APPENDIX A: UPDATE OF POTENCY FACTORS FOR LUNG CANCER (K_L) AND MESOTHELIOMA (K_M)

Estimates of risk of dying of lung cancer or mesothelioma from asbestos exposure are quantified by means of mathematical models that express risk as a function of exposure. The models utilized in the 1986 U.S. EPA Airborne Asbestos Health Assessment Update (U.S. EPA 1986) contain parameters (K_L for lung cancer and K_M for mesothelioma) that gauge the potency of asbestos for causing these health effects. USEPA calculated K_L and K_M values from a number of studies. In this section these K_L and K_M calculations are revised using the same models as in the U.S. EPA (1986) update, but incorporating newer data from more recent publications. Since the 1986 update, additional cohorts have been studied from several new exposure settings and the followup periods have been extended for several of the previously studied cohorts.

In the 1986 update, K_M values were not calculated from all of the available studies, perhaps owing to the limited number of mesotheliomas observed in some of these studies. In this update, an attempt has been made to utilize any study with suitable health and exposure data, regardless of the number of mesotheliomas reported, and to quantify the statistical uncertainty attributable to small numbers using statistical confidence limits. Since the present work utilizes somewhat different methods from the 1986 update, for consistency, all of the K_L and K_M values were recalculated, even from studies for which no new data were available. Table A-1 contains a summary of the new values for K_L and Table A-2 contains the new values for K_M. The original values from the 1986 update are also provided for comparison. These tables also contain statistical confidence limits and ad hoc "uncertainty limits" for K_L and K_M. The derivation of these limits will be described in detail in subsequent sections.

A.1 LUNG CANCER MODEL

The 1986 U.S. EPA lung cancer model (U.S. EPA 1986) assumes that the relative risk, RR, of mortality from lung cancer at any given age is a linear function of cumulative asbestos exposure (fiber-years/ml, or f-y/ml, as measured by PCM), omitting any exposure in the most recent 10 years. This exposure variable is denoted by CE_{10}. The 10-year lag embodies the assumption that exposures during the most recent 10 years do not affect current lung cancer mortality risk. The mathematical expression for this model is

$$RR = 1 + K_L * CE_{10}, \qquad \text{(Eq. A-1)}$$

where the linear slope, K_L, is the "lung cancer potency factor." To make allowance for the possibility that the background lung cancer risk in the exposed population differs from that of the comparison population, the model is expanded to the form,

$$RR = \alpha * (1 + K_L * CE_{10}). \qquad \text{(Eq. A-2)}$$

With this form of the model the relative risk at zero exposure is α rather than 1.0. Both K_L and α are estimated by fitting the model to data. The type of data usually available for applying this model are from cohort studies in which observed and expected (based on an appropriate comparison population, e.g., U.S. males) numbers of lung cancers are categorized by cumulative exposure incorporating a 10 year lag. To explore the adequacy of the model, it is useful to have the data cross-classified by one or more other variables, such as latency.

Frequently the cumulative exposure variable available from the published report of a study does not incorporate a lag (or, less frequently, incorporates a lag of less than 10 years). In this report, rather than attempting an ad hoc correction, no correction for lag has been made. Although this tends to cause K_L values to be slightly underestimated, this is unlikely to be a serious problem. For most cohorts, exposures decreased significantly over time. Also, in many studies, followup didn't begin until several years after the start of exposure and the bulk of the lung cancers occurred at older ages. All of these factors tend to mitigate the error created from use of data with no lag. Moreover, use of an ad hoc correction for lag could hinder comparisons of K_L values among studies that do not employ a lag (which includes the majority of studies).

A.2 MESOTHELIOMA MODEL

The 1986 U.S. EPA mesothelioma model (U.S. EPA 1986) can be derived by assuming that the mortality rate at time t after the beginning of exposure can be calculated by summing the contributions from exposure at each increment of time, du, in the past. The contribution to the mortality rate at time t from exposure to E(u) f/ml (as measured by PCM) at time u is assumed to be proportional to the product of the exposure rate, E(u), and $(t–u–10)^2$, the square of the elapsed time minus a lag of 10 years. Thus, as with the lung cancer model, the mesothelioma model assumes a 10-year lag before exposure has any effect upon risk. With the additional assumption that the background rate of mesothelioma is zero, the mesothelioma mortality rate at time t since the beginning of exposure is given by

$$I_M(t) = 3 * K_M * \int_0^{t-10} E(u) * (t - u - 10)^2 \, du, \qquad \text{(Eq. A-3)}$$

where t and u are in years, and $I_M(t)$ is the mortality rate per year at year t after the beginning of exposure. The proportionality factor, K_M, is called the "mesothelioma potency factor." The factor of "3" is needed to retain the same meaning of K_M as defined by U.S. EPA (1986).

If exposure is at a constant level, E, for a fixed duration, DUR, this model can be written as

$$\begin{array}{ll} 0 & 0 \le t \le 10 \\ I_M(t) = K_M * E * (t - 10)^3 & 10 \le t \le 10 + DUR \\ K_M * E * [(t - 10)^3 - (t - 10 - DUR)^3] & DUR \le t \end{array} \qquad \text{(Eq. A-4)}$$

The genesis of this model and its agreement with data were discussed in U.S. EPA (1986).

Through the courtesy of Dr. Corbett McDonald, Professor Douglass Liddell, Dr. Nicholas de Klerk, Dr. John Dement, and the National Institute for Safety and Health (NIOSH), raw data on mesothelioma mortality were obtained from a cohort of Quebec chrysotile miners and millers

(Liddell et al. 1997; McDonald et al. 1980a), a cohort of Wittenoom, Australia crocidolite miners and millers (Armstrong et al. 1988; de Klerk et al. 1994), and a cohort of workers from a plant in Charleston, South Carolina that manufactured textiles from chrysotile (Dement et al. 1983a,b, 1994; Dement and Brown 1998). These data were used to calculate K_M values in a more accurate manner for these cohorts (using the "exact" approach described below) and to explore the potential magnitude of the errors incurred by the crude application of cohort-wide averages when fitting the mesothelioma model.

A.3 STATISTICAL FITTING METHODS

The method of maximum likelihood (Cox and Oakes 1984; Venzon and Moolgavkar 1988) was used herein to fit the lung cancer and mesothelioma models to data and to estimate K_L and K_M. The profile likelihood method was used to calculate statistical confidence intervals and likelihood ratio tests were used to assess goodness-of-fit and test hypotheses.

Typically the data for calculating a lung cancer potency factor, K_L, consist of observed and expected (based on an external control group, such as U.S. males) numbers of cancer deaths categorized by cumulative exposure. The likelihood of these data is determined by assuming that the deaths in different exposure categories are independent and that the number of deaths in a particular category has a Poisson distribution with expected number given by the expected number predicted by the external control group times the relative risk given by either expression (Eq. A-1 or A-2).

In the typical situation, the published data most useful for calculating the mesothelioma potency factor, K_M, consist of the number of mesothelioma deaths and person-years of observation categorized by time since first exposure. The likelihood of these data is determined by assuming statistical independence of the number of mesothelioma deaths in different categories and that the number of mesothelioma deaths in a category has a Poisson distribution with mean equal the number of person-years in the category times expression (Eq. A-4), using average values for E, DUR, and t appropriate for that category.

The fitting of the mesothelioma model (Eq. A-3) to raw (unsummarized) mesothelioma data is accomplished using an "exact" maximum likelihood method. The cumulative mesothelioma hazard is defined as

$$H(t) = \int_0^t I_M(u)\, du. \qquad \text{(Eq. A-5)}$$

The contribution to the likelihood of a person whose followup terminated at t is $S(t) = \exp[\, -H(t)\,]$ if the followup did not terminate in death from mesothelioma, and $I_M(t) * S(t)$ if the person died of mesothelioma. The complete likelihood was defined as the product of these individual contributions. The integrals in expressions (Eq. A-3 and A-5) were evaluated numerically.

A.4 SELECTION OF A "BEST ESTIMATE" OF K_L AND K_M

For each study for which a K_L or K_M is estimated, a "best estimate" is provided. For lung cancer, the best estimate of K_L (Table A-1) was generally assumed to be the maximum likelihood estimate (MLE) obtained with α estimated. For mesothelioma, the best estimate of K_M (Table A-2) is generally the maximum likelihood estimate derived from the best-fitting model in the form (Eq. A-3) for raw data and (Eq. A-4) for published data. As described in the descriptions of the individual studies, in a few cases these general rules had to be adapted to fit the particular form of the data available.

A.5 UNCERTAINTY IN K_L AND K_M

Statistical uncertainty in K_L and K_M estimates is expressed using 95% upper and lower statistical confidence limits. These limits (summarized in Table A-1 for lung cancer and Table A-2 for mesothelioma) were computed using the profile likelihood method and (for K_L) with α estimated.

However, non-statistical sources of uncertainty, such as model uncertainty and uncertainty in exposure, are also likely to be very important. Although these uncertainties are difficult to quantify, it is important to attempt quantification, since presentation of statistical uncertainty alone may provide a misleading picture of the reliability of the estimates. Consequently, an ad hoc approach to quantifying non-statistical uncertainty was adopted in this report. In this approach, the primary sources of uncertainty are identified. Then, for each study, a factor was selected for each uncertainty source using guidelines that will be described in this appendix. The individual factors were combined with the statistical confidence bounds to arrive at an "uncertainty range" for K_L or K_M for each particular cohort. These ranges are described in detail in following sections and are summarized in Table A-1 for lung cancer and Table A-2 for mesothelioma.

Because the most serious uncertainties among published epidemiology studies are often attributable to the estimation of exposure, three factors (F1, F2, and F3) were defined to address distinct sources of uncertainty associated with exposure. Two additional factors (F4L and F4M) were defined to account for uncertainty due to special limitations that had to be addressed to facilitate estimation of exposure-response factors from specific studies for lung cancer and mesothelioma, respectively.

To define the factors we used to address uncertainty associated with exposure, we first considered that, ideally, cumulative exposure would be estimated in an epidemiology study by:

- continuously monitoring the concentrations to which the worker is exposed over their entire working life;

- measuring such concentrations using personal monitors (samplers worn by workers with sampling ports placed within a few inches of the breathing zone of the worker); and

! analyzing samples in a manner appropriate for determining the concentration of the specific range of structures of interest[1].

In practice, however, measurements are collected only periodically at fixed locations considered representative of worker exposures for jobs performed at that location (local operations). Moreover, measurements were frequently derived using analytical methods that report results in units different from those of interest, so that some type of conversion is required. Then, typically, cumulative exposures are estimated for individual workers as the sum (over the set of jobs held by that worker) of the product of the mean exposure concentration for each job and the duration over which that job is performed. Thus:

$$\overline{C}_{PCM_i} = Q\sum_j C_{LO}D_i \qquad \text{(Eq. A-6)}$$

where:

$\overline{C}_{PCM}$ is the cumulative exposure experienced by a worker to PCM fibers (f-years/ml);

Q is a factor used to convert concentration measurements in a particular study to PCM fiber concentrations whenever the measurements in the study were collected using a different method (usually dust concentrations determined by midget impinger, in which case the units of Q are f/ml/mppcf);

C_{LO} is the concentration estimated for a particular "local operation" typically derived by a combination of measurement and extrapolation; and

D_j is the duration of time that the worker spent working in local operation "j".

Note that, because exposure concentrations at specific locations have generally been observed to decrease over time due to changes in process, introduction of dust control equipment, and other factors, cumulative annual exposures are generally estimated for workers in the manner described above and the annual exposures are then summed. However, this does not change the general applicability of Equation A-6.

Based on Equation A-6, a factor, F1, is defined to account for uncertainty introduced in the manner that the C_{LO} are determined in specific epidemiology studies; a factor, F2, is used to address uncertainty associated with the determination of the conversion factors, Q, for specific studies; and F3 is defined to represent uncertainty in the manner that job matrices are developed

[1]Most comparisons of epidemiology studies involve converting estimates of cumulative exposures to fiber concentrations as determined by phase contrast microscopy (PCM) using the "membrane filter method". Thus, for the discussion above, the range of structures (exposure index) of interest would be those determined using the membrane filter method. Importantly, however, discussions in other portions of this document deal with determining asbestos concentrations using an exposure index representing the specific range of structures that contribute directly to biological activity, which should not be confused with the exposure index reported using the membrane filter method.

in specific studies to assign workers to specific local operations over specific durations. The manner in which values were assigned for each uncertainty factor is described more fully below.

A.5.1 The Factor F1

As indicated above, the factor, F1, represents the uncertainty in concentration estimates to which workers are exposed (in whatever units of exposure that are reported in a particular study). In addition to analytical uncertainty, considerations addressed when assigning values for F1 for specific epidemiology studies include:

- to what extent exposure concentrations were directly determined from measurements collected at the locations and times that worker exposures actually occurred; and

- whether measurements were derived from personal monitoring or from area monitoring (sampling a general area that is assumed representative of exposure conditions associated with jobs performed within the local area).

Regarding the latter consideration, exposure concentrations estimated in the published epidemiology studies were almost universally determined by area, rather than personal monitoring. As has been reported in several of these studies (see, for example, McDonald et al. 1983b), area monitoring can miss short-term, high-level exposures contributed by the personal actions being performed by a worker. Moreover, certain periodic activities potentially associated with extremely high exposure (typically involving cleanup) were not performed during time periods when work areas were routinely monitored.

Regarding the first bullet above, published epidemiology studies differ in the frequency and time period over which sampling was conducted. With few exceptions, little or no sampling was conducted prior to the 1950's when exposure concentrations are thought generally to be higher than those monitored more recently, due to lack of use of dust control equipment and procedures that were introduced only later. For many studies, therefore, early exposures had to be estimated by extrapolation from later measurements and the care with which such extrapolations were performed also varies from study to study.

Studies vary in the degree to which the range of local operations associated with a particular facility were individually sampled. Exposure conditions attendant to jobs performed in association with local operations not sampled directly would then be extrapolated from measurements collected for other local operations assumed to be associated with “comparable exposures.” As with extrapolations in time, the care with which such spatial extrapolations were performed varies from study to study.

Values assigned for F1 vary between 1.5 and 4 (all to the nearest 0.5). The most typical value assigned is 2.0 for studies in which additional uncertainty is introduced due to use of area samplers rather than personal samplers, lack of measurements representative of episodic but high-exposure jobs (usually associated with cleanup), and lack of direct measurements from the earliest periods of exposure (when dust control equipment and procedures were absent). To be assigned a value of 2.0, however, authors must have had access to substantial numbers of

samples representative of the majority of the local operations of interest, must have described a systematic procedure for extrapolating exposure estimates to less well studied local operations, and must have described a systematic procedure for extrapolating exposure estimates to earlier times when measurements were lacking. The logic used to assign F1 values (and values for the other uncertainty factors) for individual studies is described for each study in Section A.6 of this appendix.

A.5.2 The Factor F2

F2 is a factor used to characterize the uncertainty introduced in deriving conversion factors to convert from the exposure indices measured in a particular study to the exposure index typically reported using the membrane filter method (as determined by PCM). In about half of the studies, concentrations are estimated in millions of dust particles per cubic foot (mppcf) as determined by midget impinger (see Section 4.3). The uncertainty introduced by such conversions varies from study to study because:

- for a small number of studies, the majority of measurements were performed by the membrane filter method so that conversion was unnecessary;
- for some studies, conversion factors were derived from a statistical analysis of a set of side-by-side measurements determined, respectively, using the membrane filter method and the other method from which measurements need to be converted (typically the midget impinger method);
- for some studies, lack of side-by-side measurements required expert judgement for comparing across samples collected at different times and locations; and
- for some studies, conversion factors were not derived at all, but were adapted from other studies of similar processes.

Moreover, as has been demonstrated in several studies, the factors used to convert other measurements (primarily midget impinger) to the exposure index determined by PCM vary as a function of study environment, local operation, and time. For example, the ratio of PCM to midget impinger derived from side-by-side measurements in a single study reportedly varied between 0.3 and 30 (McDonald et al. 1980a).

Note that, given the above, the factors used to convert measured concentrations to exposure concentrations in units of interest (Q in Equation A-6) ideally should be brought into the sum on the right and determined individually for each local operation. However, with the exception of the South Carolina study by Dement and coworkers (Dement et al. 1994; Dement and Brown 1998), only average (study-wide) conversion factors are typically estimated in any particular study.

Values for F2 assigned to particular studies vary between 1.0 and 3.0. Studies in which conversions were not required (due to routine use of PCM) or studies in which conversion factors were determined for specific operations were assigned an F2 value of 1.0. Studies in which a study-wide conversion factor was determined from paired measurements are assigned a

value of 1.5. Studies in which conversion factors were adapted from other studies or for which authors did not define a conversion factor were assigned larger values for F2.

A.5.3 The Factor F3

The factor, F3, is used in this study to represent the uncertainty attributable to the manner in which job-exposure matrices were constructed in the various published epidemiology studies. Authors for some studies had detailed work histories that could be used to identify the complete set of specific jobs that each worker performed over their working life and the duration of time spent on each job. Authors from other studies did not have access to individual work histories so that crude estimates of average duration was applied to all members of the cohort. The factor, F3, is used to account for conditions in which less than optimal job histories were used to identify the set of jobs performed by each worker and the duration that each worker spent performing each such job.

A.5.4 The Factor F4L for Lung Cancer and F4M for mesothelioma

An additional factor is included (F4L for lung cancer) and (F4M for mesothelioma) to account for uncertainties in mortality data (e.g., when diagnosis is uncertain for a substantial fraction of potential mesothelioma cases) or when approximations or assumptions are required because the data are not presented in the form needed for fitting the exposure-response models. Two assigned F4L values are greater than 1.0 (1.5 and 2.0), and six F4M values are greater than 1.0; these six values range from 2.0 to 5.0.

A.5.5 Combining Individual Uncertainty Factors into an Overall "Uncertainty Range"

As indicated above, in addition to statistical confidence intervals, four uncertainty factors have been proposed: F1: exposure, general; F2: exposure conversion factor; F3: lack of individual work histories; and F4L (lung cancer) and F4M (mesothelioma): non-exposure related. Since it is unlikely that all of the uncertainty sources would cause errors in the same direction in the same study, rather than multiplying the uncertainty factors, an overall uncertainty factor, F, was calculated as:

$$F = \exp\{ [\mathrm{Ln}^2(F1) + \mathrm{Ln}^2(F2) + \mathrm{Ln}^2(F3) + \mathrm{Ln}^2(F4)]^{1/2} \},$$

where 1.0 is the default value for any factor not explicitly provided. The overall "uncertainty range" for K_L or K_M was calculated by dividing the statistical 95% lower bound by F and multiplying the 95% upper bound by F.

A.6 ANALYSIS OF INDIVIDUAL EPIDEMIOLOGY STUDIES

Predominately Chrysotile Exposure

Quebec Mines and Mills. Liddell et al. 1997 extended the followup into 1992 of a cohort of about eleven thousand workers at two chrysotile asbestos mines and related mills in Quebec that had been studied earlier by McDonald et al. 1980b (follow-up through 1975) and McDonald et al. 1993 (follow-up through 1988). Production at the mines began before 1900. The cohort

consisted of workers who worked ≥1 month and who were born between the years of 1891 and 1920. Follow-up began for each individual after 20 years from first employment. The most recent follow-up (Liddell et al. 1997) traced 9,780 men through May 1992, whereas 1,138 (10%) were lost to view, most of whom worked for only a few months prior to 1935. Of those traced, 8,009 (82%) were deceased as of 1992.

Estimates of dust levels in specific jobs were made from some 4,000 midget impinger measurements collected systematically starting in 1948 and periodically in the factory beginning in 1944. Estimates for the period prior to 1949 utilized interviews with long-term employees and comparison with more recent conditions. These dust-level estimates were matched to individual job histories to produce estimates of cumulative exposure for each worker (mppcf-years). Conversions between dust levels and PCM concentrations were derived from side-by-side samples. On the basis of over 600 side-by-side midget impinger and optical microscopy measurements, it was estimated that 3.14 fibers/ml was, on the average, equivalent to 1.0 mppcf (McDonald et al. 1980b).

Liddell et al. (1997) categorized cancer deaths after age 55 from of lung, trachea, and bronchus by cumulative asbestos exposure to that age (Liddell et al. 1997, Table 8). Standardized mortality ratios (SMRs) were calculated based on Quebec rates from 1950 onward, and Canadian, or a combination of Canadian and Quebec rates, for earlier years. Table A-4 shows the fit of the lung cancer model to these data. Although the models both with $\alpha=1$ and α variable provided reasonably adequate fits to the data, the hypothesis $\alpha=1$ can be rejected ($p=0.014$). The model with α estimated yields a best estimate of K_L of 0.00029 $(\text{f-y/ml})^{-1}$, 90% CI: (0.00019, 0.00041). With $\alpha=1$, the estimate was $K_L=0.00041$ $(\text{f-y/ml})^{-1}$, 90% CI: (0.00032, 0.00051).

Smoking history was obtained in 1970 by a questionnaire administered to current workers, and to proxies of those who had died after 1950. Although no analyses of lung cancer and asbestos exposure were presented for the 1992 follow-up (Liddell et al. 1997) that controlled for smoking, such an analysis was conducted for the follow-up that continued through 1975 (McDonald et al. 1980a). Table 9 of McDonald et al. (1980a) contained data on lung cancer categorized jointly by cumulative exposure to asbestos and by smoking habit. Two models were fit to these data: the multiplicative model for relative risk

$$RR = \alpha * (1 + b * d) * (1 + c * x),$$

and the additive model

$$RR = \alpha * (1 + b * d + c * x),$$

where d is cumulative exposure to asbestos to age 45, x is number of cigarettes smoked per day, and α,b, and c are parameters estimated from the data. The multiplicative model fit the data well, but the fit of the additive model was inadequate. This corroborates the multiplicative interaction between smoking and asbestos exposure in causing lung cancer (Hammond et al. 1979). The estimate of potency using the multiplicative model was 0.00051 $(\text{f-y/ml})^{-1}$, which was very close to that of 0.00045 $(\text{f-y/ml})^{-1}$ estimated from Table 5 of McDonald et al. (1980a), which did not utilize smoking data. This suggests that the association between lung cancer and asbestos exposure is not strongly confounded with smoking in this cohort.

By 1993, 38 deaths from mesothelioma had occurred in this cohort (Liddell et al. 1997). Through the courtesy of Dr. Corbett McDonald and Professor Douglass Liddell, the underlying mesothelioma data from this study were provided for additional analysis (Liddell 2001). These data contained the following information on each worker: the date of birth, asbestos exposure history, last date of follow-up, whether follow-up ended as a result of death from mesothelioma, location of first employment, and whether a worker had been employed at more than one location.

Nine distinct locations for first employment were coded. Locations 5–9 referred to small operations, some having very heterogeneous exposures, and were omitted from the analysis. Also, workers who worked at more than one location were omitted. After these exclusions, there remained 9,244 workers who worked at Locations 1–4, and among whom 35 deaths from mesothelioma occurred. Location 1 (4,195 men, 8 deaths from mesothelioma) was the mine and mill at the town of Asbestos. Location 2 (758 men, 5 deaths) was a factory at the town of Asbestos that, in addition to processing chrysotile, had also processed some crocidolite. Location 3 (4,032 men, 20 deaths) comprised a major mining and milling company complex near Thetford Mines. Location 4 (259 men, 2 deaths) comprised a number of smaller mines and mills also in the vicinity of Thetford Mines. Because of the small number of workers at Location 4, the fact that both locations were near Thetford Mines, and the fact that the separate K_M values obtained from Locations 3 and 4 were similar, data from these locations were combined. The remaining groups were analyzed separately, because of the crocidolite used at Location 2, and because of evidence of greater amounts of tremolite in the ore at Thetford Mines that at Asbestos (Liddell et al. 1997).

The availability of the raw data from this study made it possible calculate K_M from this study using an "exact" likelihood approach based on expression (Eq. A-3) that did not involve any grouping of data, or use of average values. For Location 1 (Asbestos mine and mill), K_M=0.013x10^{-8}, 90% CI: (0.0068x10^{-8}, 0.022x10^{-8}). For Location 2 (Asbestos factory), K_M=0.092x10^{-8}, 90% CI: (0.040x10^{-8}, 0.18x10^{-8}). For Locations 3 and 4, K_M= 0.021x10^{-8}, 90% CI: (0.014x10^{-8}, 0.029x10^{-8}). The K_M estimate from Location 1 (whose ore was reported to have a lower tremolite content) was about one-half that from Locations 3 and 4, although this difference was not significant (p=0.22). The K_M estimated from Location 2, the mill where substantial crocidolite was used, was 4–7 times higher than the K_L estimated from Location 1 and Locations 3 and 4.

For comparison purposes, K_M were also calculated using grouped data and applying expression (4), since this is the method that must be used with most studies. For Location 1 (3 and 4) the K_M estimate based on the "exact" analysis was 34% (25%) higher than that based upon grouped data. This suggests that reliance upon published data for calculating K_M may introduce some significant errors in some cases. Such errors may be further compounded by the failure of some studies to report the needed data on levels and durations of exposure in different categories of time since first exposure.

For this study F1 is set equal to 2.0. This study is the paradigm used to define the typical case (see Section A.5.1) in which increased uncertainty can be attributed to use of area rather than personal samplers, lack of measurements early in the study, and lack of direct measurements from certain episodic but high-exposure operations. At the same time, the authors of this study

appear to have used the available data in a systematic and objective manner to address the issues raised by the lack of sampling.

The uncertainty factor F2 is set equal 1.5 for this study to reflect use of a conversion factor that is derived from paired samples, but that is based on a project wide average, rather than addressing variation for specific, local operations.

All other uncertainty factors are set equal to 1.0 for this study due to lack of remarkable distinctions. Thus:

F1 = 2.0
F2 = 1.5
F3 = 1.0
F4L = 1.0
F4M = 1.0

These uncertainty factors, when coupled with the statistical confidence limits, resulted in the uncertainty ranges for K_L and K_M shown in Tables A-1 and A-2.

Italian Mine and Mill. Piolatto et al. (1990) conducted additional follow-up of workers at a chrysotile mine and mill in Italy that was earlier studied by Rubino et al. (1979). The cohort consisted of 1058 workers with at least 1 year of employment between 1946 and 1987. Follow-up extended from 1946 through 1987, which is 12 more years of follow-up than in Rubino et al. (1979). Lung cancer mortality was compared to that of Italian men.

As described in Rubino et al. (1979), fiber levels were measured by PCM in 1969. In order to estimate earlier exposures, information on daily production, equipment changes, number of hours worked per day, etc. were used to create conditions at the plant during earlier years. PCM samples were obtained under these simulated conditions and combined with work histories to create individual exposure histories.

Piolatto et al. (1990) observed 22 lung cancers compared to 11 in the earlier study (Rubino et al. 1979). Lung cancer was neither significantly in excess nor significantly related to cumulative asbestos exposure. Piolatto et al. (1990, Table 1) presented observed and expected lung cancers (based on age- and calendar-year-specific rates for Italian men) categorized by cumulative exposure in f-y/ml. The lung cancer model with fixed α provided a good fit to these data (Table A-5, p=0.75) and allowing α to vary did not significantly improve the fit. The K_L estimate with α=1 was 0.00035 $(\text{f-y/ml})^{-1}$, with 90% CI: (0, 0.0015). With α allowed to vary the estimate was K_L=0.00051 $(\text{f-y/ml})^{-1}$ with 90% CI: (0, 0.0057).

Two mesotheliomas were observed by Piolatto et al. (1990), compared to one found by Rubino et al. (1979). However, data were not presented in a form from which K_M could be estimated.

Regarding uncertainty factors, F1 is assigned a value 2.0 for this study for reasons similar to those described for Quebec. F2 is assigned a value of 1.0 because measurements were conducted using PCM so that conversion is unnecessary for this study. All other factors are also assigned a value of 1.0 because there are no other unique limitations. Thus:

F1 = 2.0
F2 = 1.0
F3 = 1.0
F4L = 1.0

These uncertainty factors, when coupled with the statistical confidence limits, resulted in the uncertainty range for K_L shown in Table A-1.

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

The cohort was defined to include any man who had been employed at the plant for at least 1 month before 1959, omitting all that had worked at a nearby asbestos textile plant that closed in 1939. This cohort consisted of 3,515 men, of whom 36% had died by the end of follow-up (December 31, 1977). Follow-up of each worker was only begun past 20 years from first employment.

Information on dust levels from impinger measurements were available for the years 1930, 1935, 1936, and 1939. There was little other exposure information available until the 1970s. An industrial hygienist used these measurements and information on processes and jobs, environmental conditions and dust controls to estimate exposures by process and by period in units of mppcf. No conversion from mppcf to f/ml value was suggested by the authors, a conversion factor or between 1.4 and 10 is suggested by other studies. The most common value seems to be around 3 f/ml per mppcf, which has been observed in diverse environments such as mining and textile manufacture. This value was provisionally applied to this cohort, although this conversion has considerable uncertainty associated with it.

Total deaths and deaths from most individual causes investigated were elevated; these elevations were due primarily to increased deaths in the group working for <1 year. This pattern holds for lung cancer in particular; the SMR for lung cancer was highest (180) for persons exposed for <1 year. A similar pattern holds when the analysis was carried out by cumulative exposure (Table A-6); the SMR in the lowest exposure category is higher than in any other category. The linear relative risk lung cancer model provided a poor fit (p=0.01) to these data when the Connecticut rates were assumed to be appropriate for this cohort (fixing the parameter α=1); use of U.S. rates gave similar results. However, the fit was adequate (p=0.28) if the background response is allowed to rise above that of Connecticut men (allowing the parameter α to vary). Although the reason for this increased response in persons that worked for a short period or have low exposures is not clear, the analysis in which the background response is allowed to vary appears to be the most appropriate. This analysis yields an estimate of K_L=0.0 $(\text{f-y/ml})^{-1}$, 90% CI: (0, 0.0017). The analysis with α=1 yielded K_L=0.0019 $(\text{f-y/ml})^{-1}$, 90% CI: (0, 0.0061).

McDonald et al. did not find any mesotheliomas in this cohort. It is useful to determine the range of mesothelioma risk that is consistent with this negative finding. Although McDonald et al. do not furnish data in the form needed for this calculation, these data can be approximated from Table 1 of McDonald et al. (1984). In this table they list 511 deaths occurring after age 65. Assuming that the overall SMR of 108.5 held for persons over 65 years of age, the expected number of deaths is 511/1.085 = 471. The death rate in U.S. white males between 65 and 75 years of age is approximately 0.050 per year (from 1971 vital statistics). Therefore the number of person years observed in persons post 65 years of age is estimated as 471/0.050=9,420.

A lower bound on the person-years of follow-up between ages 45 and 65 can be estimated by assuming that follow-up was complete for this age group. First we estimate the number of persons that would have had to have been in the cohort to experience the observed deaths. Assuming that x persons in the cohort are alive at age 45, we have the following estimates of the number entering each successive five-year age interval and the corresponding number of deaths (based on death rates in 1,971 white males).

Age	Number Entering Interval	Number of Deaths in Interval	Person-Years in Interval
45–50	x	0.032x	4.9x
50–55	$x(1-0.00638)^5=0.97x$	0.052x	4.7x
55–60	$0.97x(1-0.01072)^5=0.92x$	0.076x	4.4x
60–65	$0.92x(1-0.01718)^5=0.84x$	0.11x	3.9x
65+	$0.84x(1-0.02681)^5=0.73x$		
TOTALS		0.27x	18.0x

Since there were 616 deaths in men between the ages of 45 and 65, the expected number of deaths is estimated as 616/1.085=567.7 expected deaths between ages of 45 and 60, the number of persons entering this age interval is estimated as x=567.7/0.27=2,100. The person-years is then estimated as (2,100)(17.964)=38,000.

Using the average age of beginning work of 30.95 years (McDonald et al. [1984], Table 3) yields the data in Table A-7. Moreover, the average duration of exposure in this cohort was 8.04 years and the average exposure level was 1.84 mppcf (McDonald et al. [1984], Table 3), which is equivalent to 1.84x3=5.52 fibers/ml. These data yields an estimate of K_M=0.0 and a 90% upper bound of $K_M=1.2x10^{-9}$.

The best estimate of K_M was assumed to be zero. For uncertainty factors, F1 is assigned a value of 2.0 for reasons similar to those described for Quebec. F2 is assigned a value of 3.0 for this study because there is no conversion factor reported by the authors so that an average value of 3 for the range of conversion factors observed among the available studies (U.S. EPA 1986) was selected for use with this study. To derive an exposure-response factor for mesothelioma from this study, an upper bound had to be estimated by reconstructing the data because the authors do not provide the data in a form suitable for performing the required calculation. Therefore, F4M is assigned a value of 3 for this study. Thus:

F1 = 2.0
F2 = 3.0
F3 = 1.0
F4L = 1.0
F4M = 3.0

These values, when coupled with the statistical confidence limits, resulted in the uncertainty ranges for K_L and K_M shown in Table A-1 and A-2, respectively.

New Orleans Asbestos-Cement Plants. Hughes et al. (1987) report on follow-up through 1981 of a cohort of Louisiana workers from two asbestos cement plants studied previously by Weill et al. (1979). Although chrysotile, amosite and crocidolite were used at these plants, a group of workers at one of the plants were only exposed to chrysotile. The cohort contained 6,931 workers, of whom 95% were traced, compared to a 75% success in tracing by Weill et al. (1979). This improved trace was the result both of greater access to Social Security Administration records and greater availability of computerized secondary information sources (Dr. Hughes, personal communication).

Both of the plants have operated since the 1920s. Chrysotile was used predominantly in both plants. Some amosite was used in Plant 1 from the early 1940s until the late 1960s, constituting about 1% of some products, and crocidolite was used occasionally for approximately 10 years beginning in 1962. Plant 2 utilized only chrysotile, except that pipe production, which began in 1946 and was housed in a separate building, produced a final product that contained about 3% crocidolite. Since the total percentage of asbestos fiber in most asbestos cement products ranges from 15 to 28%, it is estimated that crocidolite constituted between 10 and 20% of the asbestos used to make cement pipe (Ontario Royal Commission 1984). Workers from Plant 2 that did not work in pipe production were exposed only to chrysotile.

Estimates of airborne dust levels were made for each job by month and year from midget impinger measurements initiated in the early 1950s. Levels estimated from initial samples in the 1950s were also assumed to hold for all earlier periods because no major dust control measures had been introduced prior to that time. New exposure data from Plant 2 became become available after the earlier study (Weill et al. 1979) was completed, and these, along with a complete review of all the exposure data, were used to revise the previous estimates of exposure. In Plant 1 the earlier and revised estimates were reasonably similar, but in Plant 2, the revised estimates tended to be about one-third of the previous estimates through the 1940s and about one-half the previous estimates thereafter. Based on 102 side-by-side measurements by midget impinger and PCM in various areas of one of the plants, Hammond et al. (1979) estimated an overall conversion factor of 1.4 fibers/ml per mppcf. There were substantial variations in this factor among different areas of the plant.

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

Hughes et al. found no significant difference between the exposure responses for lung cancer in Plant 2 among workers exposed to chrysotile only and those who were also exposed to crocidolite in pipe production. A single lung cancer exposure response model adequately describes the lung cancer data from Plants 1 and 2 combined ($p \geq 0.42$, Table A-8). The fit of this model is good when Louisiana men are assumed to be an appropriate control group (fixing the parameter $\alpha=1$). This fit provides an estimate of $K_L=0.0040$ (fiber-y/ml)$^{-1}$, 90% CI: (0.0015, 0.0070). With α allowed to vary, the estimate is 0.0025 (fiber-y/ml)$^{-1}$, 90% CI: (0, 0.0066).

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

Data were not presented in the paper in the form required for estimating K_M. However, Hughes and Weill (1986) present estimates of mesotheliomas potency from several data sets, including the cohort studied in Hughes et al. and containing six mesotheliomas, but using a model slightly different from the 1986 EPA model (3). Estimating K_M by multiplying the potency estimated by the Hughes and Weill (1986) model by the ratio of the potency values estimated for another study using the 1986 U.S. EPA model and the Hughes-Weill (1986) model yielded the following estimates of K_M for the Hughes et al. (1987) data: 0.25×10^{-8} (Selikoff et al. 1979); 0.21×10^{-8} (Dement et al. 1983b); 0.27×10^{-8}(Seidman et al. 1979); and 0.43×10^{-8} (Finkelstein 1983). Based on these calculations, $K_M=0.30 \times 10^{-8}$ seems to be a reasonable estimate for the Hughes et al. cohort.

