (C) and a cubic function (Q) of exposure duration and time since first exposure:

$$\text{Cumulative exposure for mesothelioma} = C \cdot Q$$

Consequently, in order to be considered for inclusion in the data fitting analysis, each mesothelioma study must provide, for each group, the average exposure concentration C and the average value of Q , or alternatively the average time since first exposure (T) and the average exposure duration (d), from which the value of Q may be estimated.

9.1.3 Data Requirements for Atmospheric Composition

A key assumption in characterizing the exposure atmosphere for a study is that all members of a cohort are exposed to the same atmospheric composition, with exposures differing only in level and/or duration, rather than type. If this assumption is not satisfied (that is, the cohort is composed of individuals who are exposed to differing types of atmospheres), the exposure-response data for that cohort loses the ability to support a mathematical disaggregation of potency as a function of asbestos type. Hence, studies in which the cohort is known to be composed of individuals who are exposed to differing types of atmospheres are excluded from the data fitting process.

9.2 Studies Proposed for Use

Table 9-1 provides a summary of the lung cancer studies which were identified by OSWER that satisfy the proposed rules for inclusion in the model fitting effort. Table 9-2 provides a list of the mesothelioma studies identified. Detailed descriptions of these studies, including the exposure-response data, are provided in Appendix A.

As noted above, in studies in which the cohort consisted of two or more sub-cohorts that had exposures to differing mixtures (differing ratios of chrysotile and amphibole) in the workplace atmosphere, these sub-cohorts were evaluated separately whenever the data were adequate to do so.

As seen in Table 9-1, a total of 23 cohorts were identified that provide dose response data suitable for use in fitting to the lung cancer risk model. Table 9-2 lists 8 cohorts that provide quantitative exposure response data suitable for fitting to the mesothelioma risk model. These studies include a number of different industrial settings and operations, including mining and milling, textile manufacture, cement products manufacture, friction products manufacture, insulation manufacture, and insulation installation. These studies also span a range of different asbestos atmospheres, from nearly pure chrysotile to nearly pure amphibole. Note that it is this between-cohort variation in atmosphere that allows for estimation of the bin-specific potencies.

9.3 Studies Excluded

Several studies were identified which contained quantitative exposure-response data, but which OSWER believes should be excluded for other reasons. These include the following:

Unpublished Data

In earlier investigations of bin-specific potency factors for asbestos, Aeolus (2003) utilized unpublished data on lung cancer and/or mesothelioma provided by the principal investigators for three cohorts, as follows:

- Crocidolite miners in Wittenoom (data provided by Dr. N. De Klerk)
- Chrysotile textile workers in South Carolina (data provided by Dr. T. Schnoor and Dr. J. Dement)
- Chrysotile miners in Quebec (data provided by Dr. D Liddell and Dr. C McDonald)

Because these data are not available to the public, OSWER does not consider them appropriate for use in this analysis. However, published data are available on the South Carolina cohort

(Hein et al. 2007), the Wittenoom cohort (de Klerk et al. 1989) and the Quebec cohort (McDonald et al. 1993), and these published data are proposed for use in this report.

Cohorts with Mixed Atmospheres

As noted above, because the objective of this analysis is to determine if there are important differences in potency as a function of mineral type and/or particle size, OSWER recommends that studies in which health statistics were combined across two or more sub-cohorts exposed to substantially differing workplace atmospheres should be excluded. This included the reports by Selikoff et al. (1979) and Selikoff and Seidman (1991) on insulation workers. Although this is a very important cohort, it was excluded from the model fitting effort because the study population was not exposed at a single location but was composed of individuals from across the U.S. and Canada (hence increasing the likelihood that different workers were exposed to differing types of insulation). In addition, it is known that the asbestos content of insulation changed over time. Before 1930, the insulation was mainly chrysotile. Beginning in the mid-1930's, small amounts of amosite were used, with amosite becoming more widely used during World War II and thereafter (Selikoff et al. 1979). Consequently, individuals who were exposed early in the study period would have been exposed to a differing mixture of asbestos than individuals exposed later in the study period.