It would be worthwhile to estimate mesothelioma risk using additional follow-up that included the three cases that occurred shortly after follow-up ended. However, such an estimate should be no larger than about $K_M=0.45 \times 10^{-8}$. This is because, since there were six mesotheliomas in the cohort studied by Hughes et al., even if the additional person years of follow-up post-1981 is not taken into account, the three additional mesotheliomas would increase the estimate of K_M by only about 50%.

The finding by Hughes et al. (1987) of an association with crocidolite exposure implies that a smaller K_M would correspond to the chrysotile-only exposed group in Plant 2. Although Hughes et al. didn't furnish the data needed for precise estimation of K_M from this cohort, it is possible to make some reasonable approximations to this K_M. Since none of the six mesotheliomas occurred among workers exposed only to chrysotile, $K_M=0$ would be the point estimate derived from the data used by Hughes et al.

However, one mesothelioma was discovered in a person whose employment began in 1927 and thus was not eligible for inclusion in the cohort. This person was employed continuously for 43 years in the shingle production area, where only chrysotile was used. In an attempt to compute an alternative K_M using this one case, it was noted that the duration of observation of the Hughes et al. cohort was roughly equivalent to that of the Dement et al. (1983b) cohort. If the person-years from this cohort, categorized by years since first exposure, are adjusted by the ratio of the

sizes of Dement et al. and the Hughes et al. non-crocidolite-exposed cohort from Plant 2, one mesothelioma is assumed to occur (in 30+ years from first exposure category) and the average duration of exposure (2.5 years) and fiber level (11.2 fibers/ml) appropriate for the Hughes et al. cohort are applied to these data, a K_M=0.2x10^{-8} is obtained.

The best estimate of K_M was assumed to be 0.2x10^{-8} for workers exposed only to chrysotile and 0.3x10^{-8} for workers exposed to both chrysotile and amphibole. For uncertainty factors, F1 is assigned a value of 2.0 for reasons similar to those described for Quebec. F2 is assigned a value of 1.5 because most early measurements were collected by midget impinger and the authors report using a conversion factor of 1.4 derived from paired measurements. Due to the lack of adequate data for estimating both the overall mesothelioma rate and a confidence interval for such rates and the consequent need to reconstruct the data (incorporating numerous assumptions) to be able to obtain the needed estimates, a value of 5.0 was assigned to the factor F4M for chrysotile exposures and 2.5 for mixed exposures. Thus:

F1 = 2.0
F2 = 1.5
F3 = 1.0
F4L = 1.0
F4M = 5.0

These values, when coupled with the statistical confidence limits, resulted in the uncertainty ranges for K_L and K_M shown in Tables A-1 and A-2.

South Carolina Textile Factory. Dement and coworkers (Dement et al. 1994; Dement and Brown 1998) conducted a retrospective cohort study of employees of a chrysotile textile plant in South Carolina. In an earlier study of this plant (Dement et al. 1982, 1983a,b), the cohort was defined as all white male workers who worked for one or more months between 1940 and 1965, and follow-up was through 1975. Dement et al. (1994) expanded the cohort to include black male and white female workers who met the entrance requirements, and extended follow-up through 1990, an additional 15 years. This expanded cohort included 1,247 white males (2.8% lost to follow-up), 1,229 white females (22.8% lost to follow-up) and 546 black males (7.8% lost to follow-up). A total of 1,259 deaths were identified, and a death certificate was located for all but 79 (6.2%) of the deaths.

Based on data from 5,952 air samples taken at the plant between 1930 and 1975, linear statistical models were used to reconstruct exposure levels, while taking into account textile processes, dust control methods, and job assignments (Dement et al. 1983a). For each worker, time spent in each job was multiplied by the estimated exposure level for that job to estimate cumulative exposure (f/ml-days). Based on regression analyses applied to 120 side-by-side particle and fiber counts, Dement (1980) estimated a f/ml to mppcf ratio of 2.9, 95% CI: (2.4, 3.5). Also, between 1968 and 1971 both impinger and PCM samples were collected (a total of 986 samples). Based upon a regression analysis of these data, Dement (1980) determined that a common conversion factor could be used for jobs except fiber preparation. For fiber preparation, a conversion factor of 7.8 was found, 95% CI: (4.7–9.1). For all other operations, a value of 2.5, 95% CI: (2.1–3.0) was calculated. Based on this information, Dement et al. (1983a) concluded

that a conversion factor of 3 was appropriate for all operations except preparation, for which a factor of 8 was adopted.

The underlying data for this cohort were obtained from the National Institute for Safety and Health (NIOSH). These data consisted of a work history file and a file with exposure levels by job category and time period. The work history file contained codes for race, sex, month and year of birth, vital status, month and year of death, and the department, operation, start date, and stop date for each job worked. The exposure level file contained the exposure start and stop dates and the exposure level (fiber/ml) by the plant code, the department code, and the operation code.

The cohort was defined as the white and black males and the white females who met the employment requirements described above. This cohort included 1,244 white males (1.5% lost to follow-up), 550 black males (7.5% lost to follow-up), and 1,228 white females (22.1% lost to follow-up).

Table A-9 shows observed and expected deaths for lung cancer among white males, black males and white females, categorized by cumulative exposure. This table shows an excess of lung cancers that exhibited an exposure response relationship. U.S. rates were used for calculating expected deaths, whereas South Carolina lung cancer rates are higher for white men, but slightly lower for white women and black men. Whereas twelve categories of cumulative exposure were used for fitting the model, these were been combined into seven categories for display in Table A-9. The model with $\alpha=1$ and α variable fit the data well ($p \geq 0.8$), and the hypothesis that $\alpha=1$ cannot be rejected ($p=0.19$). The estimate of K_L with $\alpha=1$ was 0.028 $(\text{f-y/ml})^{-1}$, 90% CI: (0.021, 0.037), and the estimate with α variable was $K_L=0.021$ $(\text{f-y/ml})^{-1}$, 90% CI: (0.012, 0.034). An analysis applied to white men alone gave somewhat higher estimates ($K_L=0.040$ $(\text{f-y/ml})^{-1}$ with $\alpha=1$, and $K_L=0.026$ $(\text{f-y/ml})^{-1}$ with α variable).

Two deaths were certified as due to mesothelioma on the death certificates. In addition, Dement et al. (1994) considered four other deaths as likely due to mesothelioma. The availability of the raw data from this study made it possible calculate K_M from this study using an "exact" likelihood approach based on Equation A-3 that did not involve any grouping of data, or use of average values. Using the six confirmed and suspected mesotheliomas, $K_M= 0.43\text{x}10^{-8}$, 90% CI: ($0.20\text{x}10^{-8}$, $0.79\text{x}10^{-8}$). Using the two confirmed mesotheliomas, $K_M=0.14\text{x}10^{-8}$, 90% CI: ($0.034\text{x}10^{-8}$, $0.38\text{x}10^{-8}$).

For comparison purposes, K_M were also calculated using grouped data and applying Equation A-4, since this is the method that must be used with most studies. The data were divided into 10 categories by the tabulated values of Equation A-4. The K_M estimate based on the "exact" analysis was 2% greater than that based upon grouped data.

The best estimate of K_M was assumed to be the geometric mean of the MLE estimates computed using either confirmed or both confirmed and suspected mesotheliomas ($0.25\text{x}10^{-8}$). The statistical lower bound used for this estimate was the one based on confirmed cases and the upper bound used was the one based on confirmed and suspected cases.

Regarding uncertainty factors, F1 is assigned a value of 1.5 for this study to give credit for the reasonably complete sampling coverage of exposures by a combination of midget impinger and extensive PCM, and the formal statistical evaluation conducted to derive job-specific exposure estimates. However, the exposure estimates are still based on analyses of area rather than personal samples. Because multiple factors were used to convert midget impinger measurements to PCM based on side-by-side samples collected from specific areas (associated with specific operations) within the plant, a value of 1.0 is assigned for F2 for this study. The treatment of statistical confidence limits described above was considered adequate to account for the uncertainty in the number of mesotheliomas, and a value of K_M=1 was assigned. In summary:

F1 = 1.5
F2 = 1.0
F3 = 1.0
F4L = 1.0
F4M = 1.0

These uncertainty factors, when coupled with the statistical confidence limits, resulted in the uncertainty ranges for K_L and K_M shown in Tables A-1 and A-2.

McDonald et al. (1983a) conducted a cohort mortality study in the same South Carolina textile plant that was studied by Dement et al. (1994). Their cohort consisted of all men employed for at least 1 month before 1959 and for whom a valid social security record existed. This cohort consisted of 2,410 men, of whom 36% had died by the end of follow-up (December 31, 1977). Follow-up of each worker was begun past 20 years from first employment.

McDonald et al. (1983a) had available the same exposure measurements as Dement et al. (1983b) and used these to estimate cumulative exposures for each man in mppcf-y. In their review of the environmental measurements in which both dust and fiber concentrations were assessed, they found a particle to fiber conversion range of from 1.3 to 10.0 with an average of about 6 fibers/ml per mppcf. This value, which is intermediate between the values of 3 and 8 found by Dement et al. (1983b) for different areas of the same plant, will be used in the calculations involving the McDonald et al. (1983a) study.

McDonald et al. describe two practices at the plant that entailed very high exposures and which were not reflected in either their's or Dement and coworkers estimates: cleaning of burlap bags used in the air filtration system by beating them with buggy whips during the years 1937–1953, and the mixing of fibers, which was carried out between 1945 and 1964 by men with pitch forks and no dust suppression equipment.

A strong exposure response for lung cancer was observed (Table A-10), which parallels the results of Dement et al. (1994). Unlike Dement et al., McDonald et al. used South Carolina men as the control group rather than U.S. men. Use of this control group provided an adequate description of the data and lung cancer potency values estimated both with α=1 and allowing α to vary provided excellent descriptions of the data ($p \geq 0.88$) and the hypothesis α=1 could not be rejected (p=0.80). Assuming α=1 resulted in K_L=0.012 $(\text{f-y/ml})^{-1}$, 90% CI: (0.0075, 0.016), and when α was allowed to vary, K_L=0.010 $(\text{f-y/ml})^{-1}$, 90% CI: (0.0044, 0.025). These results are

reasonably consistent with the potency estimated from Dement et al. (1994), and the differences can be largely accounted for by the different assumptions regarding the fiber/particle ratio.

McDonald et al. (1983a) found one case of mesothelioma in this cohort, apparently the same one discovered by Dement et al. (1983b): a man born in 1904 who died in 1967 and worked at the plant for over 30 years. Since this study was conducted exactly as McDonald et al. (1984), the same method used there to reconstruct person-years by years from first exposure can be applied to this cohort as well. The reconstructed data are listed in Table A-11. The estimated potency MLE is K_M=0.088 x10^{-8}, with a 90% CI: (0.0093x10^{-8}, 0.32x10^{-8}).

For uncertainty factors, F1 is assigned a value of 2.0 for reasons similar to those described for Quebec. F2 is assigned a value of 1.0 because McDonald essentially used the same data that Dement and coworkers used to estimate conversion factors (see above), although they favored a slightly higher mean value. We used the values favored by Dement when evaluating this study.

Unlike the study by Dement and coworkers (for which we received the raw data so that we could calculate the exposure-response factor and the attendant confidence interval for mesothelioma directly), the mesothelioma data published in the McDonald study of this facility was not suitable to estimating confidence bounds. Thus the data had to be reconstructed, which required incorporation of numerous assumptions. To account for the uncertainty associated with the reconstruction, F4M is assigned a value of 3 for this study. Thus:

F1 = 2.0
F2 = 1.0
F3 = 1.0
F4L = 1.0
F4M = 3.0

These uncertainty factors, when coupled with the statistical confidence limits, resulted in the uncertainty ranges for K_L and K_M shown in Tables A-1 and A-2.

Predominant Crocidolite Exposure

Wittenoom, Australia Mine and Mill. de Klerk et al. (1994) followed a cohort of 6,904 men and women employed at a crocidolite mine and mill in Wittenoom, Australia. This cohort was followed through 1999 and the raw data were obtained through the courtesy of Dr. de Klerk. The data consisted of a record number, date of birth, sex, employment start date, total days of employment, average exposure level (f/ml), cumulative exposure (f-year/ml), date of last contact, ICD code for cause of death, indicator variable for mesothelioma death, and date of death if applicable.

A number of subjects from the full cohort were removed from the analysis reported herein: 412 because the sex was not designated as male; one because the date of last contact was missing; 1,275 subjects because the follow-up period was <5 years; 41 because the number of days worked was 0 or missing. After these subjects were removed, the cohort consisted of 5,173 men who were employed at Wittenoom Gorge between 1943 and 1966.

The concentrations of fibers greater than 5 μm in length as measured by PCM were measured at various work sites in a survey conducted in 1966. Job category data were obtained from employment records and supplemented by records from the Perth Chest Clinic and the Western Australian Mineworkers Relief Fund. The concentration measurements and job category information were used to estimate the exposure level for each subject in the cohort (de Klerk et al. 1994). The exposure levels were high with a median of 17.8 (fiber/ml). The durations of employment were low with a median of 128 days.

There were 251 lung cancer deaths in the cohort. Table A-12 shows the observed, expected, and predicted lung cancer deaths among the males categorized by cumulative exposure (fiber-year/ml). The number of expected lung cancer deaths are based on Australian lung cancer mortality rates. With no allowance for difference between the background lung cancer death rates among Australia and the members of this cohort (α=1), the fit of the model is poor ($p<0.01$). Allowing for difference in the background lung cancer death rates (a variable), the model provides a reasonably good fit to the data ($p=0.10$) and estimates K_L=0.0047 (fiber-year/ml)$^{-1}$, 90% CI: (0.0017, 0.0087). The hypothesis α=1 can be rejected with high confidence ($p<0.01$).

There were 165 mesotheliomas in the cohort. The availability of the raw data from this study made it possible calculate K_M from this study using an "exact" likelihood approach based on Equation A-3 that did not involve any grouping of data, or use of average values. With this approach, $K_M=7.95\text{x}10^{-8}$, 90% CI: ($6.97\text{x}10^{-8}$, $9.01\text{x}10^{-8}$).

For comparison purposes, K_M were also calculated using grouped data and applying Equation A-4, since this is the method that must be used with most studies. The K_M estimate based on the "exact" analysis was 12% lower than the estimate based upon grouped data.

Regarding uncertainty factors, F1 is assigned a value 2.0 for this study for reasons similar to those described for Quebec. F2 is assigned a value of 1.0 because measurements were conducted using PCM so that conversion is unnecessary for this study. All other factors are also assigned a value of 1.0 because there are no other unique limitations. Thus:

F1 = 2.0
F2 = 1.0
F3 = 1.0
F4L = 1.0
F4M = 1.0

These uncertainty factors described earlier, when coupled with the statistical confidence limits, resulted in the uncertainty ranges for K_L and K_M and shown in Table A-1 and A-2.

Predominant Amosite Exposure

Patterson, N.J. Insulation Factory. Seidman et al. (1986) studied a cohort of 820 men (mostly white) who worked at an amosite asbestos factory that operated in Patterson, New Jersey from 1941 through 1954. The men began work between 1941 and 1945 and follow-up was through 1982. The follow-up of a worker began 5 years following the beginning of employment.

Workers who had prior asbestos exposure were not included in the cohort, and follow-up was stopped when a worker was known to have begun asbestos work elsewhere (6 men). Exposures were generally brief, as 76% were exposed for $\leq$2 years, although a few were exposed for as long as 10 years.

No asbestos exposure measurements are available for this plant. Estimates of exposures in particular jobs were made based on air measurements made between 1967 and 1970 at plants in Tyler, Texas and Port Allegheny, Pennsylvania that were operated by the same company and made the same products using some of the same machinery as the Patterson facility. The estimated median exposure level was 50 f/ml. Amosite was the only type of asbestos used at the plant.

Seidman et al. cross-categorized lung cancer deaths by cumulative exposure (eight categories of f-y/ml) and length of time worked (seven categories, Seidman et al. 1986, Table XXXIV). Although this table apparently was created by categorizing workers by their final cumulative exposure (rather than categorizing person-years of follow-up by the cumulative exposure to that point in time, which is more appropriate for calculating a K_L), because exposures were brief this likely made little difference. Expected number of lung cancer deaths were based on age- and year-specific rates for New Jersey white males.

Table A-13 shows the results of applying the lung cancer model to these data, after collapsing the table by summing over length-of-time worked. Results were highly dependent upon whether or not the background lung cancer mortality rate was assumed to be equal to that predicted by the comparison population of New Jersey white males (equivalent to α=1). The test for departure from the null hypothesis, α=1, was highly significant, and the maximum likelihood estimate was α=3.3. Similarly, the model gave a poor overall fit to the data with α=1 ($p<0.01$), but the fit was quite good when α was allowed to vary ($p=0.90$). The estimated potency parameter, K_L, also was highly dependent upon the assumption regarding the parameter, α. The estimate of K_L was 0.062 $(\text{f-y/ml})^{-1}$, 90% CI: (0.050, 0.076), when α was fixed at α=1, and 0.011 $(\text{f-y/ml})^{-1}$, 90% CI: (0.0058, 0.019), when α was allowed to vary, a 6-fold difference. The lung cancer model was also fit to the data cross-classified by both cumulative exposure and length of time worked, allowing α to assume a different value in each category of time worked. Although the estimated values of α tended to increase with increasing duration of exposure, allowing different values of α did not significantly improve the fit ($p=0.64$).

The reason for this behavior is not clear. There is no indication that workers with shorter durations experienced disproportionately high mortality, since, as noted above, α tended to increase with increasing duration of exposure. Although it is possible that cumulative exposure is not the appropriate exposure metric, it is difficult to envision what metric would predict this response, so long as a linear model is assumed. It is also possible that a linear model for relative risk is not correct and a supralinear model is more appropriate, or that the increased risk is not proportional to the background risk, as assumed by this simple relative risk model. Finally, it is possible that the background rate in this population is significantly greater than that in the comparison population, although it seems unlikely that it could be 3 times greater as suggested by the model.

Seidman et al. (1986) discovered 17 deaths from mesothelioma in this population. Table III of Seidman et al. categorized mesothelioma deaths and person-years of observation by years since onset of work. In order to apply the 1986 U.S. EPA mesothelioma model it is necessary to have estimates of the duration of exposure and level of exposure for each category. Using the categorization of the members of the cohort by duration of work in Table XXIII of Seidman et al., it was estimated that the mean duration of work was 1.5 years. Using data from Seidman et al. Table XIV, an average cumulative exposure was for each category of time from onset of exposure by weighting exposures according to the expected total number of deaths. These averages were divided by 1.5 years to obtain the average fiber concentrations in Table A-14. The estimated exposure levels decrease with time since onset, which is consistent with higher mortality among more heavily exposed workers.

The 1986 mesothelioma model provided an adequate fit to these data (p=0.35), although it over-predicted somewhat the number of cases in the highest latency category (>35 years). The estimate of K_M was 3.9×10^{-8}, 90% CI: (2.6×10^{-8}, 5.7×10^{-8}).

Regarding uncertainty factors, F1 is assigned a value of 3.5 for this study because exposure concentrations were not measured at this facility at all. Rather exposures were estimated (as described in Lemon et al. [1980]) based on measurements collected at another facility in Tyler, Texas (see below) that manufactured the same products from the same source of raw materials using some of the same equipment, which was moved from the Patterson plant to the plant in Tyler. Because the measurements collected in Tyler were analyzed by PCM, no conversion factor is required. Thus, F2 is assigned a value of 1.0 for this study. All other factors are also assigned a factor of 1.0 due to lack of other remarkable limitations. Thus:

F1 = 3.5
F2 = 1.0
F3 = 1.0
F4L = 1.0
F4M = 1.0

These uncertainty factors, when coupled with the statistical confidence limits, resulted in the uncertainty ranges for K_L and K_M shown in Table A-1 and A-2.

Tyler, Texas Insulation Factory. Levin et al. (1998) studied the mortality experience of 1,121 men who formerly worked at a plant in Tyler, Texas that manufactured asbestos pipe insulation. The plant operated from 1954 through February 1972. The plant used the same raw materials and some of the same equipment that was used in the Patterson, New Jersey plant that was studied by Seidman et al. (1986). The asbestos used was amosite from the Transvaal region of South Africa. The insulation was manufactured from a mixture that contained 90% amosite asbestos.

Environmental surveys were conducted at the plant in 1967, 1970, and 1971, with average fiber concentrations ranging from 15.9 through 91.4 f/ml. An average exposure of 45 f/ml is assumed for this plant, which is near the middle of this range obtained in the three surveys. It is also consistent with average levels assumed for the Patterson, New Jersey plant, which operated under very similar conditions.

The cohort consisted of 744 whites, 305 non-white (mostly black), and 72 with missing race (assumed to be white, based on hiring practices at that time). For the entire cohort, the median age of first employment was 25 years, and the mean duration of employment was 12.7 months (range of one day to 17.3 years). Follow-up was through 1993. Death certificates were obtained for 304 of the 315 men known to be dead. In the mortality analysis only white men were evaluated and follow-up started 10 years after first employment. After additional exclusions of men with missing birth dates or missing employment information, the cohort analyzed in the mortality analysis consisted of 753 former workers, among whom 222 deaths were recorded. These deaths were compared with those expected based on age, race and sex-specific U.S. rates.

There was an excess of deaths from respiratory cancer (SMR=277, based on 36 deaths, not including four deaths from mesothelioma). Table A-15 contains observed and expected numbers of deaths from respiratory cancer, categorized by duration of exposure. Cumulative exposure in f-y/ml was estimated by multiplying the duration of exposure times the assumed average fiber level of 45 f/ml. There was an excess of lung cancer deaths in the lowest exposure group (23 observed, 8.9 expected), and consequently the model with $\alpha=1$ did not fit these data ($p<0.01$), and the hypothesis $\alpha=1$ could be rejected ($p<0.01$). The K_L with α variable was $K_L=0.0013$, 90% CI: (0, 0.0060). With $\alpha=1$, $K_L=0.013$ (f-y/ml)$^{-1}$, 90% CI: (0.0055, 0.022).

Four mesotheliomas were reported in this study. However, the data are not presented in a form that would permit application of the U.S. EPA 1986 mesothelioma model.

Regarding uncertainty factors, F1 is assigned a value of 3.0 for this study because, although exposure concentrations were measured at this facility, the data are sparse so that only an overall average concentration for the entire plant could be derived. Because the measurements collected were analyzed by PCM, no conversion factor is required. Thus, F2 is assigned a value of 1.0 for this study. All other factors are also assigned a factor of 1.0 due to lack of other remarkable limitations. Thus:

F1 = 3.0
F2 = 1.0
F3 = 1.0
F4L = 1.0

These uncertainty factors, when coupled with the statistical confidence limits, resulted in the uncertainty range for K_L shown in Table A-1.

Predominant Tremolite-Actinolite Exposure

Libby, Montana Vermiculite Mine. Amandus and Wheeler (1987) conducted a retrospective cohort study of 575 men who were exposed to tremolite-actinolite while working at a vermiculite mine and mill in Libby, Montana. A dry mill began operation in 1935 and a wet mill began operating in the same building as the dry mill in 1950 (Amandus et al. 1987).

A total of 376 impinger samples were available that had been collected during 1950–1969, although only 40 of these were collected prior to 1965. In addition 4,118 PCM samples were available from the period 1967–1982. Exposure estimates for years later than 1968 were based

on historical measures of fiber concentrations (f/ml), and those for earlier years were based on concentrations measured by midget impinger (mppcf) and converted to f/ml assuming a conversion ratio of 4 f/ml per mppcf. This conversion factor was derived from 336 impinger samples collected during 1965–1969 and 81 filter samples collected during 1967–1971. Individual cumulative fiber exposure estimates (f-y/ml) were computed from job-specific exposure estimates and work histories (Amandus et al. 1987).

The cohort consisted of all men hired prior to 1970 and employed for at least 1 year in either the mine or the mill. Follow-up was through December 31, 1981. The vital statuses of 569 of the men (99%) were determined and death certificates were obtained for 159 of the 161 who were deceased.

Smoking information was available for 161 men employed between 1975 and 1982 and with at least 5 years of tenure. The proportion of these workers who smoked (current or former) was 84% compared to 67% among U.S. white males during the same time period.

A total of 20 deaths from lung cancer were observed (9 expected, SMR=223.2, using U.S. white males as the comparison population). Table A-16 (based on Amandus and Wheeler 1987, Table II) shows that the excess occurred mainly in workers whose cumulative exposure exceeded 400 f-y/ml (10 observed, 1.7 expected). The 1986 U.S. EPA lung cancer model fit these data adequately ($p \geq 0.25$) both with $\alpha=1$ and α variable, and the hypothesis $\alpha=1$ could not be rejected ($p=0.8$). With $\alpha=1$, K_L was estimated as 0.0061 $(\text{f-y/ml})^{-1}$, 90% CI: (0.0029, 0.010), and with α variable, K_L= 0.0051 $(\text{f-y/ml})^{-1}$, 90% CI: (0.0011, 0.020).

Amandus and Wheeler (1987) observed 2 deaths from mesothelioma in this cohort. However, information on these cases was not sufficient to permit application of the 1986 U.S. EPA mesothelioma model.

For uncertainty factors, F1 is assigned a value of 2.0 for reasons similar to those described for Quebec. F2 is assigned a value of 1.5 because most early measurements were collected by midget impinger and the authors report using a conversion factor of 4 derived from temporally overlapping (but not paired) measurements. All other uncertainty factors were assigned a value of 1.0. Thus:

F1 = 2.0
F2 = 1.5
F3 = 1.0
F4L = 1.0

These uncertainty factors, when coupled with the statistical confidence limits, resulted in the uncertainty range for K_L shown in Table A-1.

McDonald et al. (1986) also conducted a cohort study of workers at the Libby, Montana vermiculite mine and mill. Their cohort was composed of 406 workers employed prior to 1963 for at least 1 year. Follow-up was until July 1983. Vital status was determined for all but one man and death certificates were obtained for 163 of the 165 men who had died. Cumulative exposures (f-y/ml) were estimated for each worker using work histories based on 42 job

categories, and 1,363 environmental measurements, including samples analyzed by PCM (f/ml) and by midget impinger (mppcf).

A total of 23 deaths from lung cancer were observed (SMR=303, based on Montana rates). Table A-17 shows these deaths categorized by cumulative exposure (based on Table 4 of McDonald et al. 1986). Both the models with α=1 and α variable fit these data adequately ($p \geq 0.16$) although the test of α=1 was marginally significant (p=0.11). The estimate of K_L with α=1 was 0.011, $(\text{f-y/ml})^{-1}$, 90% CI: (0.0055, 0.017), and with α variable, K_L= 0.0039 $(\text{f-y/ml})^{-1}$, 90% CI: (0.00067, 0.012).

McDonald et al. (1986) observed 2 deaths from mesothelioma. However, information on these cases was not sufficient to permit application of the 1986 U.S. EPA mesothelioma model.

Because this study and the Amandus study used virtually the same data and very similar approaches to analysis, the same values are assigned to uncertainty factors for this study that are assigned for the Amandus and Wheeler study. These factors, when coupled with the statistical confidence limits, resulted in the uncertainty range for K_L shown in Table A-1.

Exposure to Mixed Fiber Types

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

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

Deaths from all causes were less than expected both prior to 10 years from first employment (185 observed versus 195.7 expected) and afterward (432 observed versus 450.8 expected). There was no indication of an effect of employment at the plant upon lung cancer; there were 51 lung cancers >10 years from first employment compared to 47.4 expected. A significant deficit of gastrointestinal cancers was observed after 10 years from first employment (25 observed versus 35.8 expected, p=0.04).

A linear exposure response model relating cumulative exposure and lung cancer was fit to case-control data presented by Berry and Newhouse. The resulting K_L was 0.00058 $(\text{f-y/ml})^{-1}$ and the 95% upper limit was 0.0080 $(\text{f-y/ml})^{-1}$. This estimate was used as the best estimate of K_L, and the lower confidence bound was assumed to be zero.

A case control study on mesothelioma deaths showed that 8 of the 11 cases had been exposed to crocidolite and another possibly had intermittent exposure to crocidolite. The other two had been employed mostly outside the factory and possibly had other occupational exposures to

asbestos. The case control analysis showed that the distribution of cases and controls in respect to exposure to crocidolite was quite unlikely assuming no association with crocidolite. This indicates that some, and possibly all, of the eight mesotheliomas with crocidolite exposure were related to this exposure. The data were not presented in a form that permitted a quantitative estimate of mesothelioma risk.

Regarding uncertainty factors, F1 is assigned a value of 2.0 for this study because, although the manner in which unmeasured exposure was estimated in this study is different than for that reported for the majority of other studies (see, for example, Quebec), it is unlikely to introduce greater uncertainty. Rather than extrapolating measured estimates to earlier times based on expert judgements, judgements were used to simulate earlier conditions at the plant and exposures were measured directly. Because the measurements collected were analyzed by PCM, no conversion factor is required. Thus, F2 is assigned a value of 1.0 for this study. An uncertainty factor F4L=1.5 was included to account for the fact that α was not estimated. F3 was assigned a factor of 1.0 due to lack of other remarkable limitations. Thus:

F1 = 2.0
F2 = 1.0
F3 = 1.0
F4L = 1.5

These factors, when coupled with the statistical confidence limits, resulted in the uncertainty range for K_L shown in Table A-1.

Ontario Asbestos-Cement Plant. Finkelstein (1984) studied mortality among a group of 535 exposed and 205 unexposed employees of an Ontario asbestos-cement factory who had been hired before 1960 and who had been employed for at least 1 year. This cohort contained the cohort studied by Finkelstein (1983) and which required at least 9 years of employment for membership. Follow-up continued until 1977 or 1981.

The plant produced asbestos cement pipe from 1948, asbestos cement board from 1955–1970, and manufacture of asbestos insulation materials was added in 1960. Both chrysotile and crocidolite were used in each batch processed in the pipe process, but only chrysotile was used in the cement board operation. Crocidolite constituted approximately 20% of the asbestos used in the pipe process (Ontario Royal Commission 1984).

Fiber concentrations in various work areas and for various epochs were estimated from membrane filter samples taken after 1969, impinger measurements taken during 1949, 1954, 1956, 1957, and semiannually during the 1960s, and information on changes in dust control methods. Finkelstein judged that the resulting exposure estimates were "probably accurate to within a factor of three or five." Exposures of maintenance workers were not estimated, and the exposure response analysis consequently involved only the unexposed workers (N=205) and the production workers (N=428).

Only 21 deaths from lung cancer were observed among production workers. Based on these deaths, Finkelstein compared age-standardized lung cancer mortality rates in production workers after a 20-year latency, categorized into five groups according to their cumulative exposure

through 18 years from date of first employment (Finkelstein 1984, Table 7). Mortality rates were standardized with respect to age and latency using the man-years distribution in the cohort as a whole as the standard. Using similarly standardized mortality rates in Ontario males as the comparison population, lung cancer rates were elevated in all five categories, and Finkelstein found a significant exposure-response trend. However, the trend was not monotone, as rates increased up to the middle exposure category and decreased thereafter (Table A-18).

These data may be put into a form roughly equivalent to the more conventional age-adjusted comparison of observed and expected lung cancer deaths by dividing the rates in the exposed group by that of Ontario men. (The rate for unexposed workers was not used because it was based on only 3 deaths.) The results of this are shown in Table A-18, which also shows the results of fitting the 1986 U.S. EPA lung cancer model both assuming the Ontario rates were appropriate for this cohort (fixing the parameter $\alpha=1$) and not making this assumption (allowing the parameter α to vary). Neither approach provided an adequate fit to these data ($p \leq 0.05$) and the test of $\alpha=1$ was marginally significant ($p=0.07$). The maximum likelihood estimate of α was 4.26, which seems too large to be due to differences in smoking habits. The K_L estimate with $\alpha=1$ was 0.048 $[\text{f-y/ml}]^{-1}$, 90% CI: (0.028, 0.074). With α allowed to vary the estimate was $K_L=0.0029$ $[\text{f-y/ml}]^{-1}$, 90% CI: (0, 0.037). The fact that the lower limit was zero indicates that the exposure-response trend was not significant when the background was allowed to vary.

Based on a “best evidence” classification of cause of death, Finkelstein identified 17 deaths from mesothelioma among production workers. Table 3 of Finkelstein (1984) gives these mesotheliomas categorized by years since first exposure. This table also provides the mortality rate, from which can be calculated the person-years of observation. Finkelstein states that the average cumulative exposure for production workers was about 60 f-y/ml, but does not provide information for determining duration and level of exposure separately. CHAP (1983) used an average exposure of 9 f/ml for a subcohort of production workers, although they provided no support for this assumption. If this value is assumed to be appropriate for the expanded cohort, the average duration is estimated as about 60/9=6.7 years. However these values are uncertain. Table A-19 presents the result of applying the 1986 U.S. EPA mesothelioma model to the Finkelstein (1984) data based on these assumptions. The mesothelioma model describes these data adequately ($p=0.26$) and provides an estimate of $K_M=18\text{x}10^{-8}$, 90% CI: ($13\text{x}10^{-8}$, $24\text{x}10^{-8}$).

Regarding uncertainty, F1 is assigned a value of 4 because Finkelstein indicates that exposure estimates derived for this study are probably good to within a factor of 3 or 4. Findlestein also notes that many of the assumptions employed to extrapolate exposures were only weakly supported by limited, earlier impinger measurements. The source of the conversion factor employed to link impinger measurements and PCM measurements in this study is unclear. Therefore a value of 3.0 is assigned to F2. Because data for evaluating mesothelioma incidence was not provided in a format suitable for deriving confidence intervals, so that some reconstruction was required, a value of 2.0 is assigned for F4M. All other factors are also assigned a factor of 1.0 due to lack of other remarkable limitations. Thus:

F1 = 4.0
F2 = 3.0
F3 = 1.0
F4L = 1.0
F4M = 2.0

These factors, when coupled with the statistical confidence limits, resulted in the uncertainty ranges for K_L and K_M shown in Tables A-1 and A-2.

Swedish Asbestos-Cement Plant. Albin et al. (1990) studied workers at a Swedish plant that operated from 1907 to 1978 and produced various asbestos cement products, including sheets, shingles, and ventilation pipes. The asbestos handled was mainly chrysotile (>95%). Crocidolite was used before 1966, but never exceeded 3–4% of the total asbestos. Amosite was used for a few years in the 1950s but never exceeded 18% of the total asbestos used. Fiber length classes were the commercial grades 3–7, and all asbestos was milled prior to incorporation into products.

Impinger and gravimetric dust measurements were available for 1956–1969, and PCM measurements after 1969. These data, along with information on production and dust control, were used to estimate exposures for different jobs and periods of time.

The cohort contained 2,898 men and was defined as all male employees who worked for at least 3 months between 1907 and 1977. A reference cohort was composed of 1,233 men who worked in other industries in the region and who were not known to have worked with asbestos. Vital status of both groups was determined through 1986. Follow-up of both began after 20 years from first employment.

Excluding mesothelioma, other respiratory cancers were not significantly increased. Albin et al. present relative risks of these respiratory cancers and corresponding 95% CIs for three categories of cumulative exposure (Table A-20), based on Poisson regression with control for age and calendar year. In order to obtain crude estimates of the range of K_L that are consistent with these data, the 1986 U.S. EPA lung cancer relative risk model was fit, assuming that the Ln (RR) were normally distributed with fixed variances computed from the reported confidence intervals for the RR. Although elevated, the RR did not exhibit an exposure response, and the hypothesis $\alpha=1$ was not rejected ($p=0.13$). In this analysis K_L was not significantly different from zero, regardless of whether α was fixed at 1.0 or estimated. With $\alpha=1$ the estimate of K_L was 0.019 $(\text{f-y/ml})^{-1}$, 90% CI: (0, 0.065), and $K_L=0.00067$ $(\text{f-y/ml})^{-1}$, 90% CI: (0, 0.036) with α estimated.

Thirteen mesotheliomas were identified among exposed workers and one in the referent population, and a significant exposure response was observed with increasing cumulative exposure. Unfortunately, the mesothelioma data were not presented in a format that would permit application of the 1986 U.S. EPA mesothelioma model.

Regarding uncertainty, F1 is assigned a value of 4 due to the sparsity of data and the need to extrapolate. Several assumptions were incorporated into the extrapolations performed that were

based, among other things, on the scarcity of raw-material asbestos during World War II. All other factors are also assigned a factor of 1.0 due to lack of other remarkable limitations. Thus:

F1 = 4.0
F2 = 1.0
F3 = 1.0
F4L = 1.0

These factors, when coupled with the statistical confidence limits, resulted in the uncertainty range for K_L shown in Table A-1.