Studies with Other Limitations

Two lung cancer studies (Levin et al. 1998, Texas insulation manufacturers, and Ohlson and Hogstedt 1985, Swedish cement manufacturers) with quantitative data are proposed for exclusion because the mortality data (observed and expected) were reported based on duration of exposure rather than on cumulative exposure lagged by 10 years (CE10), which is used in the risk model for lung cancer. It would be possible to estimate the average cumulative exposure for each group if the mean concentration for each group were known. However, the mean concentration was not reported by group. Use of the cohort-wide mean concentration was not considered reasonable, since workers with the highest exposure levels may tend to leave the workforce earliest, leading to an inverse relation between exposure concentration and exposure duration.

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TABLE 9-1. LUNG CANCER STUDIES PROPOSED FOR USE

Index	Reference	Location	Process	Asbestos Type	
				Primary	Secondary
1	Berry and Newhouse 1983	Ferodo, UK	Friction Product Manufacturing	Chrysotile	Crocidolite
2	Hein et al. 2007	South Carolina	Textile Manufacturing	Chrysotile	Crocidolite (negligible amounts)
3	Henderson and Enterline 1979	United States	Cement Product Manufacturing	Amosite	
4	Henderson and Enterline 1979	United States	Cement Product Manufacturing	Chrysotile	
5	Henderson and Enterline 1979	United States	Cement Product Manufacturing	Chrysotile	Crocidolite
6	Finkelstein 1984	Ontario, Canada	Cement Product Manufacturing	Chrysotile	Crocidolite
7	Hughes et al. 1987	New Orleans, LA	Cement Product Manufacturing	Chrysotile	Amosite and crocidolite
8	Hughes et al. 1987	New Orleans, LA	Cement Product Manufacturing	Chrysotile	
9	Hughes et al. 1987	New Orleans, LA	Cement Product Manufacturing	Chrysotile	Crocidolite
10	McDonald et al. 1993	Asbestos, Quebec	Mining/Milling	Chrysotile	
11	McDonald et al. 1993	Thetford, Quebec	Mining/Milling	Chrysotile	
12	McDonald et al. 1982	Pennsylvania	Textile Manufacturing	Chrysotile	Crocidolite and amosite
13	McDonald et al. 1984	Connecticut	Friction Product Manufacturing	Chrysotile	Crocidolite and anthophyllite
14	Peto et al. 1985	Rochdale, England	Textile Manufacturing	Chrysotile	Crocidolite
15	Piolatto et al. 1990	Balangero, Italy	Mining/Milling	Chrysotile	
16	Seidman et al. 1986	New Jersey	Insulation Manufacturing	Amosite	Chrysotile
17	Albin et al. 1990	Sweden	Cement Product Manufacturing	Chrysotile	Crocidolite and amosite
18	McDonald et al. 2004	Libby, MT	Mining/Milling	Libby Amphibole	
19	de Klerk et al. 1989	Wittenoom, Australia	Mining/Milling	Crocidolite	
20	Lacquet et al. 1980	Belgium	Cement Product Manufacturing	Chrysotile	Crocidolite and amosite
21	Neuberger and Kundi 1990	Austria	Cement Product Manufacturing	Chrysotile	Crocidolite and amosite
22	Yano et al. 2001	Chongqin, China	Asbestos Products Manufacturing	Chrysotile	
23	McDonald et al. 1993	Asbestos, Quebec	Asbestos Products Manufacturing	Chrysotile	

TABLE 9-2. MESOTHELIOMA STUDIES PROPOSED FOR USE

Index	Reference	Location	Process	Asbestos Type	
				Primary	Secondary
1	McDonald et al. 1983	South Carolina	Textile Manufacturing	Chrysotile	Crocidolite (negligible amounts)
2	Finkelstein 1984	Ontario, Canada	Cement Product Manufacturing	Chrysotile	Crocidolite
3	McDonald et al. 1982	Pennsylvania	Textile Manufacturing	Chrysotile	Crocidolite and amosite
4	McDonald et al. 1984	Connecticut	Friction Product Manufacturing	Chrysotile	Crocidolite and anthophyllite
5	Peto et al. 1985	Rochdale, England	Textile Manufacturing	Chrysotile	Crocidolite
6	Seidman et al. 1986	New Jersey	Insulation Manufacturing	Amosite	Chrysotile
7	Piolatto et al. 1990	Italy	Mining and Milling	Chrysotile	
8	Yano et al. 2001	Chongqin, China	Asbestos Products Manufacturing	Chrysotile	

10.0 METHOD PROPOSED FOR ESTIMATING BIN-SPECIFIC EXPOSURES

10.1 Overview

In order to derive bin-specific potency factors, it is necessary that the cumulative exposure data used in the model fitting be expressed in terms of the bins being evaluated. However, as noted above, published epidemiological studies report data on workplace concentration of asbestos and/or cumulative exposure either in terms of midget-impinger based particle concentrations (mppcf), or in terms of PCM f/cc. Therefore, it is necessary to extrapolate from the original estimates of concentration or cumulative exposure to the corresponding bin-specific values based on data from studies at other locations. It is important to emphasize that this is a substantial obstacle and source of uncertainty in the development of bin-specific potency factors. This section describes the basic equations and data used to achieve this extrapolation.