Belgium Asbestos-Cement Plant. Lacquet et al. (1980) conducted a roentgenologic, asbestosis, and mortality study in a Belgium asbestos cement factory employing about 2,400 employees that annually processed about 39,000 tons of asbestos, of which 90% was chrysotile, 8% crocidolite, and 2% amosite. The mortality study considered male workers who worked in the factory for at least 12 months during the 15-year period 1963–1977. Apparently no minimal latency was required before follow-up began.

Fiber counts were available for the years 1970–1976; fiber levels were estimated for as far back as 1928, but these estimates were considered to be "only good guesses at best." Individual exposures were estimated in fiber-years from work histories and estimated yearly concentrations in four work areas.

The incidence of respiratory cancer was very close to that which was expected in a Belgium population of matched age and sex (Table A-21). The models with α=1 (p=0.51) and α variable (p=0.39) gave similar results and the hypothesis α=1 was not rejected (p=0.77). With α=1, the estimate of K_L was 0.0 $(\text{f-y/ml})^{-1}$, 90% CI: (0, 0.0010). With α estimated, $K_L=6.8\text{x}10^{-5}$ $(\text{f-y/ml})^{-1}$, 90% CI: (0, 0.0021).

One death was due to pleural mesothelioma. Unfortunately, the data were not presented in a way that allowed the estimation of K_M.

Regarding uncertainty, F1 is assigned a value of 4 due to the sparsity of data and the need to extrapolate. Much of the data appear to be based on PCM, so that conversion is not necessary. All other factors are also assigned a factor of 1.0 due to lack of other remarkable limitations. Thus:

F1 = 4.0
F2 = 1.0
F3 = 1.0
F4L = 1.0

These factors, when coupled with the statistical confidence limits, resulted in the uncertainty range for K_L shown in Table A-1.

Retirees from U.S. Asbestos Products Company. Enterline et al. (1986) extended follow-up through 1980 for a cohort of U.S. retirees from a large asbestos products company that had been the subject of an earlier report (Henderson and Enterline 1979). Products manufactured by the company included textiles, cement shingles, sheets, insulation and cement pipe. Exposure was predominately to chrysotile in most operations, although amosite predominated in insulation production, and crocidolite in manufacture of cement pipe. Each worker's exposure was estimated from dust measurements in mppcf obtained from environmental surveys that started in the mid-1950's and were extrapolated back in time by the company industrial hygienist. No data are provided for conversion from mppcf to PCM in f/ml. Given the wide range of products manufactured, this conversion likely varied according to operation. Conversions calculated in different environments have ranged from 1.4 to 10, the most common value being around 3 f/ml per mppcf, which has been observed in diverse environments such as mining and textile manufacture. This value was provisionally applied to this cohort.

The cohort consisted of 1,074 white males who retired from the company during 1941–1967, and who were exposed to asbestos in production or maintenance jobs. The average duration of employment was 25 years. Follow-up started at age 65 or at retirement if work continued past age 65. By the end of follow-up in 1980, 88% were deceased.

Overall, respiratory cancer was significantly increased (SMR=258 in comparison to U.S. rates, based on 79 observed deaths). Enterline et al. (1986) categorized lung cancer deaths by cumulative exposure (their Table 4). Results of applying the 1986 U.S. EPA lung cancer model to these data are shown in Table A-22. Although both the model with $\alpha=1$ and α variable fit the data adequately ($p \geq 0.75$), the test of $\alpha=1$ was not rejected ($p=0.24$). With $\alpha=1$ the estimate of K_L was 0.0021 $(\text{f-y/ml})^{-1}$, 90% CI: (0.0015, 0.0027). With α variable, $K_L=0.0011$ $(\text{f-y/ml})^{-1}$, 90% CI: (0.00041, 0.0028).

From the death certificates Enterline et al. identified eight deaths from mesothelioma. These data were not presented in a form that permitted application of the 1986 U.S. EPA mesothelioma model.

Regarding uncertainty, F1 is assigned a value of 2.0 for this study for reasons similar to those described for Quebec. Because the manner employed for deriving the conversion factor used to convert impinger counts to fiber concentrations is not documented, a value of 3.0 is assigned to F2 for this study. All other factors are also assigned a factor of 1.0 due to lack of other remarkable limitations. Thus:

F1 = 2.0
F2 = 3.0
F3 = 1.0
F4L = 1.0

These factors, when coupled with the statistical confidence limits, resulted in the uncertainty range for K_L shown in Table A-1.

U.S. Insulation Applicators. Selikoff and Seidman (1991) reported on follow-up through 1986 of a cohort of 17,800 asbestos insulation applicators that had been followed through 1976 by Selikoff et al. (1979). The cohort consisted of men enrolled as members of the insulator's union in the United States and Canada. Deaths were classified both based on the information the death certificate, and using "best evidence," in which death certificate information was augmented by clinical data, histopathological material and X-rays.

Based on the composition of insulation material, it seems likely that these workers were exposed to substantial amounts of chrysotile and amosite. Data on insulator's exposures were reviewed by Nicholson (1976), who concluded that average exposures of insulation workers in past years could have ranged 10–15 f/ml and could have been 15–20 f/ml in marine construction. U.S. EPA (1986) assumed a value of 15 f/ml as an overall average, with an associated 3-fold uncertainty. This estimate of 15 f/ml will be used provisionally here as well.

The form of the data provided in Selikoff and Seidman (1991) is not particularly suitable for calculating K_L. Table 4 of Selikoff and Seidman (1991) contain observed and expected deaths from lung cancer (determined from either death certificates or best information) categorized by years from first exposure (<15, 15–19, 20–24, ..., 50+). Death certificate information was utilized herein to facilitate comparisons with expected deaths (based on the mortality experience of U.S. white males), which were also based on death certificates. Lung cancer was significantly increased over expected, except for the category of <15 years from onset of exposure. Selikoff and Seidman did not provide information on the duration of exposure. The U.S. EPA (1986, page 90) assumed an average exposure duration of 25 years. Assuming that all workers worked exactly 25 years and were exposed to 15 f/ml, the data in Table 4 of Selikoff and Seidman can be used to categorize lung cancer deaths by cumulative exposure lagged 10 years. The result is shown in Table A-23. The 1986 U.S. EPA lung cancer model provided a reasonable fit to these data with α variable ($p=0.12$), but not with $\alpha=1$ ($p<0.01$). Also, the hypothesis that $\alpha=1$ could be rejected ($p<0.01$). The estimate of K_L with α variable was 0.0018 $(\text{f-y/ml})^{-1}$, 90% CI: (0.00065, 0.0038). With $\alpha=1$, $K_L=0.0087$ $(\text{f-y/ml})^{-1}$, 90% CI: (0.0081, 0.0093).

Based on best evidence, Selikoff and Seidman (1991) found 458 mesotheliomas in this cohort. Table A-24 shows these deaths categorized by years from onset (based on Selikoff and Seidman 1991, Tables 5 and 6). Table A-24 also shows the results of fitting the 1986 U.S. EPA mesothelioma model to these data, assuming, as above, that workers worked for 25 years and were exposed to 15 f/ml. The 1986 U.S. EPA mesothelioma model provided a poor fit to these data ($p<0.01$), as it overestimates by more than a factor of 2 the number of mesothelioma deaths after 50+ years from first exposure. The estimate of K_M was $1.3\text{x}10^{-8}$, 90% CI: ($1.2\text{x}10^{-8}$, $1.4\text{x}10^{-8}$).

Regarding uncertainty, F1 is assigned a value of 4.0 for this study because data employed to estimate exposure is not facility-specific, but represents general, industry-wide exposure estimates derived from limited data. F3 is assigned a value of 2 for this study because the study provides no information on worker histories. F4L is assigned a value of 2 for this study because the data presented in the study were not provided in a form suitable for fitting the lung cancer model. Thus, the data had to be partially reconstructed. Other factors are also assigned a factor of 1.0 due to lack of other remarkable limitations. Thus:

F1 = 4.0
F2 = 1.0
F3 = 2.0
F4L = 2.0
F4M = 1.0

These factors, when coupled with the statistical confidence limits, resulted in the uncertainty ranges for K_L and K_M shown in Tables A-1 and A-2.

Pennsylvania Textile Plant. McDonald et al. (1983b) report on mortality in an asbestos plant located near Lancaster, Pennsylvania that produced mainly textiles, but also some friction materials. About 3,000 to 6,000 tons of chrysotile were processed annually at the plant, which began operation in the early 1900s. Crocidolite and amosite were used from 1924 onward; about 3–5 tons of raw crocidolite were processed annually and the use of amosite reached a peak of 600 tons during World War II.

The cohort consisted of all men employed for at least 1 month prior to 1959 and who had a valid record with the Social Security Administration. This group consisted of 4,022 men, of whom 35% had died by the end of follow-up (December 31, 1977). Follow-up of each worker was only begun past 20 years from first employment.

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

The lung cancer mortality in this cohort exhibited a significant exposure response trend (Table A-25), which was partially due to a deficit of cancers in the group exposed to <10 mppcf-y (21 with 31.4 expected). A survey of those employed in the plant in 1978 revealed a larger per cent of nonsmokers (25%) than were found in the other plants studied by these researchers (McDonald et al. 1983a, 1984), although this finding was based on a sample of only 36 workers. Regardless of the reason for this shortfall in the number of lung cancers, it appears that the most appropriate analysis is that in which the background is allowed to vary; this analysis fits the data well ($p>0.7$), whereas the analysis which assumes the Pennsylvania rates are appropriate provides a marginal fit ($p=0.08$). The hypothesis $\alpha=1$ was rejected ($p=0.01$). Consequently, the former analysis is judged to be the most appropriate (allowing the parameter α to vary). McDonald et al. (1983b) did not provide a factor for converting from mppcf to f/ml. Assuming that 3 f/ml is equivalent to one mppcf, the resulting estimate of lung cancer potency with α variable was 0.018 $(\text{f-y/ml})^{-1}$, 90% CI: (0.0075, 0.045). With $\alpha=1$, $K_L=0.0057$ $(\text{f-y/ml})^{-1}$, 90% CI: (0.0027, 0.0094).

A diagnosis of mesothelioma was specified on 14 death certificates (ten pleural and four peritoneal). Thirty other deaths were given the ICD code 199 (malignant neoplasms of other and unspecified sites) and the diagnosis given in many of these cases was said to be consistent with an unrecognized mesothelioma. McDonald et al. (1983b) Table 3 lists the average age at beginning of employment as 28.92 and the average duration of employment as 9.18 years, and their Table 1 lists 191, 667, and 534 deaths as occurring before age 45, between 45 and 65, and

after 65 years of age, respectively. Assuming that ½ of the deaths given the ICD code 199 might have been due to mesotheliomas, the total number of mesotheliomas in this cohort is estimated to be 23. Proceeding as in the mesothelioma analysis carried out for the McDonald et al. (1984) data, the data in Table A-26 were generated. Noting that the age since first exposure categories in which the mesotheliomas occurred is irrelevant as far as estimating K_M is concerned, the estimate of K_M is 1.1×10^{-8}, 90% CI: (0.76×10^{-8}, 1.5×10^{-8}). These estimates are uncertain due to the uncertainty regarding the number of mesotheliomas in the cohort.

Regarding uncertainty, F1 is assigned a value of 2.0 for this study for reasons similar to those described for Quebec. Because the manner employed for deriving the conversion factor used to convert impinger counts to fiber concentrations is not documented, a value of 3.0 is assigned to F2 for this study. A factor of 2.0 is assigned for F4M because the number of mesotheliomas observed in this study are reported to be estimates expected to be good to within a factor of 2. Thus:

F1 = 2.0
F2 = 3.0
F3 = 1.0
F4L = 1.0
F4M = 2.0

These factors, when coupled with the statistical confidence limits, resulted in the uncertainty ranges for K_L and K_M shown in Tables A-1 and A-2.

Rochdale, England Textile Factory. Peto et al. (1985) studied a textile factory in Rochdale, England that has been the subject of a number of earlier reports (Peto et al. 1977; Peto 1980a,b). Peto et al. (1985) has the most complete follow-up (through 1983) and emphasizes assessment of risk. The factory, which began working with asbestos in 1879, used principally chrysotile, but approximately 5% crocidolite was used between 1932 and 1968.

Quantitative estimates of risk were based on a subgroup of Peto et al. (1985) "principal cohort" consisting of all men first employed in 1933 or later who had worked in scheduled areas or on maintenance and had completed 5 years of service by the end of 1974. In the analyses of interest relating to lung cancer, follow-up only begins 20 years after the beginning of employment and exposure during the last 5 years of follow-up is not counted.

Routine sampling using a thermal precipitator began at 23 fixed sampling points in 1951. Comparisons of particle counts and fiber counts taken in 1960 and 1961 were used to convert between particles/ml and f/ml. Dust levels prior to 1951 were assumed to be the same as those observed during 1951–1955 for departments for which no major changes had been made. In departments in which conditions had improved, higher levels were assigned. These levels and work histories were used to assign individual exposure estimates. A conversion factor of 34 particles/ml per f/ml was determined by comparing average results obtained by the Casella thermal precipitator (particles/ml) with Ottway long running thermal precipitator (f/ml) at the same sampling point during 1960 and 1961. However, a conversion factor of 35.3 was used by Peto et al. (1985) for the sake of consistency with earlier work, and this factor will be used here as well.

After 20 years from first employment, there were 93 lung cancer deaths with only 64.6 expected. Using a lung cancer model essentially the same as the 1986 U.S. EPA model, Peto et al. estimated K_L=0.0054 (f-y/ml)$^{-1}$ for the entire cohort, and K_L=0.015 (f-y/ml)$^{-1}$ when the analysis was restricted to men first employed in 1951 or later. Peto et al. felt that the most plausible explanation for this difference was that it was largely due to chance and also possibly to the chance that exposure to the most carcinogenic fibers was not reduced as much as changes in particle counts from 1951 to 1960 would suggest.

Table A-27 displays the exposure response data based on men first employed in 1933 or later for lung cancer based on shows that the excess occurred mainly in workers whose cumulative exposure exceeded 400 f-y/ml (10 observed, 1.7 expected). The 1986 U.S. EPA lung cancer model fit these data adequately ($p \geq 0.63$) both with α=1 and α variable, and the hypothesis α=1 could not be rejected (p=0.57). With α=1, K_L was estimated as 0.0052 (f-y/ml)$^{-1}$, 90% CI: (0.0028, 0.0079), and with α variable, K_L=0.0041 (f-y/ml)$^{-1}$, 90% CI: (0.0012, 0.0087).

Ten mesotheliomas were observed in the cohort used by Peto et al. for quantitative analysis (an 11th case who was exposed for 4 months and died 4 years later was omitted because the short latency made it unlikely that this case was related to exposure at the factory). Observed mesotheliomas and corresponding person-years of observation by duration of service and years since first employment (Peto et al. 1985, Table 8) are shown in Table A-28. An overall average exposure was estimated by applying the Peto mesothelioma model to the data in Table A-28 with a single exposure estimate selecting the value that gave the smallest least squares fit of this model to the mesothelioma data. The fitting was carried out both unweighted and by weighting by the person years, with resulting estimates of 360 and 322 particles/ml, respectively; the latter value was the one selected. Using the conversion factor of 35.3 particles/ml per f/ml, the estimated average exposure is 322/35.2=9.1 f/ml. The 1986 U.S. EPA mesothelioma model fit these data well, and the resulting estimate of mesothelioma potency (Table A-28) was K_M=1.3x10^{-8}, 90% CI: (0.74x10-8, 2.1x10^{-8}).

Regarding uncertainty, F1 is assigned a value of 2.0 for this study for reasons similar to those described for Quebec. Because a conversion factor was derived for measurements collected using Otway long-running thermal precipitators and PCM measurements based on measurements of each collected under similar conditions (but not side-by-side), a value of 2 is assigned to F2. Thus:

F1 = 2.0
F2 = 2.0
F3 = 1.0
F4L = 1.0
F4M = 1.0

These factors, when coupled with the statistical confidence limits, resulted in the uncertainty ranges for K_L and K_M shown in Tables A-1 and A-2.

REFERENCES

Albin M; Jakobsson K; Attewell R; Johansson L; Welinder H. Mortality and Cancer Morbidity in Cohorts of Asbestos Cement Workers and Referents. *British Journal of Industrial Medicine*. 79(9):602–610. September. 1990.

Amandus HE; Wheeler R. The Morbidity and Mortality of Vermiculite Miners and Millers Exposed to Tremolite-Actinolite: Part II. Mortality. *American Journal of Industrial Medicine* 11:15–26. 1987.

Amandus HE; Wheeler R; Jankovic J; Tucker J. The Morbidity and Mortality of Vermiculite Miners and Millers Exposed to Tremolite-Actinolite: Part I. Exposure Estimates. *American Journal of Industrial Medicine*. 11:1–14. 1987.

Armstrong BK; de Klerk NH; Musk AW; Hobbs MST. Mortality in Miners and Millers of Crocidolite in Western Australia. *British Journal of Industrial Medicine*. 45:5–13. 1988.

Berry G; Newhouse ML. Mortality of Workers Manufacturing Friction Materials Using Asbestos. *British Journal of Industrial Medicine*. 40:1–7. 1983.

CHAP (Chronic Hazard Advisory Panel on Asbestos). Report to the U.S. Consumer Product Safety Commission. July. 1983.

Cox D; Oakes DV. *Analysis of Survival Data*. Cox DR; Hinkley DV (eds.). Chapman and Hall, London. 1984.

de Klerk NH; Musk AW; Armstrong BK; Hobbs MST. Diseases in Miners and Millers of Crocidolite from Wittenoom, Western Australia: A Further Follow-up to December 1986. *Annals of Occupational Hygiene*. 38(Suppl 1):647–655. 1994.

Dement JM. Estimation of Dose and Evaluation of Dose-Response in a Retrospective Cohort Mortality Study of Chrysotile Asbestos Textile Workers. Ph.D. Thesis. The University of North Carolina at Chapel Hill. 1980.

Dement JM; Brown DP. Cohort Mortality and Case-Control Studies of White Male Chrysotile Asbestos Textile Workers. *Journal of Clean Technology, Environmental Toxicology, and Occupational Medicine*. 7:1052–1062. 1998.

Dement JM; Harris RL; Symons MJ; Shy CM. Estimates of Dose-Response for Respiratory Cancer Among Chrysotile Asbestos Textile Workers. *Annals Occupational Hygiene*. 26(1-4):869–887. 1982.

Dement JM; Harris RL; Symons MJ; Shy CM. Exposures and Mortality Among Chrysotile Workers. Part I: Exposure Estimates. *American Journal of Industrial Medicine*. 4:399–419. 1983a.

Dement JM; Harris RL; Symons MJ; Shy CM. Exposures and Mortality Among Chrysotile Workers. Part II: Mortality. *American Journal of Industrial Medicine*. 4:421–433. 1983b.

Dement JM; Brown DP; Okun A. Follow-up Study of Chrysotile Asbestos Textile Workers: Cohort Mortality and Case-Control Analysis. *American Journal of Industrial Medicine*. 26:431–447. 1994.

Enterline PE; Harley J; Henderson V. Asbestos and Cancer -- A Cohort Followed to Death. Graduate School of Public Health, University of Pittsburgh. 1986.

Finkelstein MM. Mortality Among Long-Term Employees of an Ontario Asbestos-Cement Factory. *British Journal of Industrial Medicine*. 40:138–144. 1983.

Finkelstein MM. Mortality Among Employees of an Ontario Asbestos-Cement Factory. *American Review of Respiratory Disease*. 129:754–761. 1984.

Hammond EC; Selikoff IJ; Seidman H. Asbestos Exposure, Cigarette Smoking and Death Rates. *Annals New York Academy of Sciences*. 330:473–490. 1979.

Henderson VL; Enterline PE. Asbestos Exposure: Factors Associated with Excess Cancer and Respiratory Disease Mortality. *Annals New York Academy of Sciences*. 330:117–126. 1979.

Hughes JM; Weill H. Asbestos Exposure: Quantitative Assessment of Risk. *American Review of Respiratory Disease*. 133:5–13. 1986.

Hughes JM; Weill H; Hammad YY. Mortality of Workers Employed at Two Asbestos Cement Plants. *British Journal of Industrial Medicine*. 44:161–174. 1987.

Lacquet LM; VanderLinden L; Lepoutre J. Roentgenographic Lung Changes, Asbestosis and Mortality in a Belgian Asbestos-Cement Factory. In *Biological Effects of Mineral Fibres*, Wagner JC (ed.). IARC Sci Publ. pp. 783–793. 1980.

Lemon RA; Dement JM; Wagoner JK. Epidemiology of asbestos-related diseases. *Environmental Health Perspective*. 34:1–11. 1980.

Levin JL; McLarty JW; Hurst GA; Smith AN; Frank AL. Tyler Asbestos Workers: Mortality Experience in a Cohort Exposed to Amosite. *Occupational and Environmental Medicine*. 55:155–160. 1998.

Liddell FDK. Unpublished raw mesothelioma data provided to Dr. Wayne Berman by Dr. FDK Liddell from multiple studies of the 1891–1920 Birth Cohort of Quebec Chrysotile Miners and Millers most recently described in Liddell et al. 1997. 2001.

Liddell FDK; McDonald AD; McDonald JC. The 1891–1920 Birth Cohort of Quebec Chrysotile Miners and Millers: Development From 1904 and Mortality to 1992. *Annals of Occupational Hygiene*. 41:13–36. 1997.

McDonald JC; Liddell FDK; Gibbs GW; Eyssen GE; McDonald AD. Dust Exposure and Mortality in Chrysotile Mining, 1910–1975. *British Journal of Industrial Medicine*. 37:11–24. 1980a.

McDonald JC; Gibbs GW; Liddell FDK. Chrysotile Fibre Concentration and Lung Cancer Mortality: A Preliminary Report. In *Biological Effects of Mineral Fibres*. Wagner JC (ed). IARC Scientific Publications. pp. 811–817. 1980b.

McDonald AD; Fry JS; Wooley AJ; McDonald JC. Dust Exposure and Mortality in an American Chrysotile Textile Plant. *British Journal of Industrial Medicine*. 39:361–367. 1983a.

McDonald AD; Fry JS; Woolley AJ; McDonald JC. Dust Exposure and Mortality in an American Factory Using Chrysotile, Amosite, and Crocidolite in Mainly Textile Manufacture. *British Journal of Industrial Medicine.* 40:368–374. 1983b.

McDonald AD; Fry JS; Woolley AJ; McDonald JC. Dust Exposure and Mortality in an American Chrysotile Asbestos Friction Products Plant. *British Journal of Industrial Medicine*. 41:151–157. 1984.

McDonald JC; McDonald AD; Armstrong B; Sebastien P. Cohort Study of Mortality of Vermiculite Miners Exposed to Tremolite. *British Journal of Industrial Medicine*. 43:436–444. 1986.

McDonald JC; Liddell FDK; Dufresne A; McDonald AD. The 1891–1920 Birth Cohort of Quebec Chrysotile Miners and Millers: Mortality 1976–1988. *British Journal of Industrial Medicine*. 50:1073–1081. 1993.

Nicholson WJ. Part III. Recent Approaches to the Control of Carcinogenic Exposures. Case Study 1: Asbestos - The TLV Approach. *Annals New York Academy of Science*. 271:152–169. 1976.

Nicholson WJ; Selikoff IJ; Seidman H; Lilis R; Formby P. Long-Term Mortality Experience of Chrysotile Miners and Millers in Thetford Mines, Quebec. *Annals New York Academy of Sciences*. 330:11–21. 1979.

Ontario Royal Commission. Report of the Royal Commission on Matters of Health and Safety Arising form the Use of Asbestos in Ontario. Volume 3. 1984.

Peto J. Lung Cancer Mortality in Relation to Measured Dust Levels in an Asbestos Textile Factory. In *Biological Effects of Mineral Fibres*. Wagner JC (ed.). IARC Scientific Publications. pp. 829–836. 1980a.

Peto J. The Incidence of Pleural Mesothelioma in Chrysotile Asbestos Textile Workers. In *Biological Effects of Mineral Fibres*. Wagner JC (ed.). IARC Scientific Publications. pp. 703–711. 1980b.

Peto J; Doll R; Howard SV; Kinlen LJ; Lewinsohn, HC. A Mortality Study Among Workers in an English Asbestos Factory. *British Journal of Industrial Medicine*. 34:169–173. 1977.

Peto J; Seidman H; Selikoff IJ. Mesothelioma Mortality in Asbestos Workers: Implications for Models of Carcinogenesis and Risk Assessment. *British Journal of Cancer*. 45:124–135. 1982.

Peto J; Doll R; Hermon C; Binns W; Clayton R; Goffe T. Relationship of Mortality to Measures of Environmental Asbestos Pollution in an Asbestos Textile Factory. *Annals of Occupational Hygiene*. 29(3):305–355. 1985.

Piolatto G; Negri E; LaVecchia C; Pira E; Decarli A; Peto J. An Update of Cancer Mortality Among Chrysotile Asbestos Miners in Balangero, Northern Italy. *British Journal of Industrial Medicine.* 47:810–814. 1990.

Rubino GF; Piolatto GW; Newhouse ML; Scansetti G; Aresini GA; Murray R. Mortality of Chrysotile Asbestos Workers at the Balangero Mine, Northern Italy. *British Journal of Industrial Medicine*. 36:187–194. 1979.

Seidman H. Short-Term Asbestos Work Exposure and Long-Term Observation -- July 1984 Update. Department of Epidemiology, American Cancer Society. 1984.

Seidman H; Selikoff IJ; Hammond EC. Short-Term Asbestos Work Exposure and Long-Term Observation. *Annals New York Academy of Sciences*. 330:61–89. 1979.

Seidman H; Selikoff IJ; Gelb SK. Mortality Experience of Amosite Asbestos Factory Workers: Dose-Response Relationships 5 to 40 Years After Onset of Short-Term Work Exposure. *American Journal of Industrial Medicine*. 10(5/6):479–514. 1986.

Selikoff IJ; Seidman H. Asbestos-Associated Deaths among Insulation Workers in the United States and Canada, 1967–1987. *Annals of the New York Academy of Sciences*. 643:1–14. 1991.

Selikoff IJ; Hammond EC; Seidman H. Mortality Experience of Insulation Workers in the United States and Canada 1943–1976. *Annals New York Academy of Sciences*. 330:91–116. 1979.

U.S. EPA (U.S. Environmental Protection Agency). Airborne Asbestos Health Assessment Update. Report 600/8-84-003F, U.S. Environmental Protection Agency. 1986.

Venzon D; Moolgavkar S. A Method for Computing Profile-likelihood-based Confidence Intervals. *Applied Statistics*. 37:87–94. 1988.

Weill H. 1994. Cancer Mortality in Chrysotile Mining and Milling: Exposure-Response. Asbestos-Cement. *Annals of Occupational Hygiene*. 38(4):412. 1994.

Weill H; Hughes J; Waggenspack C. Influence of Dose and Fibre Type on Respiratory Malignancy Risk in Asbestos Cement Manufacturing. *American Review of Respiratory Disease*. 120:345–354. 1979.

Table A-1. Lung Cancer Exposure-Response Coefficients (K_L) Derived from Various Epidemiological Studies

Fiber Type	Operation	Cohort	EPA (1986) K_L*100	Reference	This Update K_L*100	90% Confidence Interval	Uncertainty Interval[a]	Reference
Chrysotile	Mining and Milling	Quebec mines and mills	0.06	McDonald et al. 1980b	0.029	(0.019, 0.041)	(0.0085, 0.091)	Liddell et al. 1997
			0.17	Nicholson et al. 1979				
		Italian mine and mill	0.081	Piolatto et al. 1990	0.051	(0, 0.57)	(0, 1.1)	Piolatto et al. 1990
	Friction Products	Connecticut plant	0.01	McDonald et al. 1984	0	(0, 0.17)	(0, 0.62)	McDonald et al. 1984
	Cement Manufacture	New Orleans plants			0.25	(0, 0.66)	(0, 1.5)	Hughes et al. 1987
	Textiles	South Carolina plant	2.8	Dement et al. 1983b	2.1	(1.2, 3.4)	(0.81, 5.1)	Dement et al. 1994[b]
			2.5	McDonald et al. 1983a	1	(0.44, 2.5)	(0.22, 4.9)	McDonald 1983a
Crocidolile	Mining and Milling	Wittenoom			0.47	(0.17, 0.87)	(0.084, 1.7)	de Klerk et al. 1994[c]
Amosite	Insulation Manufacture	Patterson, NJ factory	4.3	Seidman 1984	1.1	(0.58, 1.9)	(0.17, 6.6)	Seidman et al. 1986
		Tyler, Texas factory			0.13	(0, 0.6)	(0, 1.8)	Levin et al. 1998
Tremolite	Vermiculite Mines and Mills	Libby, Montana			0.51	(0.11, 2.0)	(0.049, 4.4)	Amandus and Wheeler 1987
					0.39	(0.067, 1.2)	(0.03, 2.8)	McDonald et al. 1986
Mixed	Friction Products	British factory	0.058	Berry and Newhouse 1983	0.058	(0, 0.8)	(0, 1.8)	Berry and Newhouse 1983

Table A-1. Lung Cancer Exposure-Response Coefficients (K_L) Derived from Various Epidemiological Studies *(continued)*

Fiber Type	Operation	Cohort	EPA (1986) K_L*100	Reference	This Update K_L*100	90% Confidence Interval	Uncertainty Interval[a]	Reference
	Cement Manufacture	Ontario factory	4.8	Finkelstein 1983	0.29	(0, 3.7)	(0, 22)	Finkelstein 1984
		New Orleans plants	0.53	Weill 1979, 1994	0.25	(0, 0.66)	(0, 1.5)	Hughes et al. 1987
		Swedish plant			0.067	(0, 3.6)	(0, 14)	Albin et al. 1990
		Belgium factory			0.0068	(0, 0.21)	(0, 0.84)	Laquet et al. 1980
	Factory workers	US. retirees	0.49	Henderson and Enterline 1979	0.11	(0.041, 0.28)	(0.011, 1.0)	Enterline et al. 1986
	Insulation Application	U.S. insulation workers	0.75	Seilkoff et al. 1979	0.18	(0.065, 0.38)	(0.012, 2.1)	Seilkoff and Seidman 1991
	Textiles	Pennsylvania plant	1.4	McDonald et al. 1983b	1.8	(0.75, 4.5)	(0.2, 16)	McDonald et al. 1983b
		Rochedale plant	1.1	Peto 1980a	0.41	(0.12, 0.87)	(0.046, 2.3)	Peto et al. 1985

[a]Uncertainty Interval formed by combining 90% confidence interval with uncertainty factors in Table A-3.
[b]With supplemental raw data from Terri Schnorr (NIOSH) and Dement
[c]With supplemental unpublished raw data with follow-up through 2001

Table A-2. Mesothelimoa Exposure-Response Coefficients (K_M) Derived from Various Epidemiological Studies

Fiber Type	Operation	Cohort	EPA (1986) K_M*100	Reference	This Update K_M*100	90% Confidence Interval	Uncertainty Interval[a]	Reference
Chrysotile	Mining and Milling	Asbestos, Quebec			0.013	(0.0068, 0.022)	(0.003, 0.049)	Liddell et al. 1997[b]
		Thedford Mines			0.021	(0.014, 0.029)	(0.0065, 0.065)	Liddell et al. 1997[b]
	Friction Products	Connecticut plant			0	(0, 0.12)	(0, 0.65)	McDonald et al. 1984
	Cement Manufacture	New Orleans plant			0.2	–	(0.033, 1.2)	Hughes et al. 1987
	Textiles	South Carolina plant			0.25	(0.034, 0.79)	(0.023, 1.2)	Dement et al. 1994[c]
					0.088	(0.0093, 0.32)	(0.0025, 1.2)	McDonald et al. 1983a
Crocidolile	Mining and Milling	Wittenoom			7.9	(7, 9)	(3.5, 18)	de Klerk et al. 1994[d]
Amosite	Insulation Manufacture	Patterson, NJ factory	3.2	Seidman 1984	3.9	(2.6, 5.7)	(0.74, 20)	Seidman et al. 1986
Mixed	Cement Manufacture	Ontario factory	12	Finkelstein 1983	18	(13, 24)	(2, 160)	Finkelstein 1984
		New Orleans plant			0.3	–	(0.089, 1)	Hughes et al. 1987
	Factory Workers	Asbestos, Quebec			0.092	(0.04, 0.18)	(0.018, 0.39)	Liddell et al. 1997[b]
	Insulation Application	U.S. insulation workers	1.5	Seilkoff et al. 1979	1.3	(1.2, 1.4)	(0.25, 6.5)	Seilkoff and Seidman 1991
	Textiles	Pennsylvania plant			1.1	(0.76, 1.5)	(0.17, 6.6)	McDonald et al. 1983b
		Rochedale plant	1	Peto 1980; Peto et al. 1982	1.3	(0.74, 2.1)	(0.28, 5.6)	Peto et al. 1985

[a]Uncertainty Interval formed by combining 90% confidence interval with uncertainty factors in Table A-3.
[b]With supplemental raw data from Liddell
[c]With supplemental raw data from Terri Schnorr (NIOSH) with Dement
dWith supplemental unpublished raw data with follow-up through 2001

Table A-3. Uncertainty Factors Used to Develop Uncertainty Intervals for Exposure-Response Coefficients (K_L's and K_M's)

		Uncertainty Factors for Estimating Exposure			Special Uncertainty Factors		Combined Uncertainty		
Fiber Type Operation	**Cohort**	**Uncertainty Estimating Exposure Concentrations F1**	**Uncertainty Converting to PCM F2**	**Uncertainty Assigning Job Histories F3**	**Uncertainty for Special Lung Cancer Limitations F4**	**Uncertainty for Special Mesothelioma Limitations F4M**	**Lung Cancer**	**Meso-thelioma**	**Reference**
Chrysotile									
Mining and Milling	Quebec	2	1.5				2.2	2.2[a]	Liddell et al. 1997
	Asbestos, Quebec	2	1.5				NR	2.2[a]	Liddell et al. 1997
	Thedford Mines	2	1.5				NR	2.2[a]	Liddell et al. 1997
	Italian mine and mill	2					2.0	ND	Piolatto et al. 1990
Friction Products	Connecticut plant	2	3			3	3.7	5.5	McDonald et al. 1984
Cement Manufacture	New Orleans plant	2	1.5			5	2.2	6.0	Hughes et al. 1987
Textiles	South Carolina plant	1.5					1.5	1.5	Dement et al. 1994[b]
	South Carolina plant	2				3	2.0	3.7	McDonald et al. 1983a
Crocidolile									
Mining and Milling	Wittenoom	2					2.0	2.0	de Klerk et al. 1994[c]
Amosite									
Insulation Manufacture	Patterson, NJ factory	3.5					3.5	3.5	Seidman et al. 1986

Table A-3. Uncertainty Factors Used to Develop Uncertainty Intervals for Exposure-Response Coefficients (K_L's and K_M's) *(continued)*

		Uncertainty Factors for Estimating Exposure			Special Uncertainty Factors		Combined Uncertainty		
Fiber Type Operation	**Cohort**	**Uncertainty Estimating Exposure Concentrations F1**	**Uncertainty Converting to PCM F2**	**Uncertainty Assigning Job Histories F3**	**Uncertainty for Special Lung Cancer Limitations F4**	**Uncertainty for Special Mesothelioma Limitations F4M**	**Lung Cancer**	**Meso-thelioma**	**Reference**
	Tyler, Texas factory	3					3.0	ND	Levin et al. 1998
Tremolite									
Vermiculite Mines and Mills	Libby, Montana	2	1.5				2.2	ND	Amandus and Wheeler 1987
	Libby, Montana	2	1.5				2.2	ND	McDonald et al. 1986
Mixed									
Friction Products	British factory	2			1.5		2.2	ND	Berry and Newhouse 1983
Cement Manufacture	Ontario factory	4	3			2	5.9	6.7	Finkelstein 1984
	New Orleans plant	2	1.5			2.5	2.2	3.4	Hughes et al. 1987
	Swedish plant	4					4.0	ND	Albin et al. 1990
	Belgium factory	4					4.0	ND	Laquet et al. 1980
Factory Workers	U.S. retirees	2	3				3.7	ND	Enterline et al. 1986
	Asbestos, Quebec	2	1.5				NR	2.2a	Liddell et al. 1997
Insulation Application	U.S. insulation workers	4		2	2		5.5	4.7	Seilkoff and Seidman 1991

Table A-3. Uncertainty Factors Used to Develop Uncertainty Intervals for Exposure-Response Coefficients (K_L's and K_M's) *(continued)*

		Uncertainty Factors for Estimating Exposure			Special Uncertainty Factors		Combined Uncertainty		
Fiber Type Operation	**Cohort**	**Uncertainty Estimating Exposure Concentrations F1**	**Uncertainty Converting to PCM F2**	**Uncertainty Assigning Job Histories F3**	**Uncertainty for Special Lung Cancer Limitations F4**	**Uncertainty for Special Mesothelioma Limitations F4M**	**Lung Cancer**	**Meso-thelioma**	**Reference**
Textiles	Pennsylvania plant	2	3			2	3.7	4.4	McDonald et al. 1983b
	Rochedale plant	2	2				2.7	2.7	Peto et al. 1985

[a]With supplemental raw data from Liddell et al. 1997 for mesothelioma
[b]With supplemental raw data from Terri Schnorr (NIOSH) with Dement
[c]With supplemental unpublished raw data with follow-up through 2001

NOTES:
Values for uncertainty factors not listed in the table are assumed to be equal to one.
A description of the manner in which each of the values presented in this table was assigned is presented under the descriptions of individual studies in Appendix A.
NR means no raw data. These are the data sets from Quebec for which we had access only to raw data for mesothelioma. Thus, lung cancer rates could not be determined.
NR means not determined. These are the data sets for which mesothelioma data were either lacking or were unuseable.

Table A-4
Cancer of Lung, Trachea, or Bronchus by Cumulative Exposure Level among Workers in Quebec Chrysotile Mines and Mills
Liddell et al. (1997)

mpcf-yr		(f-yr)/ml	SMR	Expected	Observed	Predicted	
Range	Mean	Mean				α = 1	α = 1.15
[0, 3)	1.5	4.71	1.12	67.0	75	67.1	76.9
[3, 10)	6.5	20.41	1.27	50.4	64	50.8	58.2
[10, 30)	20	62.8	1.03	59.2	61	60.8	69.2
[30, 60)	45	141.3	1.32	45.5	60	48.1	54.3
[60, 100)	80	251.2	1.45	42.1	61	46.4	51.8
[100, 200)	150	471	1.27	52.8	67	63.0	68.8
[200, 300)	250	785	1.1	31.8	35	42.1	44.8
[300, 400)	350	1099	1.46	19.9	29	28.8	30.1
[400, 1000)	700	2198	1.84	47.8	88	91.1	89.9
>= 1000	1500	4710	2.97	15.8	47	46.5	43.0
Totals				432.2	587	544.7	587.0

		α = 1 (fixed)	α = 1.15 (MLE)
K_L * 100		0.041	0.029
(90% Confidence Interval)		(0.032, 0.051)	(0.019, 0.041)
Goodness of Fit	**P-value**	0.18	0.58
Test of H_0: α = 1	**P-value**	0.014	

Table A-5
Lung Cancer Mortality among Chrysotile Asbestos Miners in Balangero, Northern Italy
Piolatto et al. (1990)

f-y/ml Range	f-y/ml Mean	Observed	Expected	Predicted α = 1	Predicted α = 0.937
< 100	50	4	5.1	5.2	4.9
[100, 400)	250	8	6.1	6.6	6.4
>= 400	600	10	8.7	10.5	10.7
Totals		22	19.9	22.3	22.0

		α = 1 (fixed)	α = 0.937 (MLE)
K_L * 100		0.035	0.051
(90% Confidence Interval)		(0, 0.15)	(0, 0.57)
Goodness of Fit	**P-value**	0.75	0.45
Test of H_0: α = 1	**P-value**	0.88	

Table A-6
Lung Cancer Mortality among Workers in a Chrysotile Asbestos Friction Products Plant in Connecticut
McDonald et al. (1984)

mpcf-yr Range	mpcf-yr Mean	(f-yr)/ml Mean	SMR	Expected	Observed	Predicted α = 1	Predicted α = 1.49
< 10	5	15	167.4	32.9	55	33.8	49.0
[10 , 20)	15	45	101.7	5.9	6	6.4	8.8
[20 , 40)	30	90	105.4	4.7	5	5.5	7.1
[40 , 80)	60	180	162.8	3.7	6	4.9	5.5
>=80	110	330	55.22	1.8	1	2.9	2.7
Totals				49.0	73	53.6	73.0

		α = 1 (fixed)	α = 1.49 (MLE)
K_L * 100		0.19	0
(90% Confidence Interval)		(0, 0.61)	(0, 0.17)
Goodness of Fit	**P-value**	0.01	0.28
Test of H_0: α = 1	**P-value**	0.001	

Table A-7
Mesothelioma Mortality among Connecticut Friction Product Plant Workers
McDonald et al. (1984)

Years After First Exposure Range	Mean	Duration of Exposure	f/ml	Person Years	Observed	Predicted
[14, 34)	22	8.04	5.52	37742	0	0.0
>= 34	39	8.04	5.52	9420	0	0.0
Totals				47162	0	0.0

$K_M * 10^8$	0
(90% Confidence Interval)	(0, 0.12)
Goodness of Fit P-Value	1.00

Table A-8
Lung Cancer Mortality among Workers Employed in Two Asbestos Cement Manufacturing Plants in New Orleans, Louisiana
Hughes et al. (1987)

mpcf-yr Range	mpcf-yr Mean	(f-yr)/ml Mean	Observed	Expected	Predicted α = 1	Predicted α = 1.14
Plant 1 Employees						
(< 6)	4	5.6	3	2.9	3.0	3.4
(6 - 24)	13	18.2	9	8	8.6	9.6
(25 - 49)	35	49	2	3.7	4.4	4.8
(50 - 99)	74	103.6	3	3.8	5.4	5.5
(>= 100)	183	256.2	5	4.1	8.3	7.7
Plant 2 Employees						
(< 6)	3	4.2	20	18.9	19.2	21.8
(6 - 24)	12	16.8	19	14.5	15.5	17.3
(25 - 49)	36	50.4	12	6	7.2	7.7
(50 - 99)	71	99.4	10	5.5	7.7	7.9
(>= 100)	164	229.6	12	5.2	9.9	9.4
Totals			95	72.6	89.0	95.0

		α = 1 (fixed)	α = 1.14 (MLE)
K_L * 100		0.4	0.25
(90% Confidence Interval)		(0.15, 0.7)	(0, 0.66)
Goodness of Fit	**P-value**	0.44	0.42
Test of H_0: α = 1	**P-value**	0.18	

Table A-9
Lung Cancer Mortality by Cumulative Exposure among Chrysotile Asbestos Textile Workers in Charleston, South Carolina
Dement et al. (1994) -- based on raw data provided by Terri Schnorr (NIOSH)

f-y/ml Range	Mean	Observed	Expected	Predicted α = 1	Predicted α = 1.22
< 0.8	0.14	7	6.8	6.8	8.3
[0.8, 2)	1.33	11	9.3	9.7	11.6
[2, 4)	2.9	12	9.2	10.0	11.8
[4, 10)	6.53	19	11	13.0	15.1
[10, 35)	19.35	19	11.9	18.4	20.2
[35, 85)	54.73	21	8.5	21.7	22.1
>= 85	143.35	33	6.6	33.5	31.9
Totals		122	63.3	113.1	121.1

		α = 1 (fixed)	α = 1.22 (MLE)
K_L * 100		2.8	2.1
(90% Confidence Interval)		(2.1, 3.7)	(1.2, 3.4)
Goodness of Fit	**P-value**	0.81	0.93
Test of H_0: α = 1	**P-value**	0.19	

Table A-10
Lung Cancer Mortality among Workers in a Chrysotile Asbestos Textiles Plant in South Carolina
McDonald et al. (1983a)

mpcf-yr Range	mpcf-yr Mean	(f-yr)/ml Mean	SMR	Expected	Observed	Predicted α = 1	Predicted α = 1.07
< 10	5	30	143.1	21.7	31	29.2	30.4
[10 - 19]	15	90	182.7	2.7	5	5.6	5.7
[20 - 39]	30	180	304.2	2.6	8	8.1	8.0
[40 - 79]	60	360	419.5	1.7	7	8.6	8.4
>= 80	110	660	1031.9	0.8	8	6.7	6.5
Totals				29.5	59	58.1	59.0

		α = 1 (fixed)	α = 1.07 (MLE)
K_L * 100		1.2	1
(90% Confidence Interval)		(0.75, 1.6)	(0.44, 2.5)
Goodness of Fit	**P-value**	0.95	0.88
Test of H_0: α = 1	**P-value**	0.80	

Table A-11
Mesothelioma Mortality among South Carolina Textile Plant Workers
McDonald et al. (1983a)

Years After First Exposure Range	Mean	Duration	f/ml	Person Years	Observed	Predicted
(19 - 39)	28	10	5.4	26280	0	0.7
(>39)	44	10	5.4	2787	1	0.3
Totals				29067	1	1.0

$K_M * 10^8$	0.088
(90% Confidence Interval)	(0.0093, 0.32)
Goodness of Fit P-Value	0.14

Table A-12
Lung Cancer Mortality Among
Asbestos Workers in Wittenoom, Australia
DeKlerk et al. (1994) -- supplemented with unpublished raw data with follow-up through 2001

(f-yr)/ml				Predicted	
Range	**Average**	**Expected**	**Observed**	**α = 1**	**α = 2.13**
0	0	4.6	5	4.6	9.8
0-0.4	0.19	7.9	27	8.0	17.0
0.4 - 1	0.69	8.2	11	8.3	17.6
1 - 2.3	1.59	11.6	22	12.1	24.9
2.3- 4.5	3.27	12.9	28	14.0	27.9
4.5 - 8.5	6.19	14.3	38	16.7	31.4
8.5 - 16	11.81	13.2	31	17.4	29.8
16 - 28	21.53	9.2	21	14.5	21.6
28 - 60	41.07	11.6	25	24.5	29.6
60 +	142.28	11.6	43	56.5	41.6
Totals		105.1	251	176.6	251.0

		α = 1 (fixed)	**α = 2.13 (MLE)**
K_L * 100		2.7	0.47
(90% Confidence Interval)		(2, 3.5)	(0.17, 0.87)
Goodness of Fit	**P-value**	< 0.001	0.10
Test of H_0: α = 1	**P-value**	< 0.001	

Table A-13
Lung Cancer Mortality by Cumulative Exposure among Amosite Asbestos Factory Workers in Paterson, New Jersey
Seidman et al. (1986)

(f-yr)/ml Range	Average	SMR	Expected	Observed	Predicted α = 1	Predicted α = 3.32
<6	3	2.8	5.3	15	6.3	18.2
6-12	9	4.2	2.9	12	4.5	10.5
12-25	18.5	4.4	3.4	15	7.3	13.5
25-50	37.5	4.7	2.8	13	9.3	13.0
50-100	75	7.1	2.4	17	13.5	14.3
100-150	125	6.0	1.5	9	13.1	11.7
150-250	200	11.4	1.3	15	17.7	13.9
250+	375	16.0	0.9	15	22.9	15.8
Totals			20.5	111	94.5	111.0

		α = 1 (fixed)	α = 3.32 (MLE)
K_L * 100		6.2	1.1
(90% Confidence Interval)		(5, 7.6)	(0.58, 1.9)
Goodness of Fit	**P-value**	< 0.001	0.90
Test of H_0: α = 1	**P-value**	< 0.001	

Table A-14
Mesothelioma Mortality among Amosite Insulation Workers in New Jersey
Seidman et al. (1986)

Years After First Exposure Range	Mean	Duration	f/ml	Person Years	Observed	Predicted
(5-9)	7.5	1.5	46.9	3952	0	0
(10-14)	12.5	1.5	48.3	3628	0	0.1
(15-19)	17.5	1.5	44.1	3198	0	1.1
(20-24)	22.5	1.5	43.2	2656	2	2.8
(25-29)	27.5	1.5	40.3	2094	5	4.2
(30-34)	32.5	1.5	33.5	1576	8	4.4
(35-39)	37.5	1.5	31.1	1086	2	4.3
Totals				18190	17	17.0

$K_M * 10^8$	3.9
(90% Confidence Interval)	(2.6, 5.7)
Goodness of Fit P-value	0.35

Table A-15
Lung Cancer Deaths among Asbestos Workers in Tyler, Texas
Levin et al. (1998)

Duration		f/ml	f-y/ml	Expected	Observed	Predicted	
Range	Mean					α = 1	α = 2.48
(< 0.5)	0.25	45	11.25	8.9	23	10.2	22.4
(0.5-1)	0.75	45	33.75	1.1	3	1.6	2.9
(1 - 5)	3	45	135	1.8	4	4.8	5.3
(> 5)	7.5	45	337.5	1.5	6	7.8	5.4
Totals				13.3	36	24.4	36.0

		α = 1 (fixed)	α = 2.48 (MLE)
K_L * 100		1.3	0.13
(90% Confidence Interval)		(0.55, 2.2)	(0, 0.6)
Goodness of Fit	**P-value**	0.004	0.81
Test of H_0: α = 1	**P-value**	< 0.001	

Table A-16
Lung Cancer Mortality by Cumulative Exposure Among Vermiculite Mine and Mill Workers Near Libby, Montana
Amandus and Wheeler (1987)

(f-yr)/ml Range	Average	SMR	Expected	Observed	Predicted α = 1	Predicted α = 1.13
(<50)	25	1.5	4.0	6	4.6	5.0
(50-99)	75	1.5	1.4	2	2.0	2.1
(100-399)	250	1.1	1.9	2	4.8	4.8
(>=400)	600	5.8	1.7	10	8.1	8.0
Totals			9.0	20	19.5	20.0

		α = 1 (fixed)	α = 1.13 (MLE)
K_L * 100		0.61	0.51
(90% Confidence Interval)		(0.29, 1)	(0.11, 2)
Goodness of Fit	**P-value**	0.41	0.25
Test of H_0: α = 1	**P-value**	0.80	

Table A-17
Lung Cancer Mortality by Cumulative Exposure Among Vermiculite Miners Near Libby, Montana
McDonald et al. (1986)

(f-yr)/ml Range	Average	SMR	Expected	Observed	Predicted α = 1	Predicted α = 1.91
(0-25)	12.5	2.04	3.4	7	3.9	6.9
(25-200)	77.3	1.97	2.5	5	4.6	6.3
(200-500)	332.4	7.53	0.9	7	4.2	4.1
(>=500)	836.1	5.58	0.7	4	7.0	5.8
Totals			7.6	23	19.7	23.0

		α = 1 (fixed)	α = 1.91 (MLE)
K_L * 100		1.1	0.39
(90% Confidence Interval)		(0.55, 1.7)	(0.067, 1.2)
Goodness of Fit	**P-value**	0.16	0.26
Test of H_0: α = 1	**P-value**	0.11	

Table A-18
Lung Cancer Mortality by Cumulative Exposure Among
Ontario Asbestos Cement Plant Workers
Finkelstein (1984)

(f-yr)/ml Range	(f-yr)/ml Average	SMR	Expected	Observed	Mortality Rate	Predicted α = 1	Predicted α = 4.26
(<=30)	15	2.307692	1.3	3	3	2.2	5.8
(30-75)	52.5	6.153846	1.0	6	8	3.4	4.8
(75-105)	90	12.07692	0.4	5	15.7	2.2	2.2
(105-150)	127.5	9	0.6	5	11.7	4.0	3.2
(>150)	200	2.692308	0.7	2	3.5	7.9	5.0
Totals			4.0	21	41.9	19.7	21.0

		α = 1 (fixed)	α = 4.26 (MLE)
K_L * 100		4.8	0.29
(90% Confidence Interval)		(2.8, 7.4)	(0, 3.7)
Goodness of Fit	**P-value**	0.03	0.05
Test of H_0: α = 1	**P-value**	0.07	

Table A-19
Mesothelioma Mortality among Employees of an Ontario Asbestos Cement Factory
Finkelstein (1984)

Years After First Exposure Range	Mean	Duration	f/ml	Person Years	Observed	Predicted
(10 - 14)	12	6.7	9	2500	1	0.03
(15 - 19)	17	6.7	9	2500	1	1.4
(20 - 24)	22	6.7	9	2963	8	7.6
(25 - 29)	27	6.7	9	2063	13	12.8
(30 - 34)	32	6.7	9	625	6	7.2
Totals				10651	29	29.0

$K_M * 10^8$	18
(90% Confidence Interval)	(13, 24)
Goodness of Fit P-value	0.26

Table A-20
Lung Cancer Mortality among Asbestos Cement Workers in Sweden
Albin et al. (1990)

Relative Risk (RR) of Dying of Lung Cancer						
(f-yr)/ml	RR	Lower Bound	Upper Bound	St. Dev.	Predicted α = 1	Predicted α = 1.82
3.1	1.8	0.8	3.9	0.39	1.1	1.8
25.6	1.9	0.7	5.3	0.52	1.5	1.8
88.2	1.9	0.5	7.1	0.67	2.7	1.9
Totals					5.2	5.6

		α = 1 (fixed)	α = 1.82 (MLE)
K_L * 100		1.9	0.067
(90% Confidence Interval)		(0, 6.5)	(0, 3.6)
Goodness of Fit	P-value	0.32	0.95
Test of H_0: α = 1	P-value	0.13	

Table A-21
Lung Cancer Mortality among Belgian Asbestos-Cement Factory Workers
Laquet et al. (1980)

(f-yr)/ml Range	Average	Expected	Observed	Predicted α = 1	Predicted α = 0.924
(0 - 49)	25	5.2	6	5.2	4.8
(50 - 99)	75	2.4	3	2.4	2.3
(100 - 199)	150	4.6	5	4.6	4.3
(200 - 399)	300	7.5	4	7.4	7.0
(400 - 799)	600	2.0	1	1.9	1.9
(800 - 1599)	1200	0.6	2	0.5	0.6
(1600 - 3200)	2400	0.2	0	0.2	0.2
Totals		22.4	21	22.1	21.0

		α = 1 (fixed)	α = 0.924 (MLE)
K_L * 100		0	0.0068
(90% Confidence Interval)		(0, 0.1)	(0, 0.21)
Goodness of Fit	**P-value**	0.51	0.39
Test of H_0: α = 1	**P-value**	0.77	

Table A-22
Lung Cancer Mortality among Retirees from a US Asbestos Company
Enterline et al. (1986)

mppcf-y Range	mppcf-y Mean	f-y/ml Mean	SMR	Observed	Expected	Predicted α = 1	Predicted α = 1.43
(< 125)	62	186	182.3	23	12.6	17.5	21.8
(125 - 249	182	546	203.1	14	6.9	14.7	15.9
(250 - 499	352	1056	322	24	7.5	23.7	23.4
(500 - 749	606	1818	405	10	2.5	11.7	10.8
(>= 750)	976	2928	698.7	8	1.1	8.1	7.1
Totals				79	30.6	75.6	79.0

		α = 1 (fixed)	α = 1.43 (MLE)
K_L * 100		0.21	0.11
(90% Confidence Interval)		(0.15, 0.27)	(0.041, 0.28)
Goodness of Fit	**P-value**	0.75	0.92
Test of H_0: α = 1	**P-value**	0.24	

Table A-23
Lung Cancer Deaths among Insulation Workers in the United States and Canada
Selikoff and Seidman (1991)

Years After First Expo Range	Mean	Duration	Person Years	f-y/ml	Observed	Expected	Predicted α = 1	Predicted α = 2.39
(<15)	12.5	2.5	61655.4	37.5	7	3.9	5.1	9.9
(15-19)	17.5	7.5	52709.5	112.5	34	11.6	23.0	33.4
(20-24)	22.5	12.5	57595.4	187.5	85	27.5	72.4	88.2
(25-29)	27.5	17.5	50518.6	262.5	172	46.6	153.1	164.8
(30-34)	32.5	22.5	37165.8	337.5	252	57.5	226.5	222.3
(35-39)	35	25	20340	375	193	46.7	These categories	
(40-44)	35	25	10200.5	375	129	30.9	combined into the	
(45-49)	35	25	5256.5	375	66	18.8	Over 35 Years	
(50+)	35	25	6151	375	71	25.4	category	
(35+)	35	25	41948	375	459	121.8	519.0	490.4
Totals					1468	390.6	519.0	490.4

Exposure Concentration is 15 f/ml

		α = 1 (fixed)	α = 2.39 (MLE)
K_L * 100		0.87	0.18
(90% Confidence Interval)		(0.81, 0.93)	(0.065, 0.38)
Goodness of Fit	**P-value**	0.002	0.12
Test of H_0: α = 1	**P-value**	< 0.001	

Table A-24
Mesothelioma Deaths among Asbestos Insulation Workers
Selikoff and Seidman (1991)

Years After First Exposure Range	Mean	Person Years	Observed Pleural	Peritoneal	Total	Predicted
(<15)	12.5	61655	0	0	0	0.2
(15-19)	17.5	52710	2	3	5	4.6
(20-24)	22.5	57595	10	8	18	23.4
(25-29)	27.5	50519	33	40	73	56.3
(30-34)	32.5	37166	40	65	105	88.0
(35-39)	37.5	20340	33	58	91	87.9
(40-44)	42.5	10201	17	42	59	71.9
(45-49)	47.5	5257	27	31	58	55.5
(50+)	55	6151	11	38	49	106.3
Totals		301593	173	285	458	494.1

Duration = 25 Years and Exposure Concentration = 15 f/ml

$K_M * 10^8$	1.3
(90% Confidence Interval)	(1.2, 1.4)
Goodness of Fit P-value	< 0.001

Table A-25
Lung Cancer Mortality among Workers in a Pennsylvania Textile Factory
McDonald et al. (1983b)

mppcf-y Range	mppcf-y Mean	f-y/ml	SMR	Observed	Expected	Predicted α = 1	Predicted α = 0.519
(< 10)	5	15	66.9	21	31.4	34.1	20.7
(10 - 20)	15	45	83.6	5	6.0	7.5	5.6
(20 - 40)	30	90	156	10	6.4	9.7	8.8
(40 - 80)	60	180	160	6	3.8	7.6	8.3
(>= 80)	110	330	416.1	11	2.6	7.6	9.6
Totals				53	50.2	66.4	53.0

		α = 1 (fixed)	α = 0.519 (MLE)
K_L * 100		0.57	1.8
(90% Confidence Interval)		(0.27, 0.94)	(0.75, 4.5)
Goodness of Fit	**P-value**	0.08	0.76
Test of H_0: α = 1	**P-value**	0.01	

Table A-26
Mesothelioma Mortality among Pennsylvania Textile Plant Workers
McDonald et al. (1983b)

Years After First Exposure	Duration	f/ml	Person Years	Observed	Predicted
15.5	9.18	6.96	17179	6	0.2
24	9.18	6.96	40868	10	8.2
41	9.18	6.96	9840	7	14.6
Totals			67887	23	23.0

$K_M * 10^8$	1.1
(90% Confidence Interval)	(0.76, 1.5)
Goodness of Fit P-value	< 0.001

Table A-27
Lung Cancer Mortality among Rochdale Asbestos Textile Factory
Peto et al. (1985)

particle-yr/ml Range	Mean	f-y/ml	Observed	Expected	Predicted α = 1	Predicted α = 1.10
(< 1000)	209	5.92	34	29.5	30.4	33.2
(1000 - 2000)	1409	39.92	8	7.7	9.2	9.8
(2000 - 3000)	2511	71.13	11	6.6	9.0	9.4
(3000 - 4000)	3474	98.41	6	5.7	8.5	8.8
(4000 - 5000)	4551	128.92	10	4.3	7.2	7.2
(>= 5000)	9057	256.57	24	10.8	25.2	24.6
Totals			93	64.6	89.6	93.0

		α = 1 (fixed)	α = 1.10 (MLE)
K_L * 100		0.52	0.41
(90% Confidence Interval)		(0.28, 0.79)	(0.12, 0.87)
Goodness of Fit	**P-value**	0.72	0.63
Test of H_0: α = 1	**P-value**	0.57	

Table A-28
Mesothelioma Mortality among Rochdale Asbestos Textile Factory
Peto et al. (1985)

Years After First Exposure				Person		
Range	Mean	Duration	f/ml	Years	Observed	Predicted
(0-19)	11.5	0.5	9.12	28015	0	0.01
(20-24)	22.5	0.5	9.12	4668	0	0.2
(25-29)	27.5	0.5	9.12	3470	0	0.3
(30-34)	32.5	0.5	9.12	2041	0	0.3
(35-39)	37.5	0.5	9.12	840	0	0.2
(>=40)	42	0.5	9.12	402	0	0.1
(0-19)	11.5	3	9.12	4786	0	0.003
(20-24)	22.5	3	9.12	877	0	0.2
(25-29)	27.5	3	9.12	632	0	0.3
(30-34)	32.5	3	9.12	421	0	0.3
(35-39)	37.5	3	9.12	238	0	0.3
(>=40)	42	3	9.12	148	1	0.2
(0-19)	11.5	7.5	9.12	8521	0	0.01
(20-24)	22.5	7.5	9.12	1417	0	0.5
(25-29)	27.5	7.5	9.12	1104	0	0.9
(30-34)	32.5	7.5	9.12	707	0	1.1
(35-39)	37.5	7.5	9.12	383	0	0.9
(>=40)	42	7.5	9.12	249	0	0.9
(0-19)	11.5	15	9.12	4814	0	0.003
(20-24)	22.5	15	9.12	1423	0	0.5
(25-29)	27.5	15	9.12	870	0	0.9
(30-34)	32.5	15	9.12	470	3	1.0
(35-39)	37.5	15	9.12	204	0	0.7
(>=40)	42	15	9.12	102	1	0.5
(20-24)	22.5	25	9.12	848	1	0.3
(25-29)	27.5	25	9.12	935	1	1.0
(30-34)	32.5	25	9.12	600	2	1.3
(35-39)	37.5	25	9.12	257	1	1.0
(>=40)	42	25	9.12	122	0	0.8
(30-34)	32.5	35	9.12	86	0	0.2
(35-39)	37.5	35	9.12	107	0	0.4
(>=40)	42	35	9.12	103	0	0.7
Totals				69861	10	16.1

$K_M * 10^8$	1.3
(90% Confidence Interval)	(0.74, 2.1)
Goodness of Fit P-value	0.80

APPENDIX B:
REPORT ON THE PEER CONSULTATION WORKSHOP TO DISCUSS A PROPOSED PROTOCOL TO ASSESS ASBESTOS-RELATED RISK

Report on the Peer Consultation Workshop to Discuss a Proposed Protocol to Assess Asbestos-Related Risk

Prepared for:

U.S. Environmental Protection Agency
Office of Solid Waste and Emergency Response
Washington, DC 20460

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FINAL REPORT
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NOTE

This report was prepared by Eastern Research Group, Inc. (ERG), an EPA contractor, as a general record of discussion for the peer consultation workshop on a proposed protocol to assess asbestos-related risk. This report captures the main points of scheduled presentations, highlights discussions among the panelists, and documents the public comments provided at the meeting. This report does not contain a verbatim transcript of all issues discussed, and it does not embellish, interpret, or enlarge upon matters that were incomplete or unclear. EPA will use the information presented during the peer consultation workshop to determine whether the proposed risk assessment methodology can be used to support decisions at asbestos-contaminated sites. Except as specifically noted, no statements in this report represent analyses by or positions of EPA or ERG.

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LIST OF ABBREVIATIONS

ATSDR	Agency for Toxic Substances and Disease Registry
EPA	U.S. Environmental Protection Agency
ERG	Eastern Research Group, Inc.
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
NIOSH	National Institute for Occupational Safety and Health
PCM	phase contrast microscopy
SEM	scanning electron microscopy
SVF	synthetic vitreous fibers
TEM	transmission electron microscopy
μm	micrometers

EXECUTIVE SUMMARY

Eleven expert panelists participated in a peer consultation workshop to review a proposed protocol to assess asbestos-related risks. The protocol is documented in the report, "Technical Support Document for a Protocol to Assess Asbestos-Related Risk, Parts I and II" (Berman and Crump 1999, 2001). At the end of the 2½-day workshop, which was open to the public, the expert panelists drafted the following summary of their findings:

The peer consultation panel strongly endorsed the conceptual approach of developing an updated cancer risk assessment methodology that takes into account fiber type and fiber dimension. The opportunity is at hand to use substantial new information from epidemiology, experimental toxicology, and exposure characterization on what continues to be an extremely important societal issue—assessing the health risks associated with environmental and occupational exposures to asbestos. The panel recommended that EPA proceed in an expeditious manner to consider the panelists' conclusions and recommendations with a goal of having an updated asbestos risk assessment methodology. It is important that EPA devote sufficient resources so that this important task can be accomplished in a timely and scientifically sound manner. The panel urges that additional analyses underpinning the document, preparation of documentation, and further review be carried out in an open and transparent manner.

Prior to the workshop, the participants received draft copies of the "Methodology for Conducting Risk Assessments at Asbestos Superfund Sites Part 1: Protocol" and "Part 2: Technical Background Document." The panelists generally found that these documents did not provide a complete and transparent description of how the data were analyzed to support the conclusions presented. The incomplete documentation of methodology precluded the replication of the findings, in advance of the meeting, by several panelists. The methodology used was clarified by the comprehensive presentations that Drs. Berman and Crump made at the workshop. However, future drafts of these documents must

clearly describe the methodologies and include sufficient data, perhaps in appendices, such that the findings can be replicated.

The panelists made the following conclusions and recommendations:

Measurement methods. Continuing advances have been made in the application of exposure measurement technology for asbestos fibers during the past two decades. These advances include the use of transmission electron microscopy (TEM) and allied techniques (e.g., energy dispersive x-ray detection, or EDS) as an alternative to phase contrast microscopy (PCM), thereby allowing the bivariate (i.e., length and width) characterization of fibers and fiber type. The proposed risk assessment methodology incorporates these advances in the development of an exposure index. The panel was in agreement that this aspect of the new risk assessment methodology represents a substantial advance over the existing methodology.

Integration of exposure and risk assessment models. A key aspect of the proposed risk assessment methodology is a linking of specific exposure characterization methodology with exposure-response coefficients. It has been emphasized that any change in the exposure characterization metrics must be accompanied by changes in the exposure-response coefficients of the risk assessment models. This was emphasized in the report and the panelists endorsed this view.

Access to additional raw data sets. The panelists strongly recommended that EPA make every attempt to acquire and analyze raw data sets from key human epidemiological studies. Where possible, it would also be desirable to obtain bivariate (i.e., length and diameter) fiber exposure information for these re-analyses. Several panelists believed that review of additional data sets offers substantial opportunity for improving the proposed risk assessment methodology. In the event that raw data cannot be obtained due to confidentiality reasons or other restrictions, the panelists suggested that the authors consider asking those who have access to the data to conduct the necessary statistical analyses and communicate their results directly to EPA for further consideration.

Fiber diameter. The proposed risk assessment methodology uses a diameter cut-off of 0.5 micrometers (μm) for considering fibers. The report states that fibers 0.7 μm in diameter can reach the respiratory zone of the lung. A few panel members indicated that the fiber diameter cut-off could be as high as 1.5 μm during oral breathing. The 0.4 μm cut-off came from rat data, but larger diameters would be expected to be respirable in humans. There was general agreement that the diameter cut-off should be between 0.5 and 1.5 μm. This issue is deserving of further analysis.

Fiber length. The Berman and Crump analyses made a significant contribution by obtaining and analyzing membrane filters from the animal inhalation studies in Edinburgh and conducting quality-assured bivariate length and distribution analyses by TEM—thereby greatly reducing the uncertainty of the exposure side of the exposure-response relationship for chronic fiber exposure in rats. Unfortunately, correspondingly detailed information on bivariate size distribution is not available for humans. This leads to the need to use the animal data, although one must always recognize the uncertainties associated with interspecies extrapolations such as anatomic characteristics and respirability between species. Future analyses may benefit from using other available laboratory animal data sets and human data sets.

The fiber length distributions for the human cohort exposures are much more uncertain. For the Wittenoom, Quebec, and South Carolina cohorts, there are limited fiber length distribution data based on TEM analysis from historic membrane filter samples, but only fiber categories longer than 5 μm and longer than 10 μm were counted. For all other cohorts, the measurements were limited to PCM fiber counts for all fibers greater than 5 μm in length in some, and particle counts (10x objective) on midget impinger samples in others. Both methods do not measure thin fibers, do not discriminate between asbestos and other mineral particles, and provide no information on the concentrations of fibers longer than 10, 20, or 40 μm, or inter-laboratory variations in optical resolution and counting rules. As one approach to addressing the varying uncertainty in assessing exposure in the different studies, Berman and Crump used the available information to make adjustments to the uncertainty ranges in the exposure-response coefficients. The workshop panel welcomed this initiative but suggested alternative approaches (see "Methods," below).

Some panelists felt that an Exposure Assessment Workshop, with participants having a broad range of expertise, could evaluate the uncertainties in historic occupational data sets' exposure measurements. They felt such a workshop could result in a more confident assessment of exposure-response relationships for populations exposed to a variety of amphiboles, chrysotile, and mixtures. With incorporation of other available knowledge on fiber type, process, smoking (if available), and the relative number of excess lung cancer and mesothelioma, it may well be possible to gain a much clearer understanding of the roles of these variables as causal factors for these asbestos-associated cancers. In addition, the workshop would prove valuable in further discussion of mineralogical, geological, and industrial hygiene issues with regard to application of the model to risk assessment in environmental sites of concern.

The Berman and Crump index assigns zero risk to fibers less than 5 μm in length. Fibers between 5 and 10 μm are assigned a risk that is one three-hundredth of the risk assigned to fibers longer than 10 μm. Panelists agreed that there is a considerably greater risk for lung cancer for fibers longer than 10 μm. However, the panel was uncertain as to an exact cut size for length and the magnitude of the relative potency. The panelists also agreed that the available

data suggest that the risk for fibers less than 5 μm in length is very low and could be zero. This specific issue was addressed by an expert panel convened by the Agency for Toxic Substances and Disease Registry (ATSDR) in October 2002. Some panelists suggested that, for mesothelioma, greater weight should perhaps be assigned to fibers in the 5 to 10 μm length range and to thinner fibers.

Fiber type. For *mesothelioma*, the panelists supported the use of different relative carcinogenic potencies for different fiber types. The panelists unanimously agreed that the available epidemiology studies provide compelling evidence that the carcinogenic potency of amphibole fibers is two orders of magnitude greater than that for chrysotile fibers. There was some discussion about the precise ratio expressed due to questions about the availability of exposure data in existing studies (e.g., Wittenoom). There was recognition that time since first exposure is an important factor in determining risk for mesothelioma and some discussion is needed on the importance of duration and intensity of exposure.

For *lung cancer*, the panelists had differing opinions on the inferences that can be made on the relative potency of chrysotile and amphibole fibers. Some panelists supported the finding that amphibole fibers are 5 times or more potent for lung cancer than are chrysotile fibers. Other panelists did not think the statistical analyses in the draft methodology document supports this relative potency and wondered if additional review of the epidemiological data might identify factors other than fiber type (e.g., industry considered) that provide further insights on the matter. These other factors can then be considered when the risk assessment is applied.

Cleavage fragments. The panel knew of little data to directly address the question as to whether cleavage fragments of equal durability and dimension as fibers would have similar or dissimilar potency for lung cancer. The general view is that data indicate that durability and dimension are critical to pulmonary pathogenesis. Therefore, it is prudent at this time to assume equivalent potency for cancer in the absence of other information to the contrary. Consideration of conducting a rat inhalation study using tremolite cleavage fragments was recommended to address this issue. For mesothelioma, it was viewed that thin fibers greater than 5 μm in length are more important. Cleavage fragments that do not meet these criteria would not contribute to risk of mesothelioma.

Other amphiboles. The panel agreed with the report's conclusion that the potency of currently regulated and unregulated amphibole fibers should be considered equal based on the reasoning that similar durability and dimension would be expected to result in similar pathogenicity.

Methods. The panelists extensively discussed the approach to conducting the meta-analysis of the large number of epidemiological studies. A number of the panelists urged that consideration be given to using more traditional approaches that would include development and application of specific criteria for inclusion of studies into the exposure-response analysis, examination of

heterogeneity and sources of the heterogeneity, and the use of sensitivity analysis to identify influential studies.

The panelists also urged, in the study-specific analysis, exploration of alternative exposure-response models other than the lung cancer and mesothelioma risk models EPA has been using since 1986. This would possibly include non-linear response models (e.g., log-linear models), examination of separate effects for concentration and duration, time since first exposure, time since cessation of exposure, possibly dropping the "α factor," and different methods for measurement error. The adequacy of different models should be examined using goodness of fit statistics across all studies. The possibility of internal analyses should be re-examined (i.e., it may be possible to obtain partial data, such as age-specific person years data, from authors). Exploration of non-linearity should also include shape of the curve in the low exposure area.