10.2 Extrapolation from Dust to PCM-Based Measures

When the original units of concentration or cumulative exposure are based on dust (expressed as mppcf), the first step is to convert from mppcf to PCM f/cc:

$$C(\text{PCM}) = C(\text{mppcf}) \cdot \text{CF}$$

or

$$\text{CE}_{10}(\text{PCM}) = \text{CE}_{10}(\text{mppcf}) \cdot \text{CF}$$

where CF is the conversion factor from mppcf to PCM f/cc. In some studies, matched measurements (i.e., measurements of the same samples by both methods) are available that allow development of a site-specific value for CF. However, in many cases, matched data are not available, so a value of CF must be assumed based on data from other locations. It is generally agreed that the value varies from location to location and that there is no single value that is appropriate in all cases. However, most values of CF are found to range between 1 and 10 PCM f/cc per mppcf (USEPA 1986). Thus, a value of 3 PCM f/cc per mppcf is often used as an approximation when location-specific data are not available. OSWER proposed use of this factor as a default when site-specific information is not provided. In either case, extrapolation from dust measurements to PCM-based exposure is certainly an uncertain step. Appendix A describes the PDFs that OSWER proposes to characterize this source of uncertainty in studies where the extrapolation is required.

10.3 Extrapolation from PCM to Bin-Specific Measures

Once exposure is expressed in terms of PCM f/cc, it is necessary to extrapolate from the PCM-based exposure values to bin-specific exposure values. Because the exposure metrics for both lung cancer (CE10) and mesothelioma (C·Q) are linear functions of concentration, this extrapolation in exposure can be achieved simply by multiplying the PCM-based exposure estimate by the ratio of the bin-specific concentration to the PCM concentration:

$$Exposure_{Bin\ b} = Exposure_{PCM} \cdot \frac{Concentration\ of\ Bin\ b}{Concentration\ of\ PCM}$$

For convenience, the ratio of the concentration of Bin b to the concentration of PCM structures is referred to in this report as k_b :

$$Exposure_{Bin\ b} = Exposure_{PCM} \cdot k_b$$

For a four bin model, in which bins 1 and 2 are amphibole and bins 3 and 4 are chrysotile, the basic equations are:

$$\begin{aligned} C_1 &= C_{total} \cdot f_{amph} \cdot f_{a1} \\ C_2 &= C_{total} \cdot f_{amph} \cdot f_{a2} \\ C_3 &= C_{total} \cdot (1-f_{amph}) \cdot f_{c3} \\ C_4 &= C_{total} \cdot (1-f_{amph}) \cdot f_{c4} \end{aligned}$$

where:

$$\begin{aligned} C_b &= \text{concentration of asbestos particles in bin } b \\ f_{amph} &= \text{fraction of total asbestos particles that are amphibole} \\ f_{ab} &= \text{fraction of amphibole particles that satisfy the size requirements for bin } b \\ f_{cb} &= \text{fraction of chrysotile particles that satisfy the size requirements for bin } b \end{aligned}$$

The value of C_{total} (amphibole plus chrysotile, all sizes) is computed from the reported value of C_{PCM} as follows:

$$C_{total} = C_{PCM} / (f_{amph} \cdot f_{ap} + (1-f_{amph}) \cdot f_{cp})$$

where:

- C_{PCM} = concentration of PCM asbestos particles (amphibole plus chrysotile)
 f_{ap} = fraction of amphibole particles that satisfy the size requirements for PCM fibers
 f_{cp} = fraction of chrysotile particles that satisfy the size requirements for PCM fibers

Combining yields:

$$\begin{aligned}
 k_1 &= f_{amph} \cdot f_{a1} / [f_{amph} \cdot f_{ap} + (1-f_{amph})f_{cp}] \\
 k_2 &= f_{amph} \cdot f_{a2} / [f_{amph} \cdot f_{ap} + (1-f_{amph})f_{cp}] \\
 k_3 &= (1-f_{amph}) \cdot f_{c3} / [f_{amph} \cdot f_{ap} + (1-f_{amph})f_{cp}] \\
 k_4 &= (1-f_{amph}) \cdot f_{c4} / [f_{amph} \cdot f_{ap} + (1-f_{amph})f_{cp}]
 \end{aligned}$$

Source of Fraction Amphibole Data

Estimates of the amphibole content of each workplace atmosphere may usually be based on information provided from each published study. Several different cases exist, as follows.