The panelists also urged alternative approaches to meta-analyses. In particular, panelists recommended meta-regression using original (untransformed) exposure-response coefficients, in which predictor variables include the estimated percentage of amphiboles, percentage of fiber greater than 10 μm, and categorical grouping of studies according to quality. Original exposure-response coefficient variances should be used in conjunction with random effects models in which residual inter-study variation is estimated. Analyses restricted to long latency and a predictor variable for industry type should be considered. A priori distribution for inter-study residual variance might also be considered. Meta-regression will allow simple inspection of likelihoods to consider the importance of different predictor variables. Sensitivity analyses should be conducted in which the inclusion or exclusion of specific studies or groups of studies is evaluated.

Cigarette smoking. Most panelists felt strongly that future analyses need to pay more attention to the effects of smoking on the lung cancer exposure-response model and extrapolations to risk. However, the current data sets have variable and limited information available on smoking. The panelists noted that smoking is the primary cause for lung cancer, but the lung cancer dose-response relationship for smoking is complex due to the effects of smoking duration, intensity, and cessation.

The impact of smoking has effects on both the estimation and the application of the model for projecting risk of lung cancer due to asbestos exposure. This may be an especially critical issue for low-exposure extrapolation. With respect to estimation, accepting the form of the proposed model, the effect of smoking may require different K_L values for smokers and non-smokers. The panelists recognized that there is limited epidemiologic data to address this issue, but recommend that it be investigated. With respect to applying the model to make risk projections for any future cohort, the background rate of lung cancer employed in the model needs to be carefully determined to capture the smoking behavior of the cohort.

Localized tremolite exposures. During the course of public comments, the panel received input from several individuals who expressed concerns about environmental exposures to tremolite asbestos from localized geologic formations in California. The individuals suggested that inadequate attention had been given to characterization of the exposures to residents of these communities. While the panel was not in a position or charged with the evaluation of this issue, the panel did feel that this was a potentially serious matter deserving of attention by the appropriate public health authorities. Evaluation of these kinds of situations would benefit from the use of the improved risk assessment methodology being considered.

The remainder of this report summarizes the discussions and observations that led to these findings, reviews the panelists' comments on many topics not listed in this executive summary, and documents the observer comments provided at the workshop.

1. INTRODUCTION

This report summarizes a peer consultation by 11 expert panelists of a proposed protocol to assess asbestos-related risks. Contractors to the U.S. Environmental Protection Agency (EPA) developed the proposed protocol, which is documented in a report titled: "Technical Support Document for a Protocol to Assess Asbestos-Related Risk" (Berman and Crump 2001). The purpose of the peer consultation workshop was to provide EPA feedback on the scientific merit of the proposed protocol. The peer consultation workshop took place in a meeting open to the public on February 25–27, 2003, in San Francisco, California.

This report summarizes the technical discussions among the expert panelists and documents comments provided by observers. These discussions largely focused on three topic areas: interpretations of the epidemiology and toxicology literature, the proposed exposure index, and general questions about key assumptions and inferences in the protocol. The remainder of this introductory section presents background information on the protocol (Section 1.1), describes the scope of the peer consultation workshop (Section 1.2), and reviews the organization of this report (Section 1.3).

1.1 Background

EPA's current assessment of asbestos toxicity is based primarily on an asbestos review completed in 1986 (EPA 1986) and has not changed substantially since that time. The 1986 assessment considers six mineral forms of asbestos and all asbestos fiber sizes longer than 5 micrometers (μm) to be of equal carcinogenic potency. However, since 1986, asbestos measurement techniques and the understanding of how asbestos exposure contributes to disease have improved substantially. To incorporate the knowledge gained over the last 17 years into the agency's toxicity assessment for asbestos, EPA contracted with Aeolus, Inc., to develop a proposed methodology for conducting asbestos risk assessments. The proposed methodology distinguishes between fiber sizes and fiber types in estimating

potential health risks related to asbestos exposure. The methodology also proposes a new exposure index for estimating carcinogenic risk.

As a key step in determining the scientific merit of the proposed risk assessment methodology, EPA decided to obtain expert input on the draft report through a peer consultation workshop. The purpose of the workshop was to obtain feedback from subject-matter experts during the development stage of the proposed risk assessment methodology; the workshop was not an official peer review. Eastern Research Group, Inc. (ERG), organized and implemented the peer consultation workshop under a contract to EPA.

1.2 Scope of the Peer Consultation Workshop

The peer consultation involved many activities before the workshop (see Section 1.2.1), at the workshop (see Section 1.2.2), and after the workshop (see Section 1.2.3). The following subsections describe these activities.

1.2.1 Activities Prior to the Peer Consultation Workshop

This section describes the major activities ERG and the expert panelists conducted prior to the peer consultation workshop:

Select expert panelists. ERG selected the expert panelists for the peer consultation workshop. ERG sought to compile a panel of experts with broad experience and expertise in the following disciplines: toxicology, epidemiology, biostatistics, asbestos sampling and analytical methods, EPA's human health risk assessment guidelines, and asbestos-related environmental and occupational health issues. Appendix A lists the expert panelists ERG selected, and Appendix B includes brief biographies that summarize the panelists' areas of expertise.

Every panelist is either a senior scientist, physician, or researcher with extensive experience in the aforementioned fields, as demonstrated by peer-reviewed publications, awards, and service

to relevant professional societies. To ensure the peer consultation offered a balanced perspective, ERG intentionally selected expert panelists with a broad range of affiliations (e.g., academia, consulting, state and federal agencies). When searching for panelists, ERG asked all candidates to disclose real or perceived conflicts of interest.

Prepare a charge to the expert panelists. ERG worked with EPA to prepare written guidelines (commonly called a "charge") for the peer consultation workshop. The charge includes 12 specific questions, organized into 4 topic areas. Discussions at the workshop largely addressed the technical issues raised in the charge, but the expert panelists were encouraged to discuss other relevant matters that were not specifically addressed in the charge questions. A copy of the charge is included in Appendix B.

Distribute review documents and other relevant information. Several weeks prior to the peer consultation workshop, ERG sent every panelist copies of the charge and the proposed risk assessment methodology (Berman and Crump 2001). These items formed the basis of the technical discussions at the workshop. In addition, ERG distributed several additional publications on related topics (see Table 1, at the end of this section, for list of the publications). The supplemental publications were provided largely in response to panelists' requests for further background information on selected issues. The panelists also circulated publications amongst themselves on specific topics. Finally, one of the meeting chairs noted for the record that, upon arriving in San Francisco, he also received a memo and copies of many abstracts and other information from Cate Jenkins of EPA. The meeting chair offered to share these materials with other panelists during the workshop.

Obtain and compile the panelists' premeeting comments. After receiving the workshop materials, the panelists were asked to prepare their initial responses to the charge questions. Booklets containing the premeeting comments were distributed to the expert panelists before the workshop and were made available to observers at the workshop. These initial comments are included in this report, without modification, as Appendix B. It should be noted that the premeeting comments are preliminary in nature. Some panelists' technical findings may have changed after the premeeting comments were submitted.

1.2.2 Activities at the Peer Consultation Workshop

The 11 expert panelists and approximately 75 observers attended the peer consultation workshop, which was held at the Westin St. Francis Hotel in San Francisco, California, on February 25–27, 2003. The workshop was open to the public, and the workshop dates and times were announced in the

Federal Register. Appendix C lists the observers who confirmed their attendance at the workshop registration desk. The workshop schedule generally followed the agenda, presented here as Appendix D.

The workshop began with introductory remarks from Ms. Jan Connery (ERG), the facilitator of the peer consultation. Ms. Connery welcomed the expert panelists and observers, stated the purpose of the workshop, identified the document being reviewed, and explained the procedure for observers to make comments. Mr. Richard Troast (EPA) then provided background information on the review document and EPA's ongoing efforts to assess asbestos toxicity (see Section 1.1). Mr. Troast identified the main differences between EPA's existing asbestos risk assessment methodology (EPA 1986) and the proposed methodology (Berman and Crump 2001). Mr. Troast noted that the expert panelists' feedback will ultimately help EPA complete its update of asbestos health risks for the Integrated Risk Information System (IRIS); he clarified that the final IRIS update will be subject to peer review or Science Advisory Board review before being implemented. Following these opening remarks, Dr. Wayne Berman and Dr. Kenny Crump—the authors of the proposed methodology—presented detailed information on the review document; Section 2 of this report summarizes their presentations.

After the background presentation, Dr. Roger McClellan and Dr. Leslie Stayner chaired the technical discussions that followed. For the remainder of the meeting, the panelists engaged in free-flowing discussions when answering the charge questions and addressing additional topics not specified in the charge. Observers were given the opportunity to provide verbal comments three different times during the workshop; these observer comments are documented in Appendix E. Representatives from EPA and the document authors provided clarifications on the proposed methodology periodically throughout the 2½-day workshop.

1.2.3 Activities Following the Peer Consultation Workshop

The primary activity following the peer consultation workshop was preparing this summary report. A technical writer from ERG who attended the meeting prepared a draft of this report, which ERG distributed to the 11 expert panelists and asked them to verify that the draft accurately reflects the tone and substance of the panelists' discussions at the workshop. After incorporating the panelists' suggested revisions to the draft report, ERG submitted the final report (i.e., this report) to EPA.

1.3 Report Organization

The structure of this report follows the order of the technical discussions during the meeting. Section 2 summarizes Dr. Berman and Crump's background presentations. Sections 3 through 6 are records of the panelists' discussions on the four main topic areas: interpretations of the epidemiology and toxicology literature (Section 3), the proposed exposure index (Section 4), general questions (Section 5), and conclusions and recommendations (Section 6). Finally, Section 7 provides references for all documents cited in the text.

The appendices to this report include background information on the peer consultation workshop. This information includes items that were on display at the workshop and items generated since the workshop (e.g., a final list of attendees). The appendices contain the following information:

List of the expert panelists (Appendix A).

The panelists' premeeting comments, the charge to the reviewers, and brief bios of the expert panelists (Appendix B).

List of registered observers of the peer consultation workshop (Appendix C).

Agenda for the peer consultation workshop (Appendix D).

Observer comments provided at the peer consultation workshop (Appendix E).

Observer post-meeting comments (Appendix F).

Table 1
References ERG Provided to the Expert Panelists

Berman, DW and Crump K. 1999. Methodology for Conducting Risk Assessments at Asbestos Superfund Sites; Part 1: Protocol. Final Draft. Prepared for U.S. Environmental Protection Agency. February 15, 1999.
Berman, DW and Crump K. 2001. Technical Support Document for a Protocol to Assess Asbestos-Related Risk. Final Draft. Prepared for U.S. Department of Transportation and U.S. Environmental Protection Agency. September 4, 2001.
Berman, DW, Crump, K., Chatfield, E., Davis, J. and A. Jones. 1995. The Sizes, Shapes, and Mineralogy of Asbestos Structures that Induce Lung Tumors or Mesothelioma in AF/HAN Rats Following Inhalation. Risk Analysis. 15:2,181-195.
Berman, DW. 1995. Errata. Risk Analysis. 15:4, 541.
Committee on Nonoccupational Health Risks of Asbestiform Fibers. Breslow, L., Chairman. 1984. Asbestiform Fibers Nonoccupational Health Risks. Washington, DC: National Academy Press.
EPA 1986. Airborne Asbestos Health Assessment Update. U.S. Environmental Protection Agency. EPA 600/8-84-003F. 1986.
NIOSH Interdivisional Fiber Subcommittee Report. Prepared by the NIOSH Interdivisional Fiber Subcommittee. 1999.

2. BACKGROUND ON THE PROPOSED PROTOCOL TO ASSESS ASBESTOS-RELATED RISK

This section summarizes presentations given by the principal authors of the proposed risk assessment methodology. These presentations were given because several panelists asked ERG, prior to the peer consultation workshop, if the authors would provide detailed background information on how the methodology was developed. This section reviews the major presentation topics, but does not present the panelists' comments on the proposed protocol. Sections 3 through 6 document the expert panelists' technical feedback on the protocol.

Motivation for developing the proposed protocol. Dr. Berman identified several reasons for developing the updated protocol for assessing asbestos-related risks. These reasons include EPA's existing asbestos models being inconsistent with inferences from the scientific literature, the need for having uniformly-applied sampling and analytical procedures to measure asbestos characteristics most predictive of risk, and the belief that EPA's current asbestos risk assessment methodology may not be adequately protective in some circumstances. To improve upon the current methodology, the authors intended to develop a risk assessment model that adequately predicts cancer risk in all studied environments and can therefore be applied with much greater confidence to environments that have not been studied. Dr. Berman outlined the general approach taken to develop the proposed protocol, as summarized in the following bulleted items.

Dr. Berman provided background information on and definitions for asbestos, other fibrous structures, asbestos morphology, and cleavage fragments. He also described the capabilities and limitations of the analytical techniques that have been used to characterize asbestos exposures, such as midget impingers, phase contrast microscopy (PCM), scanning electron microscopy (SEM), and transmission electron microscopy (TEM). Dr. Berman explained how differences in these analytical techniques must be critically evaluated when comparing results reported in all epidemiological and other types of studies that examine asbestos exposure. Dr. Berman also stressed that it is not just differences in analytical techniques, but choice of specific methods for each analytical technique that affects results. Further information on these topics is included in Chapter 4 of the proposed protocol (Berman and Crump 2001).

Re-analysis of human epidemiological data. Dr. Crump described how the authors evaluated the human epidemiological data. He displayed a list of the studies that were considered, noting that he had access to raw, individual-level data for three occupational cohorts: chrysotile textile workers in South Carolina, United States; crocidolite miners in

Wittenoom, Australia; and chrysotile miners and millers in Quebec, Canada. All data sets with exposure data were considered in the analysis, and criteria were not established for selecting studies. Dr. Crump then presented findings for asbestos-related risks for lung cancer and mesothelioma.

For lung cancer, Dr. Crump first reviewed EPA's existing lung cancer model for asbestos exposure (see equation 6.1 in the proposed protocol), which relates the relative risk of lung cancer mortality linearly to cumulative asbestos exposure, with a 10-year lag time. Dr. Crump noted that the model predicts that relative risk for developing lung cancer remains constant after asbestos exposure ceases—an assumption he showed was reasonably consistent with findings from epidemiological studies. Dr. Crump also discussed how the model assesses interactions between exposures to cigarette smoke and to asbestos—an issue the panelists revisited several times later in the workshop (e.g., see Section 3.1.1 and the executive summary). Dr. Crump presented a series of tables and figures demonstrating the adequacy of multiple lung cancer models: first using EPA's existing lung cancer model, next using a modified version of the model that accounts for differences in the background rates of lung cancer, and finally using the proposed lung cancer model, which considers an exposure index that assigns greater carcinogenic potency to amphibole fibers and to longer fibers.

Similarly, Dr. Crump reviewed the performance of EPA's mesothelioma model for asbestos exposures (see equation 6.11 in the proposed protocol), which predicts that mesothelioma risks vary linearly with the average asbestos exposure and increase quadratically with time from onset of exposure. Dr. Crump presented several tables and graphs indicating how well EPA's existing model and the proposed protocol fit the human epidemiological data. He made several conclusions about the existing risk model, including that mesothelioma risk coefficients varied considerably across the cohorts and the risk coefficients were generally higher for cohorts exposed primarily to amphibole fibers, compared to those exposed primarily to chrysotile fibers. Dr. Crump also noted that the data did not support consideration of a sub-linear or threshold dose-response relationship. This latter point generated considerable discussion later in the workshop (e.g., see Section 4.3).

Dr. Crump then described the meta-analysis the authors conducted to evaluate the relative potency of amphibole and chrysotile fibers. First, he explained how the authors weighted the different studies in the meta-analysis, based on uncertainty factors assigned to the individual studies. Dr. Crump identified the four uncertainty factors and described generally how each factor was assigned. Sources of uncertainty included representativeness of air sampling data, the availability of conversion factors to express exposures in terms of PCM concentrations, and whether data on exposure duration were available. Dr. Crump then highlighted the main conclusions from the meta-analysis. For lung cancer, the meta-analysis suggested that amphibole fibers are approximately five times more potent than are chrysotile fibers, but the difference in potency was not statistically significant (i.e., the authors could not reject the hypothesis that

chrysotile fibers and amphibole fibers are equally potent). For mesothelioma, the meta-analysis suggested that chrysotile fibers are 0.002 times as potent as amphibole fibers, and the difference in potency was statistically significant.

Inferences drawn from the broader literature. Dr. Berman described how the authors incorporated inferences from the broader scientific literature into the proposed protocol. He reviewed key findings on how various mechanisms are biologically related to how asbestos causes disease. These mechanisms included respiration, deposition, degradation, clearance, translocation, and tissue-specific biological responses. Chapter 7 of the review document provides detailed information on the relevance of these mechanisms, with emphasis on the influence of fiber type and fiber dimension.

Derivation of the exposure index. Dr. Berman explained how the authors derived the exposure index, which is largely based on an earlier re-analysis (Berman et al. 1995) of six animal inhalation studies conducted by a single laboratory. That re-analysis found that lung tumor incidence is adequately predicted using an exposure index that assigns no carcinogenic potency to fibers shorter than 5 μm, relatively low carcinogenic potency to fibers with lengths between 5 and 40 μm and diameters less than 0.4 μm, and the greatest carcinogenic potency to fibers longer than 40 μm and thinner than 0.4 μm. However, these findings could not be applied directly to the human epidemiological data, because the epidemiological studies do not include exposure measurements that quantify the relative amounts of asbestos fibers shorter and longer than 40 μm.

Dr. Berman noted that the proposed protocol includes an *ad hoc* assumption that the fiber size weighting factors optimized from the laboratory animal studies can be applied to humans, but with a length cut-off of 10 μm in the exposure index, rather than a cut-off of 40 μm. Dr. Berman emphasized that this assumption was made to model the critical characteristics of asbestos in a manner that reasonably captures cancer risks observed across multiple epidemiological studies. He acknowledged that asbestos potency is likely a continuous function of fiber length, but the exposure measurements from the available animal and epidemiological studies do not support incorporating such a continuous function in the exposure-response model. The panelists commented on the proposed exposure index when discussing topic area 3 (see Section 4).

Dr. Berman also noted that the authors selected a conservative set of dose-response coefficients (see Table 6-30 of the review document), rather than using the optimized ones from the animal studies (see Table 6-29). However, the conservative and optimized dose-response coefficients were reasonably consistent: none of the conservative coefficients differed by more than a factor of 4 from the corresponding optimized ones.

Conclusions regarding proposed protocol. Dr. Berman indicated that the proposed protocol is substantially more consistent with inferences documented in the scientific literature (i.e., that

long, thin structures contribute most to risk) than EPA's existing risk assessment methodology. Further, the proposed protocol provides a better fit to cancer risks observed in the human epidemiological studies than does EPA's existing model, and the proposed protocol appears to underestimate risks of lung cancer and mesothelioma less frequently and to a lesser degree than the existing approach. Finally, by recommending use of a standardized analytical method that links directly to the exposure index, the proposed protocol will help ensure that future risk assessments are conducted in a consistent fashion and their results can be readily compared from one study to the next.

3. COMMENTS ON TOPIC AREA 1: INTERPRETATIONS OF THE EPIDEMIOLOGY AND TOXICOLOGY LITERATURE

This section summarizes the panelists' discussions on the interpretations of the epidemiology and toxicology literature. The meeting co-chairs—Dr. McClellan and Dr. Stayner—facilitated the discussions on this topic area, which focused first on lung cancer (see Section 3.1) and then on mesothelioma (see Section 3.2). This section presents a record of discussion of the topics mentioned during the workshop. Several panelists referred to their premeeting comments (see Appendix B) for additional suggestions for how the review of epidemiology and toxicology literature can be improved.

3.1 Lung Cancer

The panelists discussed at length whether the epidemiology and toxicology literature support the proposed protocol's finding for how lung cancer potency varies with fiber type and fiber length. This section summarizes these discussions, first on fiber type (Sections 3.1.1 and 3.1.2) and then on fiber length (Sections 3.1.3 and 3.1.4). General issues regarding the lung cancer evaluation are presented in Section 3.1.5.

3.1.1 Lung Cancer and Fiber Type: Inferences from the Epidemiology Literature

According to the proposed risk assessment methodology, amphibole fibers have a 5-fold greater lung cancer potency than do chrysotile fibers. The panelists had differing opinions on whether this finding is consistent with the epidemiology literature. On the one hand, some panelists indicated that the epidemiology literature is consistent with amphibole fibers being more potent for lung cancer, though the magnitude of this increase may not be known precisely. One panelist noted, for example, that multiple analyses (e.g., Hodgson and Darnton 2000, Berman and Crump 2001, and the statistical analyses a panelist presented during this discussion) all point to a consistent increased lung cancer potency for amphibole fibers compared to chrysotile fibers, albeit a small increase. On the other hand, other

panelists did not believe the epidemiology literature supports this conclusion, for reasons stated below. Finally, other panelists were not convinced that the epidemiology literature supports the higher lung cancer potency for amphibole fibers, but they believed the difference in potency seems likely based on evidence from the animal toxicology studies (see Section 3.1.3) and lung burden studies. A summary of the panelists' discussion on this topic follows:

Comments on specific publications. Several panelists cited specific studies to support their positions on the relative lung cancer potency of chrysotile and amphibole fibers, but the panelists often had differing opinions on the inferences that should be drawn. The panelists mentioned the following specific studies:

- Some panelists noted that a recent re-analysis of 17 cohorts (Hodgson and Darnton 2000) indicates that the lung cancer potency for amphibole fibers is 10 to 50 times greater than that for chrysotile fibers. One panelist did not agree with this finding, due to the crude approach the article uses to characterize relative potency. Specifically, this panelist noted that carcinogenic potency was calculated by dividing the overall relative risk for a given cohort by the average exposure for the entire cohort, even for cohorts where the data support more sophisticated exposure-response modeling. He was particularly concerned about the authors' decision to omit the cohort of South Carolina textile workers from the meta-analysis. This decision was apparently based on the South Carolina cohort being an outlier, due to its much higher lung cancer potency when compared to other studies. The panelist noted, however, that the lung cancer risk for the South Carolina cohort is not unusually high when compared to other cohorts of textile workers. The panelist was concerned that omitting this study might have biased the article's finding regarding relative lung cancer potency. No other panelists discussed the review article.

- One panelist cited a study of Quebec chrysotile miners and millers (Liddell et al. 1997, 1998) that reports that increased lung cancer risk was limited to the mining region with the highest level of tremolite asbestos, after correction for smoking and exposure. The article was distributed to the panelists on the first day of the workshop, but no panelists commented further on the study.

- One panelist noted that his review of multiple textile cohorts (Stayner, Dankovic, and Lemen 1996) found relatively small differences in lung cancer potency, even though some of the cohorts were exposed to asbestos mixtures containing different proportions of amphibole fibers.

- One panelist indicated that further evidence on how fiber types relates to lung cancer potency can be gleaned from epidemiological studies that were not included in the meta-analysis due to inadequate exposure data for exposure-response modeling. Examples include a study of non-occupationally exposed women from two chrysotile asbestos mining regions (Camus et al. 1998) and a study of railroad workers employed by shops that processed different proportions of amphibole fibers (Ohlson et al. 1984). Both studies, she noted, provide evidence that amphibole fibers exhibit greater lung cancer potency. This panelist added that studies of auto mechanics have provided no convincing evidence of increased lung cancer due to chrysotile exposure, though she acknowledged that the absence of an effect might reflect the short fiber length in the friction brake products. One panelist cautioned about inferring too much from these studies regarding fiber type because they were not controlled for other factors, such as fiber length and level of exposure.

- One panelist added that a recent study of a cohort of Chinese asbestos plant workers (Yano et al. 2001) should be considered in future updates to the proposed protocol; the workers in the cohort had increased risks for lung cancer and were reportedly exposed to "amphibole-free" chrysotile asbestos. However, another panelist cited a publication (Tossavainen et al. 2001) that indicates that asbestos from many Chinese chrysotile mines actually does contain varying amounts of amphibole fibers.

- Several panelists noted that the proposed protocol's meta-analysis found a 5-fold difference in lung cancer potency between amphibole and chrysotile fibers. However, other panelists indicated that the reported difference was not statistically significant. Some panelists had additional reservations about the authors' meta-analysis, as summarized in the following bulleted items.

Comments on the meta-analysis approach. Several panelists commented on alternate approaches the authors could have used to conduct their meta-analysis of the epidemiology studies. One panelist noted that the lung cancer potencies reported by the various studies exhibit considerable heterogeneity. In such cases, meta-regression is conventionally used to identify which factors account for the variability in the results (i.e., in the lung cancer potencies). This panelist suggested that the meta-analysis should have considered other factors in addition to fiber type and dimension; such other factors could include industry, follow-up time for the cohort, and estimated percentage of amphibole fibers in the exposures, to the extent that data on these other factors are available.

To demonstrate how more detailed investigation might reveal further insights, one panelist presented his own initial statistical analysis of the epidemiological studies. This analysis used a fixed effects model and a random effects model, both inverse weighted by the variance of the studies. His analysis examined how industry and fiber type contribute to the heterogeneity

observed among the cohorts and found that the industry of the cohort appears to be a stronger predictor than fiber type. The panelist explained that the purpose of displaying his statistical analysis was to highlight how other approaches to conducting meta-analysis can offer different insights on the epidemiological data. This panelist recommended that the authors conduct similar meta-regression analyses to investigate the importance of various variables on the lung cancer potency.

This panelist also demonstrated how a sensitivity analysis might yield additional information on influential studies. Using a fixed effects model, the panelist first showed how lung cancer potency factors (K_L) vary with exposure to chrysotile fibers, amphibole fibers, and mixed fiber types. When all epidemiological studies were considered in his analysis, the amphibole fibers were found to be three times more potent than the chrysotile fibers. When the cohort of chrysotile miners and millers from Quebec was omitted from this analysis, however, the amphibole fibers were found to be nearly two times *less* potent than the chrysotile fibers. Conversely, when the cohort of textile workers from South Carolina was omitted, the amphibole fibers were found to be more than ten times more potent than the chrysotile fibers. Given that the conclusions drawn about the relative potency of chrysotile and amphibole fibers appear to be highly sensitive to whether single studies are omitted from the analysis, this panelist was more skeptical about whether the increased potency of amphibole fibers is a robust finding. He recommended that the authors, when completing the proposed protocol, conduct similar sensitivity analyses to help reveal the factors or studies that appear to contribute most to lung cancer.

Another panelist agreed with this feedback, and provided further comments on the meta-analysis, noting that these analyses typically start with establishing criteria for study inclusion. After selecting studies to evaluate, she said, various statistical analyses can be used to test hypotheses and to understand the concordance and disparity among the individual studies. The panelist thought such an approach is needed to help understand the variability in potency factors observed across the multiple studies and to identify for further analysis the studies found to be most descriptive of exposure-response. To clarify the authors' approach, Dr. Berman indicated that the meta-analysis considered any published epidemiological study with sufficient quantitative exposure data that allowed for a reasonable estimate of the exposure-response relationship; uncertainty factors were than assigned to give greatest weight to the most robust studies. In response, additional panelists concurred with the original comment that meta-analyses conventionally begin with establishing explicit study inclusion criteria. These panelists clarified that they are not advocating removing a majority of studies currently considered in the proposed protocol, but rather being more judicious in selecting the studies to evaluate.

One panelist offered additional comments on the meta-analysis. He supported, for instance, the use of sensitivity analyses, and encouraged the authors to conduct additional analyses to identify influential studies, factors that contribute to risk, and the impact of different weighting factors. The panelist also noted that more sophisticated statistical methodologies (e.g., Bayesian

modeling, Markov Monte Carlo) can be used to generate distributions of outputs, rather than discrete values, which might offer greater understanding of the inferences that can be drawn from the epidemiological studies.

Disparate findings from the South Carolina and Quebec cohorts. Multiple panelists noted that the issue of the relative lung cancer potency of chrysotile and amphibole fibers depends largely on how one interprets the disparate findings from the cohort of textile workers in South Carolina and the cohort of chrysotile miners and millers in Quebec. Two of these panelists indicated that the relative potency issue likely will not be resolved until the underlying reasons for the differences between these two studies are better understood. The other panelist viewed the difference in potency observed across industries (i.e., mining versus textile) as a more important matter than the difference between the two specific cohorts. When discussing these studies, two panelists indicated that the increased lung cancer risk for the South Carolina cohort might be attributed to exposure to amphibole fibers, which are known to be found in trace levels in commercial chrysotile.

Relevance of fiber durability. One panelist noted that the issue of fiber durability often enters the debate on the relative lung cancer potency of chrysotile and amphibole fibers. Though he agreed that the animal toxicology data indicate that amphibole fibers are more persistent than chrysotile fibers, the panelist noted that trends among the human epidemiological data—particularly the fact that lung cancer risk does not appear to decrease with time since last exposure, even for chrysotile—suggest that the lower durability of the chrysotile fibers might not be important.

Influence of smoking. The panelists had differing opinions on how the proposed protocol should address cigarette smoking. In terms of inferences drawn from the epidemiological literature, two panelists noted that very limited data are available on smoking, making quantitative analysis of its interactions with asbestos exposures difficult. Specifically, only one study includes detailed information on smoking, but that study found no difference in lung cancer potency between smokers and non-smokers. During this discussion, Dr. Berman explained that the proposed protocol assumes a multiplicative interaction between smoking and asbestos exposure, consistent with EPA's 1986 model. Dr. Berman noted that a multiplicative factor in the model, α, represents the background risk in the studied cohort relative to the risk in the comparison population, and both groups include smokers; he added that the influence of smoking is addressed implicitly in the model because it is a relative risk model in which the effect of asbestos is multiplied to the background risk that is present. A panelist clarified, however, that neither the potency factors nor α were derived based on observations of smoking prevalence in the epidemiological studies.

One panelist emphasized that the confounding effects of smoking greatly complicates the analysis of lung cancer potency. He noted that the relative lung cancer risk from asbestos exposure is

considerably lower than that for cigarette smoking. As a result, the panelist wondered how the meta-analysis can truly discern the relative potency of the asbestos fiber types from studies that present no information on cigarette smoking. This panelist provided an example to illustrate his concern: if a given cohort has between 5 and 10% more smokers than the typical population, this increased prevalence of smoking alone could totally confound relative risks attributed to asbestos. The panelist indicated that all future analyses of epidemiological data will suffer from similar limitations, so long as detailed information on smoking is not available.

General comments. During this discussion, some panelists offered several general comments that apply to the entire proposed protocol. These comments included concerns about the transparency of the analyses, questions about data tables being inconsistent with text in the body of the report, and some panelists' inability to reproduce certain findings from the available data. These general comments are reflected in the executive summary of this report.

3.1.2 Lung Cancer and Fiber Type: Inferences from Animal Toxicology and Mechanistic Studies

The panelists offered varying insights on the inferences that can, or should, be drawn from animal toxicology studies and mechanistic studies regarding the relative lung cancer potency for chrysotile and amphibole fibers.

Citing various publications (e.g., Lippmann 1994), multiple panelists noted that the animal toxicology studies do not support the 5-fold difference in lung cancer potency between chrysotile and amphibole fibers. Two panelists added that the absence of different potencies might result from the animal studies being of too short duration (typically no longer than 2 years) for the greater dissolution of chrysotile fibers to be an important factor. Another panelist added that exposure levels in some animal studies are not relevant to human exposures; as an example, he noted that a recent rat inhalation study (Hesterberg et al. 1998) involved exposure levels at 11,000 fibers per cubic centimeter. These panelists indicated that the animal studies are generally more informative of how lung cancer potency varies with fiber length (see Section 3.1.4), and are less informative on how potency varies with fiber type.

The panelists noted that *in vitro* studies exhibit various findings, depending on the study design and endpoint assessed. One panelist, for instance, indicated that some *in vitro* studies suggest that chrysotile fibers are actually more potent than amphibole fibers. Other panelists added that many *in vitro* studies show crocidolite being considerably more toxic than chrysotile. These panelist cautioned against drawing firm conclusions from the *in vitro* studies, however, given that the study duration is far too short for any impact of dissolution to be observed. Finally, another panelist referred to the International Agency for Research on Cancer (IARC) consensus statement on fiber carcinogenesis for an overview of inferences that can be drawn from mechanistic studies: "Overall, the available evidence in favor of or against any of these mechanisms leading to the development of lung cancer and mesothelioma in either animals or humans is evaluated as weak" (IARC 1996).

Based on the previous comments, the panelists cautioned about attempting to draw inferences from the animal toxicology for several reasons. One panelist indicated that the animal studies have limited utility because lung cancer in humans results from a complex set of exposures, including cigarette smoke, and because rats, when compared to humans, develop different types of tumors at different sites. Another panelist reiterated that the duration of most animal studies precludes one from observing dissolution effects. Given these limitations, two panelists emphasized that conclusions should be based primarily on the epidemiological data, especially considering the volume of human data that are available. Though not disagreeing with this recommendation, one panelist noted that the exposure index—one of the major outcomes of the proposed protocol—is, in fact, based on observations from animal studies.

3.1.3 Lung Cancer and Fiber Dimension: Inferences from the Epidemiology Literature

The panelists made several observations regarding what can be inferred from the epidemiology literature on how lung cancer potency varies with fiber dimension, though they first noted that most published epidemiology studies do not include detailed data on the distribution of fiber dimensions to which cohorts were exposed. Overall, the panelists generally agreed that indirect evidence from the

epidemiological studies supports the proposed protocol's finding that longer fibers have greater carcinogenic potency for lung cancer. They added, however, that the epidemiology literature provides no evidence to support or refute the magnitude of the relative potencies used in the proposed protocol (i.e., fibers longer than 10 μm being 300 times more potent than those with lengths between 5 and 10 μm). The panelists made no comments about fiber diameter when discussing this matter. Specific discussion topics follow:

Observations from the epidemiology literature. The panelists identified several studies that provide general insights on the role of fiber size in lung cancer. One panelist, for instance, noted that cohorts of textile workers, which were believed to be exposed to relatively longer asbestos fibers, exhibit higher lung cancer relative risks than do cohorts of miners or cement product workers. Another panelist indicated that studies of taconite miners from Minnesota (Cooper et al. 1988) and gold miners from South Dakota (McDonald et al. 1978) found no increased lung cancer risks among the cohorts, which were known to be exposed primarily to fibers shorter than 5 μm (see Dr. Case's premeeting comments for further information on these studies). This panelist added that the Minnesota Department of Health is currently updating the study on taconite miners and a publication is pending. Another panelist added that epidemiology studies of workers exposed to asbestos from friction brake products show no clear evidence of increased lung cancer. This panelist acknowledged that these epidemiology studies do not include exposure measurements, but other studies of this work environment have indicated that the asbestos fibers in friction brake products are predominantly short chrysotile fibers.

Relevance of fibrous structures shorter than 5 μm. Some panelists noted that no epidemiology studies have examined the relative potency specifically of fibrous structures shorter than 5 μm, thus no conclusions could be drawn from the epidemiology studies alone. While not disagreeing with this observation, one panelist reminded panelists that airborne particles and fibers have a broad distribution of fiber lengths, with a clear majority (75–90%) of fibrous structures being shorter than 5 μm. This panelist added that indirect inferences can be drawn from the epidemiology studies listed in the previous bulleted item. Another panelist noted that the fibrous structures shorter than 5 μm behave more like particles rather than fibers, at least in terms of lung deposition and clearance patterns. Finally, two panelists indicated that an ATSDR expert panel recently evaluated the issue of relative potency of fibers shorter than 5 μm; however, the final report from that expert panel meeting was not available until after the peer consultation workshop. The final report has since been released, and a conclusion from that panel was that "there is a strong weight of evidence that asbestos and synthetic vitreous fibers shorter than 5 μm are unlikely to cause cancer in humans" (ERG 2003).

Statistical analyses in the proposed protocol. As indirect evidence that longer fibers have greater carcinogenic potency, one panelist indicated that the exposure-response modeling by Drs. Berman and Crump showed an improved fit to the observed relative risk from epidemiology studies when using an exposure index that assigns greater weight to longer fibers and no risk to fibers shorter than 5 µm. Another panelist concurred, but added that the authors could have attempted to determine the specific weighting (i.e., between longer and shorter fibers) that would optimize the fit to the epidemiological studies.

3.1.4 Lung Cancer and Fiber Dimension: Inferences from Animal Toxicology and Mechanistic Studies

The panelists generally agreed that the animal toxicology studies and mechanistic studies indicate that fiber dimension—especially fiber length—plays an important role, both in terms of dosimetry and pathogenesis. However, panelists had differing opinions on the specific cut-offs that should be used for fiber diameters and lengths in the exposure-response modeling (though panelists generally concurred that fibers shorter than 5 µm should be assigned zero potency).

Fiber length. Multiple panelists noted that the animal toxicology studies provide compelling evidence that lung cancer potency increases with fiber length. Another panelist agreed, but had reservations about assigning no potency to fibrous structures shorter than 5 µm, based on a recent study of refractory ceramic fibers (Bellman et al. 2001) that found that the incidence of inflammation and fibrosis appears to be related to the presence of small fibers in the lung. This panelist indicated that exposure to small fibers likely has some bearing on the oxidative stress state and inflammation in the lung, and he suspected that the exposure-response relationship for long fibers might depend on co-exposures or past exposures to shorter fibers. Based on these observations, the panelist was hesitant to exclude fibrous structures shorter than 5 µm from the proposed risk assessment methodology. On the other hand, another panelist added that animal toxicology studies have shown that fibrosis endpoints are strongly related to fiber length, with exposures to shorter fibers showing less evidence of fibrosis or lung damage. The panelists revisited the significance of fibers shorter than 5 µm when discussing the proposed exposure index (see Section 4).

Fiber diameter. The panelists offered several comments on the role of fiber diameter in the proposed protocol. Noting that fibers with diameters up to 1.5 µm are capable of penetrating to sensitive portions of the lung during oral inhalation, one panelist indicated that this range of fiber diameters should not be excluded from future risk assessments. Other panelists shared the

concern of assigning no lung cancer potency to respirable fibers with diameters greater than 0.5 μm, especially considering that respirability patterns in laboratory animals differ from those in humans (i.e., thicker fibers are more likely to deposit in the human lung than they are in the rat lung).

The panelists also discussed a statement in the proposed protocol that "few fibers thicker than 0.7 μm appear to reach the deep lung." First, one panelist indicated that the proposed protocol includes outdated information on fiber deposition patterns; he recommended that the authors obtain more current insights from specific publications (e.g., Lippmann 1994) and from the latest lung dosimetry model developed by the International Commission on Radiological Protection. Second, another panelist questioned the relevance of deposition in the deep lung, because humans tend to develop bronchogenic carcinomas, while rats develop bronchoalveolar carcinomas. Another panelist cautioned against inferring that asbestos fibers must deposit on bronchial airways to cause lung cancer in humans, noting that significant accumulation of asbestos fibers does not occur in the airways where carcinomas develop in humans, due primarily to mucociliary clearance; this panelist suspected that deposition of fibers in the deep lung is likely related to lung cancer formation in humans, though the mechanisms of carcinogenesis are not fully understood.

3.1.5 Other Issues Related to Lung Cancer

The panelists discussed several additional issues related to the proposed protocol's evaluation of lung cancer potency. Most of the discussion focused on the utility of non-linear exposure-response modeling, but other topics were also addressed:

Consideration of non-linear exposure-response models. The panelists had differing opinions on the extent to which the proposed protocol should consider non-linear exposure-response modeling. On the one hand, one panelist strongly recommended that EPA consider exploring the applicability of non-linear exposure-response models, given his concerns with linear low-exposure extrapolation. This panelist acknowledged that the revised linear model in the proposed protocol clearly provides an improved statistical fit to the epidemiological data when compared to EPA's 1986 lung cancer model, but he advocated more detailed exploration of non-linear cancer risk models, particularly to account for observations of cohorts with low exposures. This panelist was particularly concerned about the cancer risks that would be predicted for low exposures: because the slope in any linear lung cancer model will be determined largely by highly-exposed individuals, he questioned whether the slope derived from

high exposures truly applies to lowly-exposed individuals. To demonstrate his concern, this panelist indicated that the epidemiological studies consistently show that cohorts (or subsets of cohorts) with low exposure generally exhibit no increased lung cancer risk (standardized mortality ratios not statistically different from 1.0). To account for the possibility of a threshold or non-linearity in the exposure-response relationship, this panelist recommended that EPA investigate alternate exposure-response models, such as linear-linear models (i.e., models with two linear exposure-response regions having different slopes) or log-linear models.

Other panelists generally supported these comments. One panelist, for instance, noted that EPA's Draft Revised Guidelines for Carcinogen Risk Assessment indicates that exposure-response relationships should first be evaluated over the range of exposure observations, and then various approaches to extrapolate to exposure levels outside (i.e., below) this range should be investigated. Another panelist added that some studies finding no evidence of lung cancer risks among large cohorts with low exposures should factor into the decision of whether the lung cancer model should include thresholds; he cited a study of non-occupationally exposed women from chrysotile mining regions in Canada (Camus et al. 1998) to illustrate his concern. Other panelists noted that the utility of this study is limited, because exposures were not measured for individuals; further, a panelist clarified that approximately 5% of the individuals considered in this study were occupationally exposed. Finally, one panelist indicated that evidence from the epidemiology literature strongly suggests there are asbestos exposure levels below which lung cancer will not occur; this panelist added that he is unaware of any epidemiological study that has found evidence of lung cancer risk at exposure levels below 25 fiber-years. He recommended that the proposed protocol at least acknowledge the lowest exposure level at which lung cancer effects have been demonstrated.

On the other hand, some panelists were not convinced of the utility of conducting detailed analyses at low exposures and investigating possible thresholds. One panelist, for instance, indicated that a meaningful quantitative analysis of potential thresholds will not be possible, so long as the authors do not have access to raw data from additional epidemiological studies. Further, this panelist suspected that the protocol authors would find considerable heterogeneity among exposure-response slopes for low exposures, and he questioned what conclusions could be drawn by focusing exclusively on the low exposure region. Another panelist agreed, adding that the failure to find significantly increased cancer risks among lowly-exposed cohorts very likely results from poor statistical power and other uncertainties, and not necessarily from the presence of an actual exposure threshold for asbestos-related lung cancer. Finally, one panelist indicated that the National Institute for Occupational Safety and Health (NIOSH) previously examined a threshold model for the cohort of South Carolina textile workers, and that analysis revealed that the best fit of the exposure-response data was a threshold of zero (i.e., the best fit indicated that there was no threshold).

Consideration of cigarette smoking. Several times during the workshop, the panelists debated the ability of the proposed risk assessment model to address interactions between cigarette smoking and asbestos exposure. One panelist recommended that the authors review a recent study that examined the role of cigarette smoking on lung cancer among chrysotile miners and millers in Quebec, Canada (Liddell and Armstrong 2002). Although the panelists generally agreed that smoking is an important consideration for developing and applying the model, some panelists were not convinced that the available data are sufficient to develop an exposure-response model that accurately portrays the interactive effects of asbestos exposure and smoking. The panelists further discussed this issue further later in the workshop.

Transparency of the proposed protocol. Several panelists indicated that the review of epidemiological data in the proposed protocol is not presented in a transparent fashion. One panelist, for instance, sought more information on the uncertainty factors used in the meta-analysis, such as what ranges of factors were considered, what criteria were used to assign the factors, and a table of the factors that were eventually applied. This panelist also recommended that the proposed protocol identify the α-values that were determined for each epidemiological study and provide explanations for any cases when these values are unexpectedly large. Another panelist indicated that the proposed protocol should more clearly differentiate conclusions that are based on a meta-analysis of many epidemiological studies from conclusions that are based on a detailed review of just one or two studies.

The need to obtain additional raw data sets. The panelists unanimously agreed that EPA should make every effort to try to obtain additional raw data sets for the epidemiology studies, such that the authors can further test how adequately the proposed risk assessment model predicts risk. The executive summary of this report presents the panelists' specific recommendation on this issue.

3.2 Mesothelioma

The following paragraphs document the panelists' responses to charge questions regarding inferences from the epidemiology and toxicology literature on how mesothelioma potency varies with fiber type (Sections 3.2.1 and 3.2.2) and fiber length (3.2.3 and 3.2.4).

3.2.1 Mesothelioma and Fiber Type: Inferences from the Epidemiology Literature

The expert panelists unanimously agreed that the epidemiology literature provides compelling evidence that amphibole fibers have far greater mesothelioma potency than do chrysotile fibers—a finding reported both in the review document (Berman and Crump 2001) and a recent re-analysis of 17 cohort studies (Hodgson and Darnton 2000) that reported at least a 500-fold difference in potency. Two panelists commented further that the epidemiology literature provides no scientific support for chrysotile exposures having a role in causation of mesothelioma—an observation that is generally consistent with the meta-analysis in the proposed protocol, which failed to reject the hypothesis that chrysotile fibers have zero potency for mesothelioma.

The most notable response to this charge question was the agreement among most panelists that amphibole fibers are at least 500 times more potent than chrysotile fibers for mesothelioma, as supported by two separate reviews of epidemiological studies. The panelists made additional comments on specific matters when responding to this question, as summarized below, but the key point in this discussion was the agreement that chrysotile is a far less important cause of mesothelioma than are amphiboles.

Relative roles of chrysotile and amphibole. One panelist indicated that cohort studies with individual-level exposure-response data and the broader epidemiology literature both provide no evidence of increased mesothelioma risk due to chrysotile exposure. Further, this panelist noted that 33 of 41 mesothelioma cases previously identified as occurring among workers primarily exposed to chrysotile fibers (Stayner et al. 1996) were later reported as likely resulting from exposures to tremolite fibers found in the chrysotile mines (McDonald et al. 1997). This panelist noted that a recent finding of a small mesothelioma risk from chrysotile (Hodgson and Darnton 2000) results entirely on the assumption that the 33 mesothelioma cases mentioned above result entirely from chrysotile exposures. Based on these observations, this panelist indicated that the literature suggests that chrysotile exposures have limited, if any, role in causing mesothelioma. He nonetheless supported the relative potency attributed to chrysotile in the proposed protocol as a conservative measure in the overall risk assessment process.

Specific comments on the Connecticut friction products workers. Another panelist commented on an epidemiological study of a cohort of workers employed at a friction products plant in Connecticut. The panelist noted that the original study (McDonald et al. 1984) did not identify any deaths from mesothelioma, but review of the state cancer registry (Teta et al. 1983)

revealed that three Connecticut residents who died of mesothelioma were employed by the same friction products company. One of these employees had amphibole exposures during the time he worked for a textile plant that was under the same parent company that owned and operated the friction products plant. The other two cases, the panelist noted, were females who indeed worked at the friction products plant. A pathology review found that one of these cases was a woman with probable pleural mesothelioma and 5 years of exposure; the other case was a peritoneal mesothelioma in a woman who also had asbestosis, and worked as a clerk for 30 years. This panelist noted that it was questionable to attribute the latter two mesothelioma diagnoses to the chrysotile exposures at the friction products plant, though she added that this possibility cannot be definitively ruled out. This panelist encouraged that future review of this epidemiological study should be revised given this new information.

Comments on the proposed 500-fold difference in relative potency. The panelists had several comments on the finding in the proposed risk assessment methodology that amphibole fibers are 500 times more potent for mesothelioma than are chrysotile fibers. Several panelists noted that this finding is consistent with that of a recent re-analyses of 17 epidemiological studies (Hodgson and Darnton 2000). Though not disagreeing that amphibole fibers are clearly more potent, one panelist was concerned that the risk coefficients (K_M) were largely derived from data sets with inadequate exposure-response information for mesothelioma, and assumptions had to be made to determine critical inputs to the mesothelioma model (e.g., average exposure, duration of exposure).

Other panelists commented on specific sections in the proposed protocol. One panelist, for example, recommended that the authors check the accuracy of data presented in Table 6-16 and Table 6-29 of the report, which are not reported consistently. Another panelist suggested that the authors better explain why separate risk coefficients for amphiboles and chrysotile were calculated for some cohorts (e.g., Hughes et al. 1987) but not for others (e.g., Berry and Newhouse 1983), even though the exposure information available for the studies appears to be comparable. Finally, one panelist recommended that the authors of the proposed protocol consider questions recently raised (Rogers and Major 2002) about the quality of the exposure data originally reported for the Wittenoom cohort (De Klerk et al. 1989) when evaluating exposure-response relationships for mesothelioma.

3.2.2 Mesothelioma and Fiber Type: Inferences from Animal Toxicology and Mechanistic Studies

The panelists discussed the inferences provided by animal toxicology data and mechanistic data regarding relative mesothelioma potency of different asbestos fiber types. Overall, two panelists

commented that the human epidemiological data clearly establish that exposures to amphibole asbestos fibers pose a greater mesothelioma risk than do exposures to chrysotile fibers. They added that the animal toxicology data are generally supportive of this finding, but the animal data suffer from some limitations. Two panelists, for instance, noted that the utility of animal toxicology studies is limited by the fact that rodents are rather insensitive to mesothelioma. These panelists added that the animal toxicology studies involving intra-tracheal instillation or peritoneal injection are not directly relevant to the inhalation exposures that occur in humans. These limitations notwithstanding, the panelists raised the following points when discussing the animal toxicology and mechanistic studies:

One panelist referred to one of his earlier publications (Lippmann 1994) for further insights on the occurrence of mesothelioma in animal studies. At that time, this panelist noted, the animal inhalation studies found fewer than 10 cases of mesothelioma, and the number of cases appeared to be greatest among animals that were exposed to mixtures containing higher proportions of amphibole fibers. He found this consistent with the influence of fiber type observed in the human epidemiological data (see Section 3.2.1).

During this discussion, one panelist reviewed a publication (Suzuki and Yuen 2001) that was mentioned earlier in the workshop. The publication documents the amounts and types of asbestos fibers measured in samples of pleural plaques and tumor tissue collected for legal cases. These analyses reportedly found relatively large amounts of short, thin chrysotile fibers in the pleura, suggesting that these fibers should not be excluded from the group of fibers believed to induce mesothelioma. The panelist had several criticisms of the study. First, he indicated that the samples were analyzed using a non-standard technique, without any controls. Second, he questioned the major finding of fibers being detected in the pleura, because most of the samples analyzed were actually tumor tissue, in which he would not expect to find fibers. The panelist suspected that the chrysotile fibers reportedly found in the study likely result from specimen contamination—a bias that would have been more apparent had rigorous quality control procedures been followed. Finally, the panelist noted that a more rigorous study (Boutin et al. 1996) of

asbestos fibers in the parietal pleura found a mixture of fibers, including long amphibole fibers, among living patients with asbestos-related conditions. Based on these concerns, the panelist concluded that the publication of concern (Suzuki and Yuen 2001) is seriously flawed and its recommended should be excluded from EPA's analyses.

A specific issue raised regarding the analytical technique in the study (Suzuki and Yuen 2001) was that water was used during the digestion process. Noting that water may contain large amounts (>30,000 fibers/L) of small asbestos fibers, another panelist suspected that the fibers detected in the study might have resulted from contamination introduced during the digestion process. Because control samples were not analyzed, the panelist said the study offers no evidence that the fibers detected truly were in the original pleural plaques or tumor tissues. He added that studies of lung-retained asbestos fibers routinely detect primarily short, chrysotile fibers, and that the presence of the short fibers in the pleural tissue—even if the measurements from the study are valid—would not necessarily prove that short fibers cause mesothelioma.

3.2.3 Mesothelioma and Fiber Dimension: Inferences from the Epidemiology Literature

The panelists commented briefly on how the human epidemiological data characterize the role of fiber size on mesothelioma risk. Noting that exposure measurements in most every epidemiological study do not characterize fiber length distribution, one panelist indicated that these studies provide no direct evidence of how fiber length is related to mesothelioma. He added that the studies offer conflicting indirect evidence of the role of fiber length. Specifically, the higher mesothelioma risk coefficient among textile workers in South Carolina, when compared to that for the chrysotile miners and millers in Quebec, could be supportive of longer fibers being more potent, since exposures in South Carolina had a larger percentage of long fibers. However, a cohort of cement plant workers in New Orleans was found to have a higher mesothelioma risk coefficient than that of the South Carolina cohort, even though the South Carolina workers were exposed to higher percentages of long fibers. Finally, as indirect

evidence that carcinogenic potency increases with fiber length, this panelist noted that the mesothelioma risk model using the proposed exposure index, which is heavily weighted by long fibers, provided a considerably improved fit to the epidemiological data.

The panelists briefly revisited the inferences that can be drawn from studies of lung-retained fibers. One panelist again commented that results from a recent study (Suzuki and Yuen 2001) should be viewed with caution. He added that several other lung pathology studies (e.g., McDonald et al. 1989, Rogers et al. 1991, Rödelsperger et al. 1999) have been conducted using more rigorous methods, such as using appropriate controls for age, sex, and hospital. These studies all showed that risk of mesothelioma was considerably higher for individuals with larger amounts of long fibers retained in their lungs.

One panelist indicated that results from a study of lung-retained fibers (Timbrell et al. 1988) suggest fiber diameter plays a rule in mesothelioma risk: the study observed no mesothelioma cases among a population highly exposed to anthophyllite fibers, which tend to be thicker fibers. Citing his earlier review of mesothelioma cases (Lippmann 1988), the panelist also noted that crocidolite fibers are both thinner than and more potent than amosite fibers, which further supports the hypothesis that carcinogenic potency for asbestos decreases with increasing fiber diameter.

3.2.4 Mesothelioma and Fiber Dimension: Inferences from Animal Toxicology and Mechanistic Studies

The panelists made few observations on findings from animal toxicology studies regarding mesothelioma and fiber length. One panelist indicated that findings from the animal toxicology studies generally support the overall finding that mesothelioma risks are greatest for long, thin fibers. However, another panelist noted that his earlier review of mesothelioma risks (Lippmann 1988) hypothesized that the critical fibers for mesothelioma induction are those with lengths between 5 and 10 μm. This panelist added that fibers of this dimension are more likely to translocate to the pleura than are longer fibers, but

he acknowledged that it is unclear whether fibers must first translocate to the pleura in order to cause mesothelioma.

Some panelists indicated that fiber durability likely plays a role in inducing mesothelioma, based on the fact that mesothelioma is more easily induced in animals using administration methods (e.g., peritoneal injection) that remove the importance of dissolution.

3.3 Exposure Estimates in the Epidemiology Literature

The panelists raised numerous issues when responding to the third charge question: "To what extent are the exposure estimates documented in the asbestos epidemiology literature reliable?" Recognizing that the exposure estimates from the epidemiology studies are critical inputs to the exposure-response assessment, the panelists expressed concern about the exposure data: few studies provide detailed information on fiber size distribution; many studies report exposures using outdated sampling and analytical methodologies (e.g., midget impinger); individual-level data are not available for most studies; and many studies do not report detailed information on parameters (e.g., exposure levels, exposure duration) needed to evaluate exposure-response relationships, particularly for mesothelioma. Their specific concerns on these and other matters follow:

Concerns regarding exposure estimates in specific studies. Some panelists expressed concern about the assumptions made to interpret the exposure data originally reported in the epidemiology studies. One panelist reviewed specific examples of these concerns:

- The original study of workers at a Connecticut friction products plant (McDonald et al. 1984) reports exposures measured by midget impingers (in units of mmpcf), with no information on how to convert this to PCM measurements, and the original publication includes limited data on exposure duration.

- The original study of workers at a New Jersey insulation factory (Seidman et al. 1986) did not report any exposure measurements from the factory studied, and data collected

from another plant with similar operations were used to characterize exposure-response for this cohort.

- The original study of workers at a Texas insulation factory (Levin et al. 1998) reported a range of exposure levels (15–91 fibers/mL), and the authors of the proposed protocol assigned an average exposure level (45 fibers/mL) to the entire cohort.

- The original study of U.S. insulation applicators (Selikoff and Seidman 1991) has no information on exposure. The proposed protocol assumes that all workers were exposed to 15 fibers/mL for 25 years, based on a separate review of exposures among insulation workers (Nicholson 1976).

- The original study of retirees from the U.S. Asbestos Products Company (Enterline et al. 1986) reported exposures based on midget impinger sampling, with no information on how to convert these exposures to PCM measurements.

- According to a recent letter to the editor (Rogers and Major 2002), the original study of the Wittenoom cohort (De Klerk et al. 1989) might have overestimated exposures, possibly by as much as a factor of 10.

The previous comments led to a discussion on whether certain studies should be excluded from the meta-analysis used in the proposed protocol (see next bulleted item). Prior to this discussion, one panelist expressed concern about being overly critical of the exposure estimates used for many of the studies listed above; he emphasized that all exposure estimates appear to be based on a critical review of the literature, and no estimates are completely arbitrary, as some of the panelists' comments implied.

Comments on using study inclusion criteria for the meta analysis. Given the concerns about the quality of exposure data reported in some epidemiology studies, the panelists debated whether future revisions of the proposed protocol should exclude certain studies from the exposure-response analysis. The panelists were divided on this matter.

On the one hand, several panelists recommended that the authors develop and apply study inclusion criteria in the exposure-response evaluation, as is commonly done when conducting a meta-analysis. One panelist, for instance, recommended assessing exposure-response relationships for only those studies found to have adequate exposure data, and then using a sensitivity analysis to examine the effect of excluding studies with inadequate exposure data. These panelists clarified that they are not advocating disregarding the majority of studies; rather, they are suggesting simply that the authors of the proposed protocol use study inclusion criteria and sensitivity analyses to ensure that the conclusions are based on the best available exposure data.

On the other hand, several panelists supported the current approach of using as many studies as possible and accounting for the quality of the exposure measurements in the uncertainty factors. One panelist, for example, commended the authors for being as inclusive as possible when reviewing the studies; he supported the approach of recognizing the limitations of the available exposure data and accounting for these limitations in the uncertainty factors that were ultimately used to weight the studies in the meta-analysis. This panelist acknowledged that the exposure estimates in some of the epidemiological studies might be rough estimates, but he emphasized that the estimates are not worthless and should not be discarded. Other panelists concurred with these comments, and did not support applying overly restrictive study inclusion criteria.

Comments on the uncertainty factors assigned to each study. The panelists made several comments on the uncertainty factors that the authors assigned to each study. Dr. Berman first explained the four uncertainty factors: the first factor (F1) characterizes the confidence in exposure estimates; the second factor (F2) represents the confidence in the conversion to PCM measurements from other exposure metrics (typically midget impinger analyses); the third factor (F3) characterizes the confidence the authors had on worker history data; and the fourth factor (F4) was a non-exposure related factor to account for other uncertainties (e.g., lack of information on confounders, incomplete or inaccurate mortality ascertainment). Dr. Berman described generally how the individual uncertainty factors were assigned and noted that each factor could range from 1 to 5.

The panelists' comments primarily focused on the transparency of how uncertainty factors were presented and incorporated into the meta-analysis. Multiple panelists, for instance, recommended that future revisions to the proposed protocol include a table that lists the uncertainty factors assigned to each study. Further, one panelist suggested that the revised protocol describe the assumptions inherent in the uncertainty factor weighting approach, such as explaining why some factors are assigned values over a broader range than others (e.g., why F1 values span a broader range than F4 values) and describing why the individual uncertainty factors have equal weights in generating the composite uncertainty factor. Another panelist agreed, and added that the revised protocol should more explicitly describe how the uncertainty factors were combined into the composite factor and how this composite factors affects the weighting of studies in the meta-analysis. Expanding on this point, another panelist suggested that the final document more clearly explain that the final estimates of cancer risk coefficients (K_L* and K_M*) are actually weighted averages of the epidemiological studies, with the weights assigned to each study being a function of that study's uncertainty. This panelist also recommended that the revised document clearly state how, if at all, the fraction of amphibole fibers and the fraction of fibers longer than 10 µm are reflected in the uncertainty factors.

Some panelists debated the utility of alternate approaches that could be used to assign uncertainty factors. Two panelists noted that the approach used to assigning uncertainty factors is somewhat subjective, because different groups of analysts would likely assign different

uncertainty factors. To avoid the appearance of arbitrariness, these panelists suggested using alternate meta-analysis approaches that do not require using uncertainty factors. They noted, for example, that the authors could use a random effects model in which residual inter-study variation is estimated. Another suggestion was to conduct sensitivity analyses examining the effects of including or excluding studies, depending on the uncertainty factors assigned to them.

Another panelist disagreed with these comments and supported the analyses in the proposed protocol; this panelist indicated that the authors had no choice but to make judgments based on the information documented in the epidemiology literature. He suggested that EPA consider convening a separate expert panel to assign uncertainty factors, if panelists do not support those selected by Drs. Berman and Crump.

Assumptions made to convert exposure estimates from midget impinger sampling. Several panelists noted that the original publications for many epidemiology studies document exposure estimates based only on midget impinger sampling and do not include any information on how to convert these exposures to levels that would be measured by more modern methods (e.g., PCM, TEM). The panelists noted that the conversion factor (from mmpcf to fibers/mL) can vary considerably from one occupational setting to the next.

Interpretations of the study of South Carolina textile workers. The panelists had different opinions on interpretations of the study of South Carolina textile workers (Dement et al. 1994). One panelist, for instance, found this particular study to be an outlier among the other epidemiological studies, and he recommended that the authors exclude this study from the exposure-response analysis until the causes for the increased relative risks observed for this cohort are better understood. Another panelist suggested that the proposed protocol should classify the South Carolina cohort as being exposed to mixed asbestos fibers, rather than being exposed to chrysotile fibers. He indicated that some workers in the cohort were exposed to amosite and crocidolite, in addition to being exposed to chrysotile.[1]

Other panelists, however, did not think the South Carolina study should be excluded from EPA's analysis. One panelist was troubled about criticisms of the exposure estimates for this cohort, given that this is one of few studies in which co-located samples were collected and analyzed using different methods, thus providing site-specific data for converting midget impinger

[1] After reviewing a draft of this report, one panelist indicated that it is important to note that exposure data for the South Carolina cohort are available from more than just one reference (Dement et al. 1994). He suggested that EPA use data from studies conducted by McDonald in the 1980s of a parallel cohort in the same plant. However, he cautioned EPA against treating multiple studies of the same relatively small group of workers as separate studies, considering the large overlap of workers studied by the two groups of investigators. This panelist encouraged EPA to consider other data sources for this cohort, given that a recent re-analysis of epidemiological studies (Hodgson and Darnton 2000) severely criticized the data source EPA uses (Dement et al. 1994), to the point of those data being dropped from the recent re-analysis altogether.

sampling results to PCM measurements. Another panelist challenged suggestions that the South Carolina study is an outlier; he indicated that the South Carolina study is one of the more rigorous epidemiology studies available for asbestos exposures, and he found no valid scientific reasons for discarding it. During this discussion, one panelist point out in response that the South Carolina study is indeed an outlier among the textile cohorts, with a slope which is higher than either of the two textile cohorts; this panelist did acknowledge that the lung cancer risk among the textile cohorts is greater than that among the mining cohorts. This panelist added that scientists need a better explanation for why the lung cancer risk among the South Carolina cohort is greater than that of other cohorts before the South Carolina study can achieve credibility, especially considering that exposures in South Carolina were supposedly to “pure” chrysotile.

4. COMMENTS ON TOPIC AREA 2: THE PROPOSED EXPOSURE INDEX

This section summarizes the panelists' responses to the charge questions pertaining to the proposed exposure index. Section 4.1, 4.2, and 4.3 document the panelists' responses to charge questions 4, 5, and 6, respectively.

4.1 Responses to Charge Question 4

Charge question 4 asks: "The proposed exposure index does not include contributions from fibers shorter than 5 μm. Please comment on whether the epidemiology and toxicology literature support the conclusion that asbestos fibers shorter than 5 μm present little or no carcinogenic risk." The panelists discussed this matter earlier in the workshop (see Sections 3.1.3 and 3.1.4 for these comments), and provided additional insights on the matter. Overall, the panelists agreed that carcinogenic potency increases with fiber length, particularly for lung cancer. Most panelists supported assigning no potency to fibrous structures smaller than 5 μm. Some panelists agreed that the short fibrous structures are clearly less potent than long fibers, but they had reservations about assigning zero potency to the structures smaller than 5 μm; these panelists acknowledged that the toxicity of the short fibrous structures might be adequately addressed by EPA's air quality standards for particulate matter. Specific comments on this charge question follow:

Reference to ATSDR's expert panel workshop on the role of fiber length. Two panelists noted that ATSDR convened an expert panel in October 2002 to discuss the role of fiber length on toxicity, and much of that discussion specifically addressed fibrous structures smaller than 5 μm. A main conclusion of that panel was that there is "a strong weight of evidence that asbestos and synthetic vitreous fibers shorter than 5 μm are unlikely to cause cancer in humans" (ERG 2003). The panelists encouraged EPA to review the summary report prepared for that workshop, which was officially released on March 17, 2003, and is available on-line at: www.atsdr.cdc.gov/HAC/asbestospanel.

Evidence from epidemiological studies. One panelist indicated that the epidemiological studies do not provide direct evidence of the role of fibrous structures shorter than 5 μm.

However, the panelist indicated that a growing body of evidence suggests that the cohorts predominantly exposed to shorter fibers (e.g., friction brake workers, gold miners, taconite miners) do not have statistically significant increased cancer risks. This panelist added that the mechanistic studies provide the strongest evidence for assigning no potency to fibrous structures (see next bulleted item). Another panelist agreed with these statements, and added that his interpretation of data compiled by the National Cancer Institute provide additional indirect evidence of short fibrous structures presenting little or no carcinogenic risk (see page 102 of the premeeting comments in Appendix B).

The panelists briefly revisited the findings from a recent publication (Suzuki and Yuen 2001) that reported finding relatively large amounts of short, thin chrysotile fibers in malignant mesothelioma tissue. Several panelists encouraged that these findings not be considered in the risk assessment methodology for reasons cited earlier in the workshop (see Section 3.2.2).

Evidence from mechanistic studies. The panelists offered different interpretations of mechanistic studies. One panelist indicated that mechanistic studies have shown that shorter fibers are cleared more readily than long fibers from the alveolar region of the lung by phagocytosis, and therefore provide supporting evidence that short fibers play little or no role in carcinogenic risk. This panelist acknowledged that extremely high doses of particular matter and other non-fibrous structures can generate biological responses (e.g., inflammation), but he doubted that such "overload" conditions would be relevant to the environmental exposures that the proposed protocol will be used to evaluate.

Another panelist agreed that long fibers are clearly more potent than short fibrous structures, but he questioned the conclusion that short fibrous structures have no impact on carcinogenic risk. This panelist noted that mechanistic studies have demonstrated that short fibrous structures and spherical particles, like silica, can elicit the same toxic responses (e.g., generate reactive species, stimulate proliferative factors) identified for asbestos fibers. This panelist added, referring to his premeeting comments, that exposure to short fibers could cause inflammation and generation of oxidative species that might increase the response to long fibers (see Bellman et al. 2001). Overall, this panelist acknowledged that long fibers are more persistent than short fibers in the lung and should be weighted more heavily in the exposure index, but he was hesitant to assign the short fibrous structures zero potency.

Implications on sampling and analytical methods. One panelist commented on the practical implications, from a sampling perspective, of any changes to the exposure index. This panelist indicated that measuring all fibers (including structures shorter than 5 μm) in environmental samples would not only be expensive, but also would compromise the sensitivity of measuring the longer fibers that are most predictive of cancer risk. This panelist acknowledged that human exposure is predominantly to fibrous structures less than 5 μm, but he noted that the amounts of short fibrous structures retained by the lung tend to be very strongly

correlated with the amounts of long fibers retained by the lung. Due to this correlation, this panelist noted that measuring long fibers with sufficient accuracy would allow one to estimate amounts of short fibrous structures in a sample. This panelist added, however, that he sees no benefit of characterizing exposures to fibrous structures smaller than 5 µm, given the conclusion that such fibers do not cause cancer (ERG 2003).

4.2 Responses to Charge Question 5

Charge question 5 asks: "The proposed exposure index is weighed heavily by fibers longer than 10 µm. Specifically, Equation 7.13 suggests that the carcinogenic potency of fibers longer than 10 µm is more than 300 times greater than that of fibers with lengths between 5 and 10 µm. How consistent is this difference in carcinogenic potency with the epidemiology and toxicology literature?" The panelists' responses to this question follow:

Consistency with epidemiological literature. The panelists noted that the original epidemiology studies did not collect exposure information that provides direct evidence of the relative potency assigned to the two different fiber length categories: fibers longer than 10 µm, and fibers with lengths between 5 and 10 µm. During this discussion, one panelist recommended that EPA consider the results of a case-control study (Rogers et al. 1991) that suggests that mesothelioma risks are greater for individuals with larger amounts of the shorter fibers (i.e., between 5 and 10 µm) retained in their lungs. Another panelist was not convinced of the findings from this study, due to possible biases from selection of controls not matched for hospital of origin. This panelist encouraged EPA to refer to more rigorous lung-retained fiber studies (e.g., McDonald et al. 1989, Rödelsperger et al. 1999) that have found that the majority of cancer risk for mesothelioma is attributed to exposures to longer fibers, even when measurements of short fibers are taken into account.

Questions about the fiber length-dependence used for mesothelioma. Some panelists were not convinced that the relative potencies assigned to different fiber lengths were appropriate for mesothelioma. One panelist, for instance, noted that his previous review of the literature (Lippmann 1994) suggests that cancer risk for mesothelioma is most closely associated with exposure to fibers between 5 and 10 µm long. He indicated that this assessment is consistent with other human lung evaluations (e.g., Timbrell et al. 1988), which have reported that fibers retained by the lung tend to be longer than fibers that translocate to the pleura. This panelist added that the epidemiology literature clearly suggests that lung cancer and

mesothelioma have different risk factors, as the relative amounts of lung cancer and mesothelioma cases vary considerably from one cohort to the next. Based on these concerns, this panelist suggested that EPA consider developing separate fiber length weighting schemes for lung cancer and mesothelioma.

Another panelist indicated that the epidemiology studies provide indirect evidence that carcinogenic potency appears to increase with fiber length. Specifically, he noted that the studies consistently show that mesothelioma has a very long latency period—a trend that suggests that the most durable fibers (i.e., the longer fibers) are the most potent. The panelist added that the analyses in the proposed protocol provide further indirect evidence of mesothelioma risks increasing with fiber length: when the exposure index was used in the mesothelioma model, the proposed risk assessment methodology generated an improved fit to the epidemiological data.

During this discussion, a panelist cautioned about inferring that only those fibers that reach the pleura are capable of causing mesothelioma, because researchers have not determined the exact mechanisms by which mesothelioma is induced. Further, he cautioned about inferring too much from a single study (Timbrell et al. 1988), given that many additional studies are available on lung-retained fibers.

Questions about the relevance of animal toxicology data. Some panelists expressed concern about basing the proposed weighting factors for different fiber lengths on observations from animal data. First, one panelist noted that the weighting factors were derived strictly based on lung cancers observed in laboratory animals, and he questioned whether one can assume that the weighting factors can be defensibly applied to mesothelioma. Second, other panelists noted that extrapolating the weighting factors from rodents to humans also involves uncertainty, due to inter-species differences in respiratory anatomy, macrophage sizes, and sites of lung cancers.

Suggested follow-up analyses. Given the concerns about basing the proposed exposure index entirely on data from animal toxicology studies, two panelists recommended that EPA attempt to optimize the weighting factors applied to different fiber length categories using the available human epidemiological data. One panelist suggested that this optimization could be performed using the data compiled in Table 6-15 in the proposed protocol, which presents estimates of the fiber length distribution for different occupational cohorts. A panelist also suggested that EPA consider deriving separate weighting factors for lung cancer and mesothelioma, rather than assuming the same fiber length dependence for both outcomes.

4.3 Responses to Charge Question 6

Charge question 6 asks: "Please explain whether the proposed exposure index will allow meaningful comparisons between current environmental exposures to asbestos and historical exposures to asbestos that occurred in the work place." The panelists discussed several topics when addressing the question, because some panelists had different impressions of what the question was asking. Some panelists viewed the question as asking about the validity of low-dose linear extrapolations (see Section 3.1.5 for more information on this topic), and others viewed the question as asking about whether the proposed methodology is an improvement over EPA's current risk assessment model. A summary of the panelists' specific responses follows:

Is the proposed exposure index an improvement to asbestos risk assessment? When answering this charge question, multiple panelists focused on whether the proposed exposure index is an improvement over EPA's 1986 asbestos risk models. These panelists agreed that the proposed approach is more consistent with the overall literature on health risks from asbestos, which show that cancer risks vary with fiber type and fiber dimension. Two panelists were hesitant to call the proposed approach an improvement for evaluating mesothelioma risks, because the fiber length weighting factors are based entirely on lung cancer data in animals. These panelists were particularly concerned that the proposed methodology might assign lower risks for mesothelioma in certain circumstances, because the fiber-length dependence in the methodology is not based on any toxicological or epidemiological studies of mesothelioma.