“Chrysotile Only” Studies. A number of studies were performed at locations where chrysotile was stated to be the only form of asbestos that was used in the workplace. It would seem that an assignment of zero to fraction amphibole might be appropriate in such cases. However, the issue is complicated by the fact that amphibole asbestos may occur in the same deposit as chrysotile asbestos (e.g., Williams-Jones et al. 2001), and hence commercial forms of chrysotile may contain trace levels of amphibole asbestos. As discussed in greater detail in Appendix C, Addison and Davies (1990) measured the amphibole content of 81 different samples of commercial chrysotile, and found detectable levels in 28 of them, at levels ranging from about 0.1% to 0.6%. Based on these data, the point estimate for fraction amphibole in “pure” chrysotile may be derived as the count-weighted average tremolite concentration, treating non-detects at ½ the average detection limit. The resulting value is 0.05% (see Appendix C, Section 5.1).

Chrysotile plus Amphibole. In some studies, the description of the workplace and its operations makes clear that both chrysotile and amphibole were used in the workplace. Ideally, data from TEM studies of air samples collected from the workplace would serve as the basis for estimation of the relative amounts of chrysotile and amphibole in the exposure atmosphere. However, in the absence of such data, information on the relative amounts of different types of asbestos purchased or processed can be used as a rough surrogate for the relative amounts in the atmosphere.

Amphibole Only. Some epidemiological studies focus on workers who are exposed only to amphibole asbestos. No data were located to indicate that chrysotile occurs as a

common trace contaminant of amphibole asbestos, so the fraction amphibole term was generally assumed to be 100% in these cases.

Appendix A summarizes the available data on the fraction of amphibole asbestos present in the atmosphere for each workplace, and identifies the best estimate and the plausible range proposed for use in this evaluation. These values are summarized in Table 10-1.

Source of Size Fraction Data

Bi-variate particle size distribution data from TEM measurements are available from studies in a number of different workplace settings (Dement and Harris 1979, Gibbs and Hwang 1980, Hwang and Gibbs 1981), and these may be used to approximate the bin-specific concentration ratios that are needed. The first step in the application of these data is to select the TEM data set(s) that is(are) most closely matched to the epidemiological study being evaluated. The procedure that OSWER proposes for making this selection is as follows:

For Chrysotile:

1. Only chrysotile TEM data sets may be used to estimate f_{cb} and f_{cp} values.
2. Of the available chrysotile TEM data sets, prefer those that are based on the same industry. If there is more than one TEM data set for the industry, prefer data that are based on the same or similar operation, or are otherwise judged to be most relevant. If there is no reason to prefer one data set over another, then combine across all relevant TEM sets by averaging the data before calculating the k_b terms.
3. If there is no match on industry, then prefer data that are judged to be most relevant based on other considerations (e.g., the source of the chrysotile). If there is no reason to prefer one data set over another, then combine across all relevant TEM sets by averaging the data before calculating the k_b terms.

For Amphibole:

1. Only amphibole TEM data sets may be used to estimate f_{ab} and f_{ap} values.
2. Of the available amphibole TEM data sets, prefer those that are based on the same industry and the same amphibole type. If there is more than one set that matches on industry and type, prefer data that are based on the same or similar operation, or are otherwise judged to be most relevant. If there is no reason to prefer one data set over another, then combine across all relevant data sets by averaging the data before calculating the k_b values.
3. If there are no matches based on both industry and type, then identify data sets that are matched either on industry (but not type) or on type (but not industry). If there is more than one such data set, prefer the set that is judged to be most appropriate based on other

considerations (e.g., the source of the amphibole, the similarity of the industry, etc.). If there is no reason to prefer one TEM data set over another, then combine across all sets by averaging the data before calculating the k_b values.