Does the proposed risk assessment model support extrapolation from occupational exposures to environmental exposures? Some panelists commented on the applicability of the proposed risk assessment model to exposure doses below the ranges considered in the occupational studies. Referring to observer comments provided earlier in the workshop, two panelists indicated that some environmental exposures in areas with naturally-occurring asbestos do not appear to be considerably lower than those experienced by occupational cohorts. Another panelist agreed, and cautioned about distinguishing environmental exposures from occupational exposures; he instead encouraged EPA and the panelists to focus on the exposure magnitude, regardless of whether it was experienced in an occupational or environmental setting.

One panelist recommended that EPA investigate how cancer risks for lung cancer and mesothelioma vary between EPA's 1986 model and the proposed risk assessment methodology: for different distributions of fiber types and dimensions, does the proposed methodology predict higher or lower risks than the 1986 model? Dr. Berman indicated that the proposed methodology, when compared to EPA's 1986 model, generally predicts substantially higher risks for environments with longer, thinner fibers and environments with larger amounts of

amphibole fibers and predicts somewhat lower risks for environments with shorter, thicker fibers and environments that contain only chrysotile fibers. One panelist recommended that future revisions to the proposed protocol include sample calculations, perhaps in an appendix, for several hypothetical environments to demonstrate how estimated cancer risks compare between the new methodology and the 1986 model.

5. COMMENTS ON TOPIC AREA 3: GENERAL QUESTIONS

This section summarizes the panelists' responses to charge questions 7–10 and 12. Responses to charge question 11 are included in Section 6, because this charge question sought the panelists' overall impressions of the proposed risk assessment methodology, rather than focusing on any one specific issue.

5.1 Responses to Charge Question 7

This charge question asks: "The proposed risk assessment approach assigns carcinogenic potency to individual fibers and to cleavage fragments (or 'bundles that are components of more complex structures'). Please comment on whether cleavage fragments of asbestos are as toxicologically significant as fibers of the same size range." The panelists raised the following points when responding:

Terminology used in the charge question. One panelist took strong exception to the wording in this question (see pages 30–33 in Appendix B) and strongly recommended that the panelists use correct terminology during their discussions. This panelist noted, for instance, that cleavage fragments are not equivalent to bundles, nor do cleavage fragments meet the regulatory definition of asbestos, as the charge question implies. He clarified that he defines cleavage fragments as non-asbestiform amphiboles that are derived from massive amphibole structures. This panelist was concerned that none of the panelists at the workshop has the mineralogical expertise needed to address issues pertaining to cleavage fragments. Another panelist echoed these concerns and agreed that this charge question raises complex issues.

Significance of cleavage fragments with respect to human health effects. The previous concerns notwithstanding, several panelists commented on the role of cleavage fragments in the proposed risk assessment methodology. One panelist, for example, indicated that there is no reason to believe that cleavage fragments would behave any differently in the human lung than asbestiform fibers of the same dimensions and durability; he added that this conclusion was also reached by the American Thoracic Society Committee in 1990 (Weill et al. 1990). This panelist acknowledged, however, that expert mineralogists have differing opinions on the role of cleavage fragments. Several other panelists agreed that it is reasonable to assume that cleavage fragments and asbestos fibers of the same dimension and durability would elicit similar toxic responses.

Review of selected epidemiological and toxicological studies. The panelists briefly discussed what information has been published on the toxicity of cleavage fragments. One panelist indicated that Appendix B in the proposed protocol (see pages B-3 through B-10) interprets results from an animal study (Davis et al. 1991) that evaluated exposures to six tremolite samples, including some that were primarily cleavage fragments. This panelist noted that the study provides evidence that cleavage fragments can cause mesothelioma in animals.

Another panelist, however, cautioned against inferring too much from this animal study for several reasons: the study was not peer reviewed; the fiber measurements in the study reportedly suffered from poor reproducibility; and the mesotheliomas observed in the study might have reflected use of intra-peritoneal injection model as the dose administration method. This panelist recommended that EPA conduct a more detailed review on the few studies that have examined the toxicity of cleavage fragments, possibly considering epidemiological studies of taconite miners from Minnesota (Higgins et al. 1983) and cummingtonite-grunerite miners from South Dakota (McDonald et al. 1978); he noted that a pending publication presents updated risks among the taconite miners.

Practical implications of measuring cleavage fragments in environmental samples. One panelist added, and another agreed, that measuring cleavage fragments in environmental samples presents some challenges, because microscopists cannot consistently distinguish cleavage fragments from asbestiform fibers, even when using TEM.

5.2 Responses to Charge Question 8

Charge question 8 asks: "Please comment on whether the proposed cancer assessment approach is relevant to all amphibole fibers or only to the five types of amphibole fibers (actinolite, amosite, anthophyllite, crocidolite, tremolite) designated in federal regulations." The panelists made the following general comments in response:

Review of evidence from toxicological and epidemiological studies. The panelists identified few studies that address the toxicity of amphibole fibers other than actinolite, amosite, anthophyllite, crocidolite, and tremolite. One panelist indicated that animal toxicology studies have demonstrated that synthetic vitreous fibers with differing chemistry, but having similar durability and dimensions, generally exhibit similar potency for fibrosis, lung cancer, and mesothelioma. Another panelist added that lung cancer and mesothelioma exposure-response

relationships for a cohort of vermiculite miners from Libby, Montana, have been published for both asbestiform richterite and winchite.

Appropriateness of applying the model to non-asbestiform amphiboles. Several panelists agreed that the proposed risk assessment methodology is relevant to amphibole fibers other than those listed in the federal regulations. The panelists noted that, in the absence of more detailed information on the matter, it is prudent to assume that fibers of similar dimension and durability will exhibit similar toxic effects. Two panelists expressed some hesitation on applying the proposed model to the non-asbestiform amphiboles: one panelist asked how confidently one can apply the cancer risk coefficients to amphibole fibers that have not been studied, and another panelist indicated he was not convinced that the model should be applied to the other amphiboles, let alone for the amphiboles that are listed in the federal regulations.

Given the amount of naturally occurring amphiboles in the Earth's crust, one panelist suggested that the proposed protocol clearly state that the non-asbestiform amphiboles being evaluated are only those with the same dimensional characteristics and biodurability as the corresponding asbestiform amphiboles.

5.3 Responses to Charge Question 9

Charge question 9 asks: "The review document recommends that asbestos samples be analyzed by transmission electron microscopy (TEM) and count only those fibers (or bundles) longer than 5 μm. Such counting practices will provide no information on the amount of asbestos fibers shorter than 5 μm. To what extent would data on shorter fibers in samples be useful for future evaluations (e.g., validation of the cancer risk assessment methodology, assessment of non-cancer endpoints)?"

The panelists expressed varying opinions on this matter: some panelists saw no benefit of measuring fibrous structures shorter than 5 μm, based on responses to earlier charge questions (see Sections 3.1.3, 3.1.4, and 4.1); other panelists indicated that there is some utility to collecting information on shorter fibrous structures, particularly if the incremental analytical costs are not prohibitively expensive and if counting short fibers does not compromise accurate counts of longer fibers. The panelists raised the following specific issues when discussing measurement methods:

Support for using TEM in future sampling efforts. The panelists unanimously supported the recommendation in the proposed protocol of using TEM, rather than PCM or some other method, to characterize exposures in future risk assessments. The panelists also emphasized that future measurement methodologies must focus on generating accurate counts of the most biologically active fibers, or fibers longer than 5 μm.

Practical implications of counting fibers shorter than 5 μm. One panelist indicated that analyzing samples for fibrous structures shorter than 5 μm would compromise analysts' ability to accurately count the amounts of longer fibers that are of greater biological concern. Some panelists and an observer further discussed the costs associated with counting fibers in multiple length categories, including shorter than 5 μm. The panelists did not cite firm cost figures for these analyses. However, noting that environmental samples typically contain more than 90% short fibrous structures, one panelist suspected that counting the shorter structures would considerably increase the time a microscopist needs to analyze samples, and therefore also would considerably increase the cost of the analysis. A panelist indicated that the costs and benefits of counting fibers shorter than 5 μm might be more appropriately debated between microscopists and risk assessors, with inputs from industrial hygienists and mineralogists.

Relevance of fibers shorter than 5 μm for non-cancer endpoints. One panelist noted that exposures to fibrous structures shorter than 5 μm can contribute to asbestosis in occupationally exposed individuals (Lippmann 1988), but he doubted that the exposure levels found to be associated with asbestosis would be experienced in non-occupational settings. Another panelist added that the role of shorter fibrous structures for other non-cancer endpoints is not known, such as the pleural abnormalities and active pleural fibrosis observed in Libby, Montana. No panelists were aware of any authoritative statements made on the role that short fibers play, if any, on these other non-cancer endpoints. During this discussion, one panelist indicated that the toxicity of fibrous structures shorter than 5 μm might be adequately addressed by EPA's particulate matter standards.

5.4 Responses to Charge Question 10

Charge question 10 asks: "The proposed risk assessment methodology suggests that exposure estimates should be based only on fibers longer than 5 μm and thinner than 0.5 μm. Is this cut-off for fiber diameter appropriate?" Before the panelists responded to the question, Dr. Berman first clarified that the exposure index optimized from the animal studies (see Equation 7.12 in the proposed protocol)

assigns a far greater carcinogenic potency to fibers longer than 40 μm, with diameters less than 0.4 μm; he noted that the proposed diameter cut-off (0.5 μm) was based on an *ad hoc* adjustment.

The panelists agreed that the proposed cut-off for fiber diameter (0.5 μm) would likely include most fibers of health concern; however, they also unanimously agreed that the exposure index should not exclude thicker fibers that are known to be respirable in humans. The main argument given for increasing the cut-off is that fibers with diameters as large as 1.5 μm (or with aerodynamic diameters as large as 4.5 μm) can penetrate to small lung airways in humans. Other panelists provided additional specific comments, generally supporting inclusion of thicker fibers in the proposed exposure index. One panelist, for example, advised against basing the fiber diameter cut-off strictly on observations from rat inhalation studies, due to inter-species differences in respirability. Further, noting that the proposed cut-off for fiber diameter would likely exclude some amosite fibers and a considerable portion of tremolite fibers with known carcinogenic potency, another panelist encouraged that the proposed exposure index include contributions from thicker fibers.

The panelists noted that consideration of fibers thicker than 0.5 μm was viewed as being most important for the lung cancer risk assessment model, as risks for mesothelioma appear to be more closely linked to exposures to long, thin fibers (see Section 3.2.3). Further, some panelists suspected that increasing the fiber diameter cut-off in the exposure index should be accompanied by changes to the exposure-response coefficients in the risk assessment models, but the panelists did not unanimously agree on this issue.

5.5. Responses to Charge Question 12

Charge question 12 asks: "Section 8.2 of the review document presents three options for assessing cancer risks from asbestos exposure. Please comment on the technical merit of the proposed risk assessment options." The panelists briefly reviewed the strengths and weaknesses of the three options presented in the proposed protocol for assessing asbestos-related cancer risks. The panelists agreed that the first option—direct use of EPA's lung cancer and mesothelioma risk assessment models—allows for the greatest flexibility in evaluating site-specific exposure scenarios, particularly those with time-varying exposures. Dr. Crump indicated that he envisioned this option being coded into a computer program, into which users enter their site-specific exposure information. Most panelists endorsed developing such a program. The panelists did not reject use of the second and third options, provided that EPA ensures that all three options generate equivalent risk estimates for the same exposure scenario.

The one issue discussed in greater detail was how sensitive predictions using the first option are to the mortality rates used in the evaluation. Noting that mortality rates as functions of age and sex differ from one location to the next, this panelist encouraged EPA to consider carefully whether nationwide mortality estimates would be programmed into the risk assessment model or whether risk assessors would have the option of entering site-specific mortality rates. The panelist also suggested that the authors of the risk assessment conduct sensitivity analyses to quantify how strongly the mortality data affect cancer risk estimates. These comments also raised questions about the fact that two populations with different underlying mortality rates could have different cancer risks, even though their asbestos exposure levels are equivalent.

6. COMMENTS ON TOPIC AREA 4: CONCLUSIONS AND RECOMMENDATIONS

This section reviews the panelists' individual conclusions and recommendations regarding the proposed protocol (Section 6.1), as well as how the panelists developed their overall conclusions and recommendations that appear in the executive summary of this report (Section 6.2).

6.1 Responses to Charge Question 11

Charge question 11 asks: "Discuss whether the proposed cancer assessment approach, as a whole, is a reasonable evaluation of the available health effects data. What aspects of the proposed cancer assessment approach, if any, are inconsistent with the epidemiology or toxicology literature for asbestos?" The panelists offered individual summary statements, which were not discussed or debated among the panel. Following is a summary of the panelists' individual summary statements in the order they were given:

Dr. Lippmann's summary statement. Dr. Lippmann commended Drs. Berman and Crump on developing the proposed risk assessment protocol and supported use of a model that accounts for the factors (e.g., fiber type and dimension) that are most predictive of cancer risk. Dr. Lippmann supported the authors' attempt to make full use of the existing data and to interpret the results from the epidemiological studies. He strongly recommended that EPA make every effort to obtain individual-level data from additional epidemiological studies. Dr. Lippmann suggested that a follow-up workshop with experts in exposure assessment could help EPA evaluate the uncertainties in exposure measurements from historic occupational data sets. Dr. Lippmann supported an observer's suggestion to conduct an animal inhalation study using tremolite cleavage fragments to help resolve the issue of these fragments' carcinogenic potency. Overall, he encouraged that future work on the proposed protocol continue, through use of additional expert panels, to make more informed usage of the human exposure data.

Dr. Teta's summary statement. Dr. Teta indicated that the proposed protocol is an impressive integration of the animal toxicology data and the human epidemiology data. She commended the authors for developing a scientific methodology that successfully reduces the variability in results across the epidemiological studies, suggesting that the studies might be more consistent than were previously thought. Dr. Teta recommended improvements to the meta-analysis of

epidemiological studies, such as establishing and applying criteria for use of human data in characterizing exposure-response relationships. Overall, Dr. Teta found no inconsistencies between the proposed protocol and the larger body of epidemiology literature, including studies of cohorts (e.g., gas mask workers, railroad workers, friction brake workers) that do not have well-defined exposure information. Though not disagreeing with the utility of other panelists' recommendations, such as re-analyzing data from additional epidemiological studies and convening additional expert panels, Dr. Teta encouraged EPA to move forward expeditiously with completing the proposed protocol and discouraged implementing additional steps that might delay the overall project.

Dr. Hoel's summary statement. Dr. Hoel encouraged the use of more sophisticated modeling that incorporates data on exposure-response (including non-linear models), duration of exposure, cessation of exposure, and uncertainty in exposure. Dr. Hoel also strongly recommended that EPA attempt to obtain individual-level data from additional epidemiology studies, or at least obtain partial data sets. He encouraged Drs. Berman and Crump to use more sophisticated uncertainty analysis techniques, such as generating prior and posterior distributions of uncertainty. To ensure that the lung cancer model is not confounded by cigarette smoking, Dr. Hoel recommended that Drs. Berman and Crump more closely evaluate all available data on the interactions between asbestos exposure and cigarette smoking.

Dr. Steenland's summary statement. Dr. Steenland indicated that the proposed protocol is a step forward in asbestos risk assessment; however, he had several recommendations for improving the analysis of epidemiological studies. For instance, Dr. Steenland suggested that the authors conduct meta-regression analyses using the original exposure-response coefficients, in which predictor variables include fiber size, fiber type, the estimated percentage of amphiboles, percentage of fiber greater than 10 μm, and categorical grouping of studies according to quality. He indicated that these factors can be examined using both fixed effects and random effects models. Dr. Steenland recommended that the proposed protocol explicitly state and defend the basis for choosing the 10 μm cut-off for fiber length in the exposure index. He suggested that EPA should consider using Bayesian techniques or other methods to determine which relative potencies assigned to different fiber length categories optimize the model's fit to the epidemiological data.

Focusing on specific topics, Dr. Steenland indicated that he disagrees with the approach of assigning amphibole fibers five times greater lung cancer potency than chrysotile fibers, especially considering that the statistical analysis in the proposed protocol could not reject the hypothesis that amphibole fibers and chrysotile fibers are equally potent. Further, he advocated suggestions of exploring the adequacy of other exposure-response models (e.g., non-linear models). Finally, Dr. Steenland suspected that cigarette smoking likely will not be a confounding factor in exposure-response analyses for two reasons. First, he noted that differences in smoking practices between working populations and general populations typically do not cause

substantial differences in standardized mortality ratios. Second, he indicated that it is highly unlikely that prevalence of smoking varies with workers' exposure levels. Dr. Steenland encouraged that EPA refer to a recent publication (Liddell and Armstrong 2002) for similar insights on interactions between asbestos exposure and cigarette smoking.

Dr. Crapo's summary statement. Dr. Crapo complimented Drs. Berman and Crump on preparing the cancer risk assessment methodology, and he supported the general approach of expressing cancer risk as a function of asbestos fiber type and fiber dimension. Dr. Crapo indicated that the proposed protocol reaches several defensible conclusions, such as assigning greater mesothelioma potency to amphibole fibers and to longer fibers while assigning no risk to fibers less than 5 μm in length. However, he was concerned about some specific issues that are not yet adequately resolved. For instance, Dr. Crapo felt additional data are needed to rigorously define how mesothelioma potency varies with fiber length (i.e., fibers longer than 10 μm being 300 times more potent than fibers with lengths between 5 and 10 μm). Dr. Crapo recommended that EPA, when revising the proposed protocol, explore more sophisticated modeling techniques, including non-linear exposure-response models and consideration threshold effects. He supported more detailed analyses of interactions between asbestos exposure and cigarette smoking, again through the use of non-linear models.

Dr. Sherman's summary statement. Dr. Sherman first indicated that she concurred with several recommendations made by Drs. Hoel and Steenland. She focused her summary statements on the proposed exposure index, recommending that Drs. Berman and Crump use the epidemiology data to further investigate other formulations of an exposure index. Dr. Sherman recommended, for example, examining the goodness of fit of other formulations of the exposure index (e.g., assigning zero potency to all fibers shorter than 10 μm). Further, she recommended that the authors attempt to optimize the potency weighting factors in the exposure index to the epidemiological data. Finally, given that panelists expressed concern regarding how potency varies with fiber length for mesothelioma, Dr. Sherman suggested that Drs. Berman and Crump consider developing two different exposure indexes—one optimized for lung cancer, and the other for mesothelioma. Dr. Sherman added that she generally supported the lung cancer and mesothelioma exposure-response models, and questioned whether using more complicated models would necessarily lead to a better understanding of the data.

Dr. Castranova's summary statement. Dr. Castranova concluded that the proposed protocol is a significant advance in asbestos risk assessment methodology. He strongly supported the recommendation that future measurements be performed using TEM, rather than PCM. Dr. Castranova also supported the approach of assigning equal carcinogenic potency to cleavage fragments and asbestos fibers of similar dimension—a finding, he noted, that could be tested in an animal inhalation study. Further, Dr. Castranova agreed that non-asbestiform amphiboles and asbestos amphiboles of the same dimension should be assigned equal carcinogenic potency. Dr. Castranova indicated that the epidemiology and toxicology literature clearly indicate that

mesothelioma potency varies with fiber type, but he was not convinced that this literature supports a difference in lung cancer potency between amphibole and chrysotile fibers.

Dr. Price's summary statement. Dr. Price found the proposed protocol to be an impressive compilation of the epidemiology and toxicology literature into a cancer risk assessment model that addresses most, but not all, risk factors debated since EPA's 1986 model. Dr. Price urged EPA to explore exposure-response models other than the models that involve linear, low-dose extrapolations, which he viewed as being inconsistent with the epidemiology literature. Dr. Price indicated that future revisions to the protocol should definitely consider non-linear models and threshold effects.

As an additional comment, Dr. Price emphasized that the two main elements of the protocol—the proposed exposure index and the exposure-response analysis—are closely inter-related and subsequent changes to the proposed exposure index could affect the robustness of the overall modeling effort. As an example of his concern, Dr. Price noted that increasing the fiber diameter cut-off in the exposure index from 0.5 µm to 1.5 µm could (according to an observer comment) lead to dramatic differences in the number of cleavage fragments counted in environment samples; however, he indicated that the animal studies used to derive the original exposure index did not include cleavage fragments. Such scenarios raise questions about using an exposure index derived from very specific exposure conditions in animal studies to evaluate human health risks associated with exposures of an entirely different character. Dr. Price encouraged further study of cleavage fragments, perhaps in an animal inhalation study, to resolve the role of cleavage fragments.

Dr. Case's summary statement. Dr. Case congratulated Drs. Berman and Crump for compiling what he viewed as a reasonable evaluation of the available toxicology and epidemiology literature, and he strongly supported the general approach of factoring fiber type and fiber dimension into cancer risk assessment. Dr. Case indicated that he agreed with the finding that amphibole fibers have slightly greater lung cancer potency than do chrysotile fibers, although he believed that fiber dose, fiber length, and especially smoking history and type of industry have greater importance in this regard. Dr. Case recognized that how one views the differences between the Quebec and South Carolina cohorts affects the conclusions drawn on this issue, and he encouraged EPA to classify the cohort of South Carolina textile workers as being exposed to mixed asbestos fibers, rather than being exposed to only chrysotile fibers.[2]

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[2] When presenting the summary statements, one panelist (LS) indicated that NIOSH is re-analyzing filters that were collected in the 1960s from the South Carolina textile plant, and these re-analyses should indicate the distribution of fiber types in this cohort's exposures. Another panelist (BC) noted that these re-analyses will not characterize earlier exposures to amosite fibers, which are believed to have occurred primarily before 1950 (based on findings from studies of lung-retained fibers).

Dr. Case made several recommendations for further evaluating the existing epidemiological data and for collecting additional data. First, Dr. Case indicated that it is critically important for any lung cancer risk model to consider confounding effects of cigarette smoking, and he encouraged EPA to incorporate interactions with cigarette smoking into the lung cancer model to the greatest extent possible. Second, Dr. Case supported Dr. Lippmann's recommendation of convening an additional expert panel workshop to critically review inferences that should be drawn from the exposure measurements made in the epidemiological studies; such a panel, Dr. Case noted, would require inputs from experts in mineralogy, industrial hygiene, and measurement methodologies. Third, he supported comments recommending that EPA examine non-linear and threshold exposure-response models. Finally, Dr. Case agreed that conducting an animal inhalation study is probably the best way to examine whether tremolite cleavage fragments produce lung cancer, but did not advocate using rat inhalation studies to examine whether these fragments induce mesothelioma, because results from rat inhalation studies have been shown to be a poor model for mesothelioma in humans. He added, however, that it would quite probably be impossible to design an experiment in which rats were exposed only to "cleavage fragments" or "non-asbestiform fibers" with no asbestiform fibers present at all.

Dr. Stayner's summary statement. Dr. Stayner supported the general concept of incorporating fiber type and fiber dimension into cancer risk assessment, but he recommended that additional work be conducted before EPA accepts the proposed protocol as a new risk assessment paradigm. Dr. Stayner indicated that his confidence in the proposed protocol varies between the lung cancer and mesothelioma models.

For lung cancer, Dr. Stayner indicated that the available epidemiological data should be able to support a new risk assessment model, but he recommended that EPA consider the panelists' many recommendations for how the meta-analysis can be improved (e.g., using different statistical models, developing and applying minimal study inclusion criteria, conducting additional sensitivity analyses). Concurring with Dr. Steenland's summary statement, Dr. Stayner added that cigarette smoking is very unlikely to be a confounding factor in the lung cancer model and he questioned whether the available data would support a quantitative assessment of the interaction effects. While Dr. Stayner supported the recommendation for evaluating non-linear exposure-response models, he noted that the individual-level data needed to construct these models are not available for most epidemiological studies. Dr. Stayner added that obtaining raw data from additional occupational cohorts would provide the best opportunity for more detailed exploration of non-linear exposure-response relationships.

Dr. Stayner expressed greater concern about the foundation of the mesothelioma risk model. He indicated, for instance, that the relative potencies included in the proposed exposure index are based entirely on toxicology studies for lung cancer, and not on any epidemiology or toxicology studies specific to mesothelioma. Despite these concerns about the biological basis for the proposed mesothelioma model, Dr. Stayner noted that the proposed model does provide an

improved fit to the findings from the epidemiological studies. He recommended that EPA consider optimizing the relative potencies in the exposure index to the human data, especially if EPA can access raw data from additional occupational cohorts to evaluate how exposure-response varies with fiber size and fiber type.

Dr. McClellan's summary statement. Dr. McClellan congratulated Drs. Berman and Crump for integrating the toxicological and epidemiological data into a reasonable evaluation of asbestos cancer risks. Overall, Dr. McClellan found the proposed protocol to be a substantial improvement over EPA's 1986 models and urged EPA to continue to move forward with completing the protocol based on the panelists' feedback. Though he found the presentation of information in the draft document to lack transparency on many important matters, Dr. McClellan indicated that the authors' presentations at the workshop addressed many of his concerns regarding the transparency of how the proposed model was developed. One suggested improvement to the protocol's transparency was to clearly describe what literature were reviewed and to specify what studies actually factored into the quantitative analyses.

Addressing specific topics, Dr. McClellan indicated that the analyses in the proposed protocol adequately characterize the general roles that fiber type and fiber dimension play in cancer risk. He supported suggestions for involving additional experts, perhaps in another expert panel review, to further review interpretations of the epidemiological studies. Further, Dr. McClellan agreed with other panelists' recommendation that EPA explore the utility of non-linear exposure-response models, consistent with the agency's proposed revised Cancer Risk Assessment Guidelines. If linear, low-dose extrapolation models are ultimately used, he suggested that EPA explicitly acknowledge the uncertainties associated with such an approach. Dr. McClellan indicated that obtaining raw data from additional epidemiological studies might be particularly helpful in the exposure-response modeling. Finally, Dr. McClellan emphasized that the exposure characterization in the proposed protocol is closely linked to the exposure-response assessment; thus, the authors must carefully consider how revisions to the exposure characterization affect the assumptions in the exposure-response assessment, and vice versa.

6.2 Development of Final Conclusions and Recommendations

After presenting their individual conclusions and recommendations, the panelists worked together to draft summary statements for the peer consultation workshop. Every panelist was asked to write a brief synopsis of a particular topic debated during the workshop. These draft statements were then displayed to the entire panel and observers, edited by the panelists, and then compiled into this document's

executive summary, which should be viewed as the expert panel's final conclusions and recommendations regarding the proposed protocol.

7. REFERENCES

B Bellmann, H Muhle, O Creutzenberg, et al. 2001. Effects of nonfibrous particles on ceramic fiber (RCF1) toxicity in rats. Inhalation Toxicology 13(10):877–901.

DW Berman, KS Crump, EJ Chatfield, JMG Davis, AD Jones. 1995. The Sizes, Shapes, and Mineralogy of Asbestos Structures that Induce Lung Tumors or Mesothelioma in AF/HAN Rats Following Inhalation. Risk Analysis 15(2).

DW Berman and KS Crump 1999. Methodology for Conducting Risk Assessments at Asbestos Superfund Sites; Part 1: Protocol. Final Draft. Prepared for U.S. Environmental Protection Agency. February 15, 1999.

DW Berman and KS Crump 2001. Technical Support Document for a Protocol to Assess Asbestos-Related Risk. Final Draft. Prepared for U.S. Environmental Protection Agency and U.S. Department of Transportation. September 4, 2001.

G Berry and ML Newhouse. 1983. Mortality of Workers Manufacturing Friction Materials Using Asbestos. British Journal of Industrial Medicine 40:1–7.

C Boutin, P Dumortier, F Rey, et al. 1996. Black spots concentrate oncogenic asbestos fibers in the parietal pleura. American Journal of Respiratory Critical Care and Medicine 153:444–449.

M Camus, J Siematycki, B Meek. 1998. Nonoccupational exposure to chrysotile asbestos and the risk of lung cancer. New England Journal of Medicine 338:1565–1571.

WC Cooper, O Wong, and R Graebner. 1988. Mortality of workers in two Minnesota taconite mining and milling operations. Journal of Occupational Medicine 30(6):506–511.

JMG Davis, J Addison, C McIntosh, BG Miller, and K Niven. 1991. Variations in the Carcinogenicity of Tremolite Dust Samples of Differing Morphology. Annals of the New York Academy of Sciences, 473–490.

PE Enterline, J Harley, and V Henderson. 1986. Asbestos and Cancer—A Cohort Followed to Death. Graduate School of Public Health, University of Pittsburgh.

N De Klerk, B Armstrong, A Musk, M Hobbs. 1989. Cancer mortality in relation to measures of exposure to crocidolite at Wittenoom Gorge in Western Australia. British Journal of Industrial Medicine 46:529–536.

JM Dement, DP Brown, A Okun. 1994. Follow-up Study of Chrysotile Asbestos Textile Workers: Cohort Mortality and Case-Control Analysis. American Journal of Industrial Medicine 26:431–447.

EPA 1986. Airborne Asbestos Health Assessment Update. U.S. Environmental Protection Agency. EPA 600/8-84-003F. 1986.

ERG. 2003. Report on the Expert Panel on Health Effects of Asbestos and Synthetic Vitreous Fibers: The Influence of Fiber Length. Prepared by Eastern Research Group, Inc., for the Agency for Toxic Substances and Disease Registry. March 17, 2003.

TW Hesterberg, GA Hart, J Chevalier, et al. 1998. The importance of fiber biopersistence and lung dose in determining the chronic inhalation effects of X607, RCF1, and chrysotile asbestos in rats. Toxicology and Applied Pharmacology 153:68–82.

ITT Higgins, JH Glassman, MS Oh, and RG Cornell. 1983. Mortality of reserve mining company employees in relation to taconite dust exposure. American Journal of Epidemiology 118(5):710–719.

J Hodgson and A Darnton. 2000. The Quantitative Risk of Mesothelioma and Lung Cancer in Relation to Asbestos Exposure. Annals of Occupational Hygiene 44(8):565–201.

JM Hughes, H Weill, YY Hammad. 1987. Mortality of Workers Employed at Two Asbestos Cement Plants. British Journal of Industrial Medicine 44:161–174.

IARC. 1996. AB Kane, P Boffetta, R Saracci, and JD Wilbourn. Mechanisms of Fibre Carcinogenesis. International Agency for Research on Cancer. Oxford University Press 140:1–9.

JL Levin, JW McLarty, GA Hurst, AN Smith, and AL Frank. 1998. Tyler Asbestos Workers: Mortality Experience in a Cohort Exposed to Amosite. Occupational and Environmental Medicine 55:155–160.

FD Liddell and BG Armstrong. 2002. The combination of effects on lung cancer of cigarette smoking and exposure in Quebec chrysotile miners and millers. Annals of Occupational Hygiene 46(1):5–13.

FD Liddell, AD McDonald, and JC McDonald. 1997. The 1891-1920 Birth Cohort of Quebec Chrysotile Miners and Millers: Development from 1904 and Mortality to 1992. Annals of Occupational Hygiene 41:13–36.

FD Liddell, AD McDonald, and JC McDonald. 1998. Dust exposure and lung cancer in Quebec chrysotile miners and millers. Annals of Occupational Hygiene 42(1):7–20.

M Lippmann. 1988. Review: Asbestos exposure indices. Environmental Res 46:86–106.

M Lippmann. 1994. Deposition and retention of fibers: Effects on incidence of lung cancer and mesothelioma. Occupational and Environmental Medicine 51:793–798.

JC McDonald, GW Gibbs, FD Liddell, and AD McDonald. 1978. Morality after long exposure to cummingtonite-grunerite. American Review of Respiratory Disease 118(2):271–277.

AD McDonald, JS Fry, AJ Woolley, and JC McDonald. 1984. Dust Exposure and Mortality in an American Chrysotile Asbestos Friction Products Plant. British Journal of Industrial Medicine 41:151–157.

JC McDonald, B Armstrong, B Case, et al. 1989. Mesothelioma and asbestos fiber type. Evidence from lung tissue analysis. Cancer 63:1544–1547.

AD McDonald, BW Case, A Churg, A Dufresne, GW Gibbs, P Sebastien, and JC McDonald. 1997. Mesothelioma in Quebec chrysotile miners and millers: epidemiology and aetiology. Annals of Occupational Hygiene 41(6):707–719.

JC McDonald, J Harris, and B Armstrong. 2002. Cohort mortality study of vermiculite miners exposed to fibrous tremolite: an update. Annals of Occupational Hygiene 46(S1):93–94.

WJ Nicholson. 1976. Part III: Recent Approaches to the Control of Carcinogenic Exposures. Case Study 1: Asbestos—The TLV Approach. Annals of New York Academy of Science 271:152–169.

C-G Ohlson, T Rydman, L Sundell, et al. 1984. Decreased lung function in long-term asbestos cement workers: A cross-sectional study. American Journal of Industrial Medicine 5:359–366.

K Rödelsperger, H-J Woitowitz, B Brückel, et al. 1999. Dose-response relationship between amphibole fiber lung burden and mesothelioma. Cancer Detection and Prevention 23(3):183–193.

AJ Rogers, J Leigh, G Berry, et al. 1991. Relationship between lung asbestos fiber type and concentration and relative risk of mesothelioma. Cancer 67:1912–1920.

A Rogers and G Major. 2002. Letter to the Editor: The Quantitative Risks of Mesothelioma and Lung Cancer in Relation to Asbestos Exposure: The Wittenoom Data. Annals of Occupational Hygiene 46(1):127–129.

H Seidman, IJ Selikoff, and SK Gelb. 1986. Mortality Experience of Amosite Asbestos Factory Workers: Dose-Response Relationships 5 to 40 Years after onset of Short-Term Work Exposure. American Journal of Industrial Medicine 10:479–514.

IJ Selikoff and H Seidman. 1991. Asbestos-Associated Deaths among Insulation Workers in the United States and Canada, 1967–1987. Annals of the New York Academy of Sciences 643:1–14.

LT Stayner, DA Dankovic, RA Lemen. 1996. Occupational Exposures to Chrysotile Asbestos and Cancer Risk: A Review of the Amphibole Hypothesis. American Journal of Public Health 86(2):176–186.

V Timbrell, T Ashcroft, B Goldstein, et al. 1988. Relationships between retained amphibole fibers and fibrosis in human lung tissue specimens. In: Inhaled Particles VI. Annals of Occupational Hygiene 32(S1):323–340.

Y Suzuki and S Yuen. 2001. Asbestos Tissue Burden Study on Human Malignant Mesothelioma. Industrial Health 39:150–160.

MJ Teta, HC Lewinsohn, JW Meigs, et al. 1983. Mesothelioma in Connecticut: 1955–1977: Occupational and geographic associations. Journal of Occupational Medicine 25(10):749–756.

A Tossavainen, M Kotilainen, K Takahashi, G Pan, and E Vanhala. 2001. Amphibole Fibers in Chinese Chrysotile Asbestos. Annals of Occupational Hygiene 45(2):145-152.

H Weill, JL Abraham, JR Balmes, B Case, AM Churg, J Hughes, M Schenker, and P Sebastien. 1990. Health Effects of Tremolite. Official statement of the American Thoracic Society. American Review of Respiratory Disease 142(6):1453–1458.

E Yano, ZM Wang, XR Wang, MZ Wang, and YJ Lan. 2001. Cancer Mortality among Workers Exposed to Amphibole-free Chrysotile Asbestos. American Journal of Epidemiology 154(6):538–543.

The following Appendices:

Appendix A - List of Expert Panelists
Appendix B - Consultants' Premeeting Comments
Appendix C - List of Registered Observers
Appendix D - Agenda
Appendix E - Observer Comments Provided at the Peer Consultation Workshop
Appendix F - Observer Post-Meeting Comments

Are available at: http://www.epa.gov/superfund/programs/risk/asbestos/index.htm

Appendix A

List of Expert Panelists

Appendix B

Premeeting Comments, Alphabetized by Author
(includes bios of panelists and the charge to the panelists)

Note: This appendix is a copy of the booklet of the premeeting comments that ERG distributed at the peer consultation workshop. One panelist (Dr. Bruce Case) submitted an edited form of his premeeting comments to ERG at the workshop. That edited version appears in this appendix.