4. If there are no data sets that match either on industry or type, then identify the data set(s) that are considered to be the most nearly relevant. If there is no reason to prefer one data set over another, then combine across all relevant TEM sets by averaging the data before calculating the k_b terms.

Table 10-2 presents an example of how a TEM data set is used to estimate f_b and f_p values. The data in the table are a hypothetical bivariate stratification of TEM-based asbestos fiber counts from a workplace that is judged to be similar to a workplace where an epidemiological study has occurred. Each value represents the fraction of the total TEM fibers that fall within the width-length bin. Note that the sum of the fractions totals 1.00. The first step is to estimate f_p , which is the fraction of fibers that would have been counted as PCM fibers. For convenience, structures observed under TEM that meet the counting rules for PCM are generally referred to as PCM-equivalents (PCME). Recalling that PCM fibers are > 0.25 μm in width and 5 μm or more in length, the PCME fraction is computed as the sum of the fractions shown by the cells enclosed by the heavy black line. The resulting value in this example is 0.46. The second step is to compute f_1 , which is the fraction of TEM structures that meet the definition of Bin 1. In this example, Bin 1 is defined as all particles that are thinner than 1.0 μm and have a length between 5-10 μm . These structures are indicated by the cells shaded yellow, and the sum of these cells is 0.33. Thus, in this example, the value of k_1 is:

$$k_1 = f_1 / f_p = 0.33 / 0.46 = 0.72$$

If the first group in the epidemiological study had a mean cumulative exposure of 15 PCM f/cc-yr, the corresponding mean cumulative exposure to Bin 1 structures would then be:

$$\text{CE}_{10}(1) = 15 \cdot 0.72 = 10.8 \text{ Bin 1 f/cc-yr}$$

Appendix B provides a detailed presentation of the TEM data that are available from a variety of workplace settings, along with the selection of TEM data sets for matching to each epidemiological study and the tables used to calculate the values of f_b , f_p , f_{cb} and f_{cp} used in this assessment.

As noted above, it is apparent that use of TEM data measured in one location to represent the particle size distribution in another location is a source of uncertainty. Appendix C describes a general approach for specifying PDFs that characterize this uncertainty, depending of the degree

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to which the source of the TEM data set is matched to the conditions of the workplace to which it is applied.

TABLE 10-1 SUMMARY OF PROPOSED FRACTION AMPHIBOLE VALUES

Panel A: Lung Cancer

Index	Reference	Location	Process	Fraction Amphibole		
				Lower Bound	Point Estimate	Upper Bound
1	Berry and Newhouse 1983	Ferodo, UK	Friction Product Manufacturing	0.0	0.005	0.02
2	Hein et al. 2007	South Carolina	Textile Manufacturing	3.4E-05	5.4E-04	1.9E-03
3	Henderson and Enterline 1979	United States	Cement Product Manufacturing	1.0	1.0	1.0
4	Henderson and Enterline 1979	United States	Cement Product Manufacturing	3.4E-05	5.4E-04	1.9E-03
5	Henderson and Enterline 1979	United States	Cement Product Manufacturing	0.15	0.2	0.25
6	Finkelstein 1984	Ontario, Canada	Cement Product Manufacturing	0.05	0.1	0.15
7	Hughes et al. 1987	New Orleans, LA	Cement Product Manufacturing	0.03	0.05	0.07
8	Hughes et al. 1987	New Orleans, LA	Cement Product Manufacturing	3.4E-05	5.4E-04	1.9E-03
9	Hughes et al. 1987	New Orleans, LA	Cement Product Manufacturing	0.11	0.14	0.2
10	McDonald et al. 1993	Asbestos, Quebec	Mining/Milling	0.002	0.006	0.018
11	McDonald et al. 1993	Thetford, Quebec	Mining/Milling	0.012	0.037	0.11
12	McDonald et al. 1982	Pennsylvania	Textile Manufacturing	0.005	0.01	0.02
13	McDonald et al. 1984	Connecticut	Friction Product Manufacturing	0.001	0.005	0.02
14	Peto et al. 1985	Rochdale, England	Textile Manufacturing	0.02	0.026	0.032
15	Piolatto et al. 1990	Balangero, Italy	Mining/Milling	3.4E-05	5.4E-04	1.9E-03
16	Seidman et al. 1986	New Jersey	Insulation Manufacturing	0.95	0.99	1.0
17	Albin et al. 1990	Sweden	Cement Product Manufacturing	0.0	0.02	0.05
18	McDonald et al. 2004	Libby, MT	Mining/Milling	1.0	1.0	1.0
19	de Klerk et al. 1989	Wittenoom, Australia	Mining/Milling	1.0	1.0	1.0
20	Lacquet et al. 1980	Belgium	Cement Product Manufacturing	0.08	0.1	0.12
21	Neuberger and Kundi 1990	Austria	Cement Product Manufacturing	0.05	0.1	0.2
22	Yano et al. 2001	Chongqin, China	Asbestos Products Manufacturing	0	0	0
23	McDonald et al. 1993	Asbestos, Quebec	Asbestos Products Manufacturing	0.002	0.006	0.018

Panel B: Mesothelioma

Index	Reference	Location	Process	Fraction Amphibole		
				Lower Bound	Point Estimate	Upper Bound
1	McDonald et al. 1983	South Carolina	Textile Manufacturing	3.4E-05	5.4E-04	1.9E-03
2	Finkelstein 1984	Ontario, Canada	Cement Product Manufacturing	0.05	0.1	0.15
3	McDonald et al. 1982	Pennsylvania	Textile Manufacturing	0.005	0.01	0.02
4	McDonald et al. 1984	Connecticut	Friction Product Manufacturing	0.001	0.005	0.02
5	Peto et al. 1985	Rochdale, England	Textile Manufacturing	0.02	0.026	0.032
6	Seidman et al. 1986	New Jersey	Insulation Manufacturing	0.95	0.99	1.0
7	Piolatto et al. 1990	Italy	Mining/Milling	3.4E-05	5.4E-04	1.9E-03
8	Yano et al. 2001	Chongqin, China	Asbestos Products Manufacturing	0	0	0

TABLE 10-2 EXAMPLE USE OF TEM DATA TO ESTIMATE VALUES FOR k(i)

In this example, Bin 1 is defined as fibers with length 5-10 um and thickness < 1.0 um.

Width (um)	Length (um)		
	< 5	5 - 10	> 10
<0.25	0.13	0.08	0.04
0.25-0.5	0.15	0.12	0.06
0.5-1.0	0.08	0.13	0.05
1.0-1.5	0.04	0.04	0.04
>1.5	0.02	0.01	0.01

PCME = 0.46
(heavy line)

Bin 1 = 0.33
(yellow shading)

$$k(1) = \text{Bin 1} / \text{PCME} = 0.72$$

11.0 UTILIZING POTENCY FACTORS TO COMPUTE LIFETIME RISK

It is important to emphasize that bin-specific potency values are not analogous to cancer slope factors or unit risks. Rather, potency factors, when combined with the basic risk models described in Section 8.1, allow computation of relative risk of lung cancer or incidence of mesothelioma in an individual at some specified age of life. In order to derive estimates of the excess life time risk of cancer to an exposed individual, it is necessary to implement a life-table approach, as detailed in USEPA (1986). In brief, given some specified level of exposure to an asbestos mixture of specified composition, risks of dying from asbestos induced lung cancer or mesothelioma are computed for each year of life, and these risks are combined with the probability of death from other causes to yield an estimate of the lifetime total probability of dying from the asbestos exposure. The total probability of death from cancer divided by the exposure concentration yields the unit risks for the scenario being evaluated. USEPA (1986) used this approach to generate tables of unit risk values for lung cancer and mesothelioma for a number of scenarios that differed in the age at first exposure and the duration of exposure. EPA is currently developing a spreadsheet tool that will facilitate these computations by risk assessors using bin-specific potency factors.

One of the complications in performing these calculations is that there is uncertainty associated with the potency factors. Thus, there will be uncertainty in the calculated lifetime excess risk values. There are several alternative strategies for characterizing the uncertainty in the lifetime risk calculations. The simplest approach is to select some conservative (high end) value from the uncertainty distribution for each bin-specific potency factor, and utilize these values in the calculations. The disadvantage of this approach is that the probability that the true value of each potency factor is at the upper end of its uncertainty distribution is small. An alternative approach is to utilize the full matrix of bin-specific potency factors, and use these to compute an uncertainty distribution of the potency factor for some specified asbestos mixture of concern at a site. Lifetime risks from exposure to that mixture can then be computed from any statistic of interest from the mixture-specific potency factor uncertainty distribution (e.g., central tendency value, high end value), as deemed appropriate by risk managers.

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