Appendix C

List of Registered Observers of the Peer Consultation Workshop

Appendix D

Agenda for the Peer Consultation Workshop

Appendix E

Observer Comments Provided at the Peer Consultation Workshop

Note: The peer consultation workshop included three observer comment periods, one on the first day of the workshop and two on the second day of the workshop. This appendix includes verbatim transcripts (to the extent that specific remarks were audible from recordings) of the observer comments, in the order the comments were given.

Appendix F

Observer Post-Meeting Comments

APPENDIX C:
COMPENDIUM OF MODEL FITS TO ANIMAL INHALATION DATA IN SUPPORT OF THE BERMAN ET AL. (1995) STUDY AND POST-STUDY WORK

The attached tables are a compendium of raw outputs for the fits of various (exposure index) models to the Davis et al. animal inhalation studies. Each entry lists the date of the run, the size categories included in the run, the maximum likelihood estimate for the run, the degrees of freedom, the P-value for the fit, and the coefficients representing the relative potency assigned to each size category for the model.

Equation?	MLE	ChiSquare	DF	P-Value	Coefficients?
"05/29/1992" "17:52:38" "PS PCM <5, 5-10, 10-20, >20 "	-62.1949	18.14	11	7.8315E-02	.0000 .0000 .7472 5.2207E-03 6.7064E-05
"05/29/1992" "17:52:42" "SC PCM 20-30, >30, <0.1, 0.1-0.2, 0.2-0.3, 0.3-0.4, >0.4 "	-60.5687	13.56	8	9.4038E-02	.0000 .2042 .0000 3.7528E-02 .0000 .0000 .0000 .5381 3.7282E-11 4.3022E-03 5.1364E-03
"05/29/1992" "17:53:01" "SC PCM 20-30, 30-40 >40 "	-60.7224	13.89	10	.1782	7.6677E-02 3.2929E-13 5.1206E-03 6.2222E-04
"05/29/1992" "17:53:06" "SC PCM 20-30, >30, AR<10<AR<20<AR "	-60.9782	14.77	10	.1407	.0000 .7915 .2085 .0000 4.1600E-13 3.7200E-03 1.2185E-03
"05/29/1992" "17:53:16" "SC PCM <20, 20-40, 40-60, >60 "	-61.1790	15.12	11	.1772	.0000 1.000 2.0226E-11 4.2164E-03 1.8379E-04
"05/29/1992" "17:53:23" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, 5-60, >60, <0.2, >0.2 "	-60.1211	13.15	10	.2155	.0000 .0000 .0000 .0000 .0000 .7552 .0000 .0000 .2448 .0000 .0000 .0000 .0000 1.3025E-10 2.9064E-03 2.4831E-03
"05/29/1992" "17:53:42" "SC PCM 10-20, 20-30, 30-40, >40, AR<100, 100-200, AR>200 "	-59.8032	12.80	8	.1189	.0000 .2092 .0000 .0000 .0000 .2265 8.0142E-02 .0000 .4841 .0000 -6.0482E-08 4.1242E-03 6.7554E-03
"05/29/1992" "17:54:06" "SC PCM <5, 5-10, 10-20, >20 "	-61.7831	17.00	11	.1080	.0000 .0000 .7619 4.7177E-03 7.9308E-05
"05/29/1992" "17:54:11" "PS PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, 50-60, >60, <0.2, >0.2 "	-59.6135	12.25	7	9.2727E-02	.0000 .0000 .0000 .0000 2.7635E-02 4.6469E-04 .5748 .0000 .3849 1.2251E-02 .0000 .0000 .0000 .0000 -1.5614E-08 5.6502E-03 9.6600E-03
"05/29/1992" "17:55:00" "PS(no C or M)PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, 50-60, >60, <0.2, >0.2 "	-59.5425	13.53	8	9.4748E-02	.0000 .0000 .0000 .0000 1.7508E-02 4.3916E-02 .6920 .2466 .0000 .0000 .0000 .0000 .0000 .0000 1.9732E-10 4.4931E-03 1.5296E-03
"05/29/1992" "17:55:34" "SC(no C or M)PCM <5, 5-10, 10-2, 20-30, 30-40, 40-50, 50-60, >60, <0.2, >0.2 "	-60.5424	14.20	9	.1155	.0000 .0000 .0000 .0000 .0000 7.8183E-03 .6538 .0000 .0000 .3383 .0000 .0000 .0000 .0000 -2.8277E-10 3.8208E-03 1.8162E-03
"05/29/1992" "17:55:52" "SC PCM 20-30, 30-40, 40-50, <0.15, 0.15-0.25, 0.25-0.35, >0.35 "	-59.1475	11.74	6	6.7916E-02	.1315 .0000 .0000 3.6828E-03 3.8012E-05 .0000 .0000 1.4520E-02 .0000 .3824 -1.7330E-08 4.4091E-03 1.9861E-02
"05/29/1992" "17:56:15" "PS PCM 20-30, 30-40, 40-50, <0.15, 0.15-0.25, 0.25-0.35, >0.35 "	-59.3960	12.11	10	.2776	.0000 .0000 .8224 .0000 .0000 .0000 .0000 .0000 .1776 .0000 .0000 4.3492E-10 4.2216E-03 2.6240E-03
"05/29/1992" "17:56:20" "PS(no C or M)PCM 20-30, 30-40, 40-50, <0.15, 0.15-0.25, 0.25-0.35, >0.35 "	-59.8255	13.54	5	1.8790E-02	.1467 .0000 1.2200E-02 .2542 .1467 .0000 .0000 .0000 .1467 .1467 3.5740E-11 3.4723E-03 4.9456E-03
"05/29/1992" "17:56:25" "SC(no C or M)PCM 20-30, 30-40, 40-50, <0.15, 0.15-0.25, 0.25-0.35, >0.35 "	-58.9800	11.67	7	.1120	9.8451E-02 .0000 .0000 9.7985E-03 .0000 .0000 .0000 .0000 1.5661E-03 .0000 .4401 -3.8840E-08 4.1576E-03 2.1421E-02
"05/29/1992" "17:56:50" "PS PCM 20-30, 30-40, 40-50, <0.2, 0.2-0.3, 0.3-0.4 "	-59.6295	12.32	7	9.0528E-02	.0000 5.2419E-02 .1732 .1111 .0000 .0000 6.4495E-02 .5343 7.5079E-03 9.4402E-03
"05/29/1992" "17:56:54" "SC PCM 20-30, 30-40, 40-50, <0.2, 0.2-0.3, 0.3-0.4 "	-59.0333	11.22	8	.1897	9.2764E-02 .0000 .0000 .0000 4.9612E-02 .1239 .0000 1.2642E-10 5.0996E-03 1.1890E-02
"05/29/1992" "17:57:02" "SC PCM <5, 5-10, 10-20, >20, <0.25, >0.25 "	-61.4230	15.59	10	.1119	.0000 .0000 .0000 .0000 .0000 2.5766E-02 2.3627E-10 4.0282E-03 1.0973E-03
"05/29/1992" "17:57:16" "SC PCME(SC) <5, 5-10, 10-20, >20 "	-60.4908	14.03	11	.2312	.0000 .0000 1.0128E-11 4.0590E-03 3.4073E-05
"05/29/1992" "17:57:20" "FBC PCM <5, 5-10, 10-20, >20, <0.25, >0.25 "	-61.5539	15.72	9	7.3068E-02	.0000 .0000 3.1396E-03 .0000 4.8616E-02 .0000 6.2996E-03 4.2436E-03 1.6013E-03

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 "05/29/1992" "17:57:37" "SC PCM  5-10, 10-20, 20-30, >30                                                    "  -61.6197      16.18      10  9.4624E-02   .0000      1.7645E-02
4.2799E-13  4.2822E-03  2.1632E-04
 "05/29/1992" "17:57:42" "SC PCM, AR>10, 5-10, 10-20, 20-30, >30                                            "  -61.6197      16.18      10  9.4624E-02   .0000      1.7645E-02
4.2799E-13  4.2822E-03  2.1632E-04
 "05/29/1992" "17:57:46" "SC PCM, AR>10, 5-10, 10-20, >20, <0.25, > 0.25                                    "  -61.4230      15.59      10   .1119       .0000       .0000
.0000      2.5766E-02  1.9480E-11  4.0282E-03  1.0973E-03
 "05/29/1992" "17:57:54" "SC PCM, 10-20, >20, <0.1,  0.1-0.2,  0.2-0.5,  >0.5                               "  -60.8243      15.06       9  8.9374E-02   .6025       .0000
.0000      3.9377E-02   .3581       .0000     -2.6301E-10  3.7544E-03  1.9807E-03
```

Equation?	MLE	ChiSquare	DF	P-Value	Coefficients?											
"06/04/1992" "15:59:53" "PS M <5, 5-10, 10-20, 20-30, 30-40, 40-50, 50-60, >60 "	-325.410	72.32	12	.0000	2.5437E-04	.0000	.0000	.0000	.3350	.0000	.6647	3.3093E-02	2.7314E-02			
"06/04/1992" "16:00:06" "PS M <5, 5-10, 10-20, 20-30, 30-40, 40-50, 50-60, >60 (without) "	-289.768	40.91	10	.0000	1.2826E-04	.0000	.0000	.0000	.3131	.0000	.6868	2.3751E-02	3.0330E-02			
"06/04/1992" "16:00:34" "PS PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, 50-60, >60 "	-279.861	24.45	9	2.8979E-03	.0000	.0000	1.0642E-02	.0000	.1925	.0000	.3962	2.6431E-02	1.3497E-02			
"06/04/1992" "16:09:39" "SC M <5, 5-10, 10-20, 20-30, 30-40, 40-50, 50-60, >60 "	-324.088	69.36	12	.0000	1.2222E-04	.0000	.0000	.0000	.4181	.0000	.5818	3.3111E-02	3.1739E-02			
"06/04/1992" "16:09:53" "SC M <5, 5-10, 10-20, 20-30, 30-40, 40-50, 50-60, >60 (without) "	-288.190	37.50	9	.0000	2.5206E-05	.0000	1.8243E-03	.0000	.3599	.0000	.6382	2.3345E-02	3.4731E-02			
"06/04/1992" "16:10:22" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, 50-60, >60 "	-279.958	24.27	9	3.1396E-03	.0000	.0000	9.7585E-03	.0000	.1659	.0000	.1266	2.5546E-02	1.7443E-02			
"06/04/1992" "16:25:02" "FBC M <5, 5-10, 10-20, 20-30, 30-40, 40-50, 50-60, >60 "	-327.491	76.80	12	.0000	.0000	.0000	1.1391E-02	.0000	.0000	.4578	.5308	3.2501E-02	7.0673E-02			
"06/04/1992" "16:25:16" "FBC M <5, 5-10, 10-20, 20-30, 30-40, 40-50, 50-60, >60 (without) "	-292.240	48.03	10	.0000	.0000	.0000	1.0616E-02	.0000	.0000	.4798	.5095	2.3348E-02	7.4414E-02			
"06/04/1992" "16:25:29" "FBC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, 50-60, >60 "	-280.941	27.21	10	1.5744E-03	.0000	.0000	1.9830E-02	.0000	.0000	.9802	2.1638E-13	2.4967E-02	2.1750E-02			
"06/04/1992" "17:01:04" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, 50-60, >60 "	-279.958	24.27	9	3.1396E-03	.0000	.0000	9.7585E-03	.0000	.1659	.0000	.6978	2.5546E-02	1.7443E-02			
"06/08/1992" "14:23:24" "SC PCM, USING SUM OF AR INSTEAD OF THE SUM OF THE NUMBER OF STRUCTURES "	-320.998	128.1	11	.0000	.5002	.1054	9.7772E-07									
"06/08/1992" "14:23:27" "SC PCM, USING SUM OF (L^2/W) INSTEAD OF THE SUM OF THE NUMBER OF STRUCTURES "	-304.439	92.38	11	.0000	.5002	4.9910E-02	3.5523E-07									
"06/08/1992" "15:17:31" "SC PCM 10-20, 20-30, 30-40, 40-50, 50-60, >60, AR>100 "	-282.372	31.86	9	.0000	.3233	.1434	.0000	.3697	.1637	2.7318E-02	8.6314E-02						
"06/08/1992" "15:17:38" "SC PCM 10-20, 20-30, 30-40, 40-50, 50-60, >60, AR>50 "	-282.195	29.24	9	.0000	2.9482E-02	.1058	.0000	.8647	1.5222E-11	2.4334E-02	2.8640E-02						
"06/08/1992" "15:17:43" "SC PCM 10-20, 20-30, 30-40, 40-50, 50-60, >60, AR>30 "	-284.342	33.22	9	.0000	2.5570E-02	3.1076E-02	.0000	.9434	6.3283E-14	2.5224E-02	2.2209E-02						
"06/08/1992" "15:17:50" "SC PCM 10-20, 20-30, 30-40, 40-50, 50-60, >60, AR>10 "	-282.527	28.52	9	2.6697E-05	1.0006E-02	.0000	7.9477E-02	.0000	-7.6669E-10	2.4802E-02	2.8345E-02						
"06/08/1992" "15:18:00" "SC PCM 10-20, 20-30, 30-40, 40-50, 50-60, >60, <0.1, >0.1 "	-277.397	21.06	8	6.1426E-03	.5520	5.5765E-04	6.5890E-02	.0000	.0000	4.0257E-02	.0000	.0000	.0000	.0000	.3413	2.6604E-02	3.2997E-02
"06/08/1992" "15:18:16" "SC PCM 10-20, 20-30, 30-40, 40-50, 50-60, >60, <0.2, >0.2 "	-274.192	14.21	9	.1142	.0000	3.8278E-03	8.9823E-02	.0000	.9063	.0000	.0000	.0000	.0000	.0000	3.9421E-11	2.4470E-02	9.5869E-02
"06/08/1992" "15:18:33" "SC PCM 10-20, 20-30, 30-40, 40-50, 50-60, >60, <0.3, >0.3 "	-273.570	13.47	9	.1417	7.5561E-03	.0000	.0000	.0000	.0000	.0000	.8731	.0000	.0000	1.6883E-02	.1024	2.5219E-02	7.8163E-02
"06/08/1992" "15:18:48" "SC PCM 10-20, 20-30, 30-40, 40-50, 50-60, >60, <0.5, >0.5 "	-277.042	18.60	7	8.7967E-03	7.1726E-03	7.7336E-03										

1.8013E-02 .0000 3.6580E-02 .0000 .7005 .0000 .0000 .0000 .2300 2.3656E-02 3.0589E-02
"06/08/1992" "15:19:15" "SC PCM 10-20, 20-30, 30-40, 40-50, 50-60, >60, <1, >1 " -276.804 18.60 9 2.8109E-02 1.0869E-02 .0000
.0000 .0000 .1691 .1142 .0000 .0000 .0000 .0000 .7058 2.5210E-02 1.7712E-02
"06/08/1992" "15:19:23" "SC PCM 10-20, 20-30, 30-40, 40-50, 50-60, >60, AR>200 " -314.551 102.3 9 .0000 .0000 3.2936E-02
.4112 .0000 4.5280E-02 .1237 .2896

"06/09/1992" "09:36:19" "SC PCM 10-20, 20-30, 30-40, 40-50, 50-60, >60, <0.4, >0.4 " -273.752 13.77 8 8.7091E-02 7.5744E-03 2.1524E-03
.0000 .0000 .0000 .0000 .9036 .0000 .0000 3.9774E-02 4.6900E-02 2.4767E-02 5.8149E-02
"06/09/1992" "09:36:44" "SC PCM 10-20, 20-30, 30-40, 40-50, 50-60, >60, AR>20 " -282.130 28.46 10 6.8359E-04 2.4648E-02 .0000
.0000 .9754 5.0787E-11 2.4409E-02 2.0780E-02
"06/09/1992" "09:36:50" "SC PCM 10-20, 20-30, 30-40, 40-50, 50-60, >60, AR>5 " -280.428 24.35 9 3.0278E-03 1.0293E-02 .0000
4.9270E-02 .0000 4.6592E-02 2.4754E-02 2.5388E-02
"06/09/1992" "09:37:02" "SC PCM 10-20, 20-30, 30-40, 40-50, 50-60, >60, AR>3 " -280.621 25.34 9 1.8654E-03 9.1834E-03 .0000
.1396 .0000 9.8428E-02 2.5738E-02 1.9572E-02
"06/09/1992" "09:51:30" "PS PCM 10-20, 20-30, 30-40, 40-50, 50-60, >60, <0.2, >0.2 " -273.982 14.15 8 7.7092E-02 .0000 1.7037E-03
8.9222E-02 2.5453E-04 .9088 .0000 .0000 .0000 .0000 .0000 -2.0902E-08 2.4482E-02 .2017
"06/09/1992" "09:51:53" "FBC PCM 10-20, 20-30, 30-40, 40-50, 50-60, >60, <0.2, >0.2 " -276.214 18.66 8 1.5954E-02 .0000 3.9259E-03
9.9701E-02 .0000 .8806 .0000 1.5773E-02 .0000 .0000 .0000 -7.8124E-08 2.5377E-02 .1086
"06/09/1992" "09:52:08" "PS PCM 10-20, 20-30, 30-40, 40-50, 50-60, >60, <0.3, >0.3 " -276.577 19.01 8 1.3996E-02 .0000 3.5134E-03
.2282 2.9401E-03 .3567 .0000 .0000 .0000 .0000 .0000 .4087 2.5828E-02 2.8763E-02
"06/09/1992" "09:52:36" "FBC PCM 10-20, 20-30, 30-40, 40-50, 50-60, >60, <0.3, >0.3 " -285.851 39.03 8 .0000 .0000 1.4957E-02
.2383 .0000 .0000 .2039 .5428 .0000 .0000 .0000 -2.1203E-06 1.7593E-02 2.3597E-02
"06/09/1992" "10:49:30" "SC PCM <5, >5, <0.1, 0.1-0.2, 0.2-0.3, 0.3-0.5, 0.5-1, 1-2, >2 " -306.621 96.83 9 .0000 .0000 .0000
.0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 1.0368E-02 .2379 .3233 5.4390E-02 9.2242E-04
"06/09/1992" "10:49:54" "SC PCM <10, >10, <0.1, 0.1-0.2, 0.2-0.3, 0.3-0.5, 0.5-1, 1-2, >2 " -288.155 44.97 9 .0000 .0000 .0000
.0000 .0000 .0000 .0000 .0000 .7228 .0000 .0000 .0000 8.3293E-02 .1248 2.6367E-02 9.8343E-03
"06/09/1992" "10:50:29" "SC PCM <20, >20, <0.1, 0.1-0.2, 0.2-0.3, 0.3-0.5, 0.5-1, 1-2, >2 " -277.141 18.94 9 2.4998E-02 .0000 .0000
.0000 .0000 .0000 .0000 .0000 .3188 .5973 .0000 4.5484E-02 .0000 3.8390E-02 2.2548E-02 4.7097E-02
"06/09/1992" "10:42:08" "SC PCM <30, >30, <0.1, 0.1-0.2, 0.2-0.3, 0.3-0.5, 0.5-1, 1-2, >2 " -278.516 21.96 8 4.1566E-03 .0000 .0000
1.3378E-04 .0000 .0000 .0000 .0000 .0000 .4087 .4290 5.4099E-02 .0000 .1080 2.6150E-02 5.0063E-02
"06/09/1992" "10:43:04" "SC PCM <40, >40, <0.1, 0.1-0.2, 0.2-0.3, 0.3-0.5, 0.5-1, 1-2, >2 " -274.113 13.89 9 .1256 1.4143E-04 .0000
.0000 .0000 .0000 .0000 2.8445E-04 .0000 .0000 .9300 .0000 .0000 6.9566E-02 2.6644E-02 9.1119E-02
"06/09/1992" "10:43:44" "SC PCM <50, >50, <0.1, 0.1-0.2, 0.2-0.3, 0.3-0.5, 0.5-1, 1-2, >2 " -285.544 42.63 10 .0000 .0000 .0000
.0000 .0000 5.0791E-04 .0000 .0000 .0000 .0000 .9601 .0000 .0000 3.9410E-02 3.3774E-02 .1998

"06/10/1992" "09:42:52" "SC PCM(different order)<40, >40, <0.1, 0.1-0.2, 0.2-0.3, 0.3-0.5, 0.5-1, 1-2, >2" -274.113 13.89 9 .1256 1.4143E-04 .0000
.0000 .0000 .0000 .0000 2.8445E-04 .0000 .0000 .9300 .0000 .0000 6.9566E-02 2.6644E-02 9.1119E-02
"06/10/1992" "10:46:34" "SC M 10-20, 20-30, 30-40, >40, AR<100, 100<AR<200, AR>200 " -301.303 21.78 10 1.5441E-02 .0000 9.9225E-02
.0000 .0000 3.6258E-03 .0000 .0000 .0000 .7186 2.4978E-03 .1761 2.6786E-02 .6618
"06/10/1992" "10:47:09" "SC M 10-20, 20-30, 30-40, >40, AR<100, 100<AR<200, AR>200 (without) " -271.722 9.472 8 .3034 .0000 7.9714E-02
.0000 .0000 9.5295E-03 .0000 .0000 .0000 .7246 4.7535E-03 .1814 2.3813E-02 .6408
"06/10/1992" "10:47:42" "SC PCM 30-40, 40-50, <0.2, 0.2-0.3 " -328.264 132.1 10 .0000 .4994 .0000

.3992 .1441 .1207
"06/10/1992" "10:47:44" "SC PCM 30-40, >40, <0.2, 0.2-0.3 " -328.362 132.3 10 .0000 .4486 .0000
.4357 .1441 .1141
"06/10/1992" "10:47:46" "SC PCM 30-40 AND <0.2, 40-50 AND 0.2-0.3 " -328.264 132.1 11 .0000 .4443 .1441
.1084
"06/10/1992" "10:47:47" "SC PCM 30-40 AND <0.2, >40 AND 0.2-0.3 " -328.362 132.3 11 .0000 .4927 .1441
.1009
"06/10/1992" "10:47:49" "SC PCM <40, >40, 0.2-0.3 " -277.294 19.14 11 5.7976E-02 .9997 2.7463E-02
.1226
"06/10/1992" "10:47:55" "SC PCM <40, >40, <0.1, 0.1-0.2, 0.2-0.3, 0.3-0.4, 0.4-0.6, 0.6-1, >1 " -274.426 14.08 7 4.9035E-02 5.2545E-05 .0000
1.7299E-04 .0000 .0000 .0000 1.6964E-04 .0000 .0000 .7574 .2283 .0000 1.3866E-02 2.6012E-02 .1065
"06/10/1992" "15:23:45" "SC PCM <40, >40, <0.3, >2 " -274.857 14.75 9 9.7473E-02 5.4764E-05 2.5762E-04
4.5248E-02 2.5944E-02 9.8491E-02
"06/10/1992" "15:24:05" "SC PCM <40, >40, <0.4, >2 " -275.922 17.20 9 4.4919E-02 1.0871E-04 1.0373E-03
5.9914E-02 2.7518E-02 4.8515E-02
"06/10/1992" "15:24:25" "SC PCM <40, >40, <0.3, >3 " -274.995 14.95 9 9.1591E-02 5.9029E-05 3.1457E-03
6.6660E-02 2.5536E-02 9.0266E-02
"06/10/1992" "15:24:36" "SC PCM <40, >40, <0.3, >5 " -274.006 13.41 9 .1442 7.1369E-05 4.9037E-03
.1224 2.6666E-02 8.0706E-02
"06/10/1992" "15:24:48" "SC PCM <40, >40, <0.3, >10 " -274.370 14.68 9 9.9294E-02 7.5858E-05 1.2275E-02
.1842 2.9171E-02 8.2945E-02
"06/10/1992" "15:25:11" "SC PCM 20-40, >40, <0.3, >2 " -283.427 31.70 9 .0000 3.7466E-02 9.1336E-02
-1.5012E-12 2.5325E-02 8.2712E-02
"06/10/1992" "15:25:17" "SC PCM 20-40, >40, <0.4, >2 " -276.234 17.96 9 3.4871E-02 9.9336E-02 7.5388E-02
1.7035E-02 2.4296E-02 3.6304E-02
"06/10/1992" "15:25:24" "SC PCM 20-35, >35, <0.3, >2 " -282.898 30.25 10 .0000 .1302 .0000
.2507 2.6694E-02 2.8991E-02
"06/10/1992" "15:25:27" "SC PCM 20-45, >45, <0.3, >2 " -286.727 36.13 9 .0000 2.3230E-02 3.3283E-02
-7.5830E-12 2.4133E-02 .2121
"06/10/1992" "15:25:34" "SC PCM <20, 20-40, >40, <0.3, >2 " -274.850 14.73 9 9.7945E-02 5.4613E-05 2.7873E-04
.0000 .0000 4.5312E-02 2.5936E-02 9.8583E-02

"06/11/1992" "15:31:51" "SC PCM <40, >40 " -289.830 50.85 11 .0000 .9995 4.0751E-02
5.9240E-03
"06/11/1992" "15:31:56" "SC PCM <20 20-40, >40, <0.3, >5 " -273.833 13.04 8 .1098 7.4307E-05 .0000
1.0718E-02 2.5619E-02 .1163 2.5487E-02 7.6466E-02
"06/11/1992" "15:32:29" "SC PCM <10 10-40, >40, <0.3, >2 " -274.688 14.64 9 .1005 4.4249E-05 .0000
2.4070E-03 .0000 4.5564E-02 2.5144E-02 9.3422E-02
"06/11/1992" "15:32:48" "SC PCM <10 10-40, >40, <0.3, >5 " -273.349 12.40 8 .1337 4.5873E-05 .0000
5.1824E-03 5.4184E-03 .1346 2.4875E-02 7.0329E-02
"06/11/1992" "15:33:31" "SC PCM <20 20-40, >40, with AR>100 or w>5 " -279.057 23.32 10 8.7947E-03 .1284 .4497
2.4093E-02 1.6167E-02

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 "06/11/1992" "15:33:37" "SC PCM <20 20-40, >40, with AR>200 or w>5                                    "  -287.783       57.24      10   .0000      4.7695E-02   .6415
5.4238E-02  2.0059E-02
 "06/11/1992" "16:05:03" "SC M <10, 10-20, 20-30, 30-40, 40-50, 50-60, >60, <0.4, >0.4                  "  -279.728       23.25       8  2.2192E-03  3.6878E-05   .0000
.0000       .0000       .0000       .0000      2.0091E-02   .0000       .3376       .0000       .6323       .0000      9.9335E-03  2.1964E-02   .3872
 "06/11/1992" "16:06:22" "SC M <20, >20, <0.2,  0.2-0.3,  0.3-0.4,  0.4-2, 2-5, 5-8, >8 (without)         "  -290.051       43.31       9   .0000      1.0731E-04   .0000
.0000       .0000       .0000       .0000       .0000       .0000       .0000       .4395      1.5005E-02   .0000       .5454      2.3980E-02  3.3505E-02
 "06/11/1992" "16:06:57" "SC M <30, >30, <0.2,  0.2-0.3,  0.3-0.4,  0.4-2, 2-5, 5-8, >8 (without)         "  -278.334       19.29       7  6.5724E-03  5.7529E-05   .0000
.0000       .0000       .0000       .0000       .0000       .8490       .0000      9.9544E-02   .0000      1.6664E-04  9.9650E-04  2.1948E-02   .3498
 "06/11/1992" "16:08:07" "SC M <40, >40, <0.2,  0.2-0.3,  0.3-0.4,  0.4-2, 2-5, 5-8, >8 (without)         "  -277.968       19.74       9  1.8859E-02  8.5360E-05   .0000
.0000       .0000       .0000       .0000       .0000       .0000       .5169       .4323       .0000       .0000      5.0666E-02  2.2914E-02   .2941
 "06/11/1992" "16:08:44" "SC M <10, 10-20, 20-30, 30-40, 40-50, 50-60, >60, <0.2, >0.2                  "  -280.135       24.37       8  1.1420E-03  5.8051E-06   .0000
1.4206E-02   .0000       .0000       .0000       .9699      1.3334E-02   .0000       .0000       .0000       .0000      2.5917E-03  2.1348E-02   .3422
 "06/11/1992" "16:09:50" "SC M <10, 10-20, 20-30, 30-40, 40-50, 50-60, >60, <0.3, >0.3                  "  -298.689       63.37       8   .0000       .0000       .0000
4.3934E-02   .0000       .0000       .0000       .4960      9.9726E-02  5.7563E-02   .0000       .0000       .0000       .3028      4.6309E-02  3.6312E-02

 "06/12/1992" "12:45:29" "SC PCM, USING SUM OF (AR)^1.8 INSTEAD OF THE SUM OF THE NUMBER OF STRUCTURES    "  -316.759      120.5       11   .0000       .5002      8.6106E-02
1.0976E-07
 "06/12/1992" "12:46:51" "SC PCM   MIMICS RJ LEE                                                         "  -314.904      103.8       11   .0000       .4998       .1020
2.5583E-08
 "06/12/1992" "14:25:51" "SC PCM <10, 10-20, 20-30, 30-40, 40-50, 50-60, >60 and ,0.2, >0.2              "  -274.192       14.22       8  7.5497E-02   .0000       .0000
.0000      3.7448E-03  8.7979E-02   .0000       .8868       .0000      2.1443E-02   .0000       .0000       .0000     -4.0984E-06  2.4473E-02  9.7935E-02
 "06/12/1992" "14:26:39" "SC PCM <10, 10-20, 20-30, 30-40, 40-50, 50-60, >60 and ,0.3, >0.3              "  -273.570       13.47       9   .1417       .0000       .0000
7.5561E-03   .0000       .0000       .0000       .0000       .0000       .8731       .0000       .0000      1.6883E-02   .1024      2.5219E-02  7.8163E-02
 "06/12/1992" "14:27:33" "SC PCM <10, 10-20, 20-30, 30-40, 40-50, 50-60, >60 and ,0.4, >0.4              "  -273.752       13.77       8  8.7091E-02   .0000       .0000
7.5744E-03  2.1524E-03   .0000       .0000       .0000       .0000       .9036       .0000       .0000      3.9774E-02  4.6900E-02  2.4767E-02  5.8149E-02
 "06/12/1992" "14:28:40" "SC PCM <20, >20 and <0.2,  0.2-0.3,  0.3-0.4,  0.4-2, 2-5, 5-8, >8             "  -273.104       12.30       8   .1378       .0000       .0000
.0000       .0000      2.8541E-03   .0000       .0000       .3170      8.8019E-03   .2178       .0000       .0000       .4536      2.4370E-02  2.3120E-02
 "06/12/1992" "14:30:01" "SC PCM <30, >30 and <0.2,  0.2-0.3,  0.3-0.4,  0.4-2, 2-5, 5-8, >8             "  -274.535       15.28       8  5.3177E-02   .0000       .0000
.0000       .0000      3.1038E-03  8.3599E-02   .0000       .0000      1.5371E-02   .5256       .0000       .0000       .3723      2.5364E-02  3.0722E-02
 "06/12/1992" "14:31:34" "SC PCM <40, >40 and <0.2,  0.2-0.3,  0.3-0.4,  0.4-2, 2-5, 5-8, >8             "  -318.182      153.4       10   .0000       .0000       .0000
3.9080E-02  3.7648E-02   .0000       .0000       .0000       .0000       .0000       .0000       .0000       .0000       .9233      3.8196E-02  1.0287E-03
 "06/12/1992" "14:32:09" "SC PCM <50, >50 and <0.2,  0.2-0.3,  0.3-0.4,  0.4-2, 2-5, 5-8, >8             "  -282.887       38.07       9   .0000       .0000       .0000
5.5882E-04  3.2760E-04   .0000       .0000       .0000       .0000       .0000       .7592       .0000       .0000       .2399      3.7498E-02  6.3278E-02
 "06/12/1992" "14:33:06" "SC PCM <5, 5-40, >40 and <0.3, >5                                             "  -272.935       12.19      10   .2716       .0000       .0000
1.7176E-03   .0000       .1453      2.5612E-02  7.0424E-02
 "06/12/1992" "14:33:22" "SC PCM <5, 5-40, >40 and <0.4, >5                                             "  -301.510       78.09       9   .0000       .0000       .0000
2.6148E-02  2.3396E-02  6.1184E-02  6.3939E-02  5.3121E-03
 "06/12/1992" "14:33:37" "SC PCM <10, 10-40, >40 and <0.4, >5                                           "  -273.662       13.27       8   .1023      2.6086E-05   .0000
7.5831E-03  5.6428E-02  3.3751E-14  2.4070E-02  4.5074E-02
 "06/12/1992" "14:33:58" "SC PCM <20, 20-40, >40 and <0.4, >5                                           "  -337.543      281.4       10   .0000      2.7954E-02   .0000
.2053       .0000       .7667      3.7371E-02  3.2598E-04
 "06/12/1992" "14:34:10" "SC PCM <20, 20-40, >40 and <0.3, >8                                           "  -345.304      353.5       9   .0000       .2255       .0000
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5.5410E-02 .0000 6.1022E-02 3.8161E-02 4.0910E-05
"06/12/1992" "14:34:49" "SC PCM <20, 20-50, >50 and <0.3, >5 " -277.024 18.84 8 1.4921E-02 6.7283E-05 .0000
6.0514E-02 1.3755E-02 .1895 2.4667E-02 6.5813E-02
"06/12/1992" "14:36:04" "SC PCM <20, 20-50, >50 and <0.4, >5 " -349.979 404.9 9 .0000 .3496 .0000
.1835 2.0935E-02 .4459 2.9928E-02 2.6012E-05
"06/12/1992" "14:36:54" "SC PCM <10, 10-40, >40, with AR>=50 or WIDTH>=5 (6 categories) " -274.917 15.55 11 .1582 .0000 .0000
6.8066E-02 .0000 .9319 2.4370E-02 1.4888E-02
"06/12/1992" "14:36:59" "SC PCM <10, 10-40, >40, with AR>=100 or WIDTH>=5 (6 categories) " -275.017 15.94 10 .1006 .4137 .0000
.2309 .0000 .3555 2.5908E-02 3.4688E-02
"06/12/1992" "14:37:04" "SC PCM <10, 10-40, >40, with AR>=200 or WIDTH>=5 (6 categories) " -286.452 56.19 9 .0000 .0000 .0000
.3874 4.7852E-02 .2899 5.2688E-02 4.5503E-02
"06/12/1992" "14:37:11" "SC AR>=100 OR (C and CS only) WIDTH>=5, PCM, <10, 10-40, >40 " -275.017 15.94 10 .1006 .4137 .0000
.2309 .0000 .3555 2.5908E-02 3.4688E-02
"06/12/1992" "14:37:15" "FBC AR>=100 OR SC(C and CS only) WIDTH>=5, PCM, <10, 10-40, >40 " -275.121 16.15 10 9.4586E-02 .4119 .0000
.2258 .0000 .3623 2.5958E-02 3.4841E-02
"06/12/1992" "14:37:21" "SC PCM <40, >40, and <0.3, >0.3 " -276.137 17.09 9 4.6680E-02 1.6030E-05 1.8285E-04
2.2757E-02 2.5509E-02 9.4588E-02
"06/12/1992" "16:47:32" "SC PCM <20, 20-40, >40 and >8, <0.3 " -273.463 12.58 8 .1262 .0000 8.1316E-05
7.5406E-02 2.7083E-02 .7421 2.5097E-02 6.9122E-02

"06/15/1992" "11:06:50" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 and <0.2, >8 " -296.708 70.84 8 .0000 .0000 .0000
3.1957E-02 .0000 .0000 .0000 4.3341E-02 .0000 .6315 1.6485E-03 .0000 .0000 .2916 2.8411E-02 1.6238E-02
"06/15/1992" "11:08:19" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 and <0.3, >8 " -301.032 82.76 10 .0000 .0000 .0000
4.7120E-02 .0000 2.9985E-02 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .9229 2.5358E-02 5.3733E-03
"06/15/1992" "11:08:49" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 and <0.4, >8 " -272.385 11.16 8 .1922 .0000 .0000
9.6472E-04 .0000 4.3486E-03 .0000 .0000 .0000 .0000 .1754 .7476 .0000 7.1640E-02 2.5317E-02 6.4120E-02
"06/15/1992" "11:10:43" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 and <0.5, >8 " -272.858 11.87 7 .1043 .0000 .0000
.0000 .0000 1.3893E-03 .0000 5.2414E-02 .0000 6.0335E-02 .3280 .0000 .3594 .1984 2.4085E-02 4.6887E-02
"06/15/1992" "11:12:36" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 and <0.6, >8 " -273.029 12.11 7 9.6208E-02 .0000 .0000
.0000 .0000 3.7626E-03 .0000 3.8885E-02 .0000 .1015 .4142 .0000 7.0023E-02 .3717 2.4532E-02 3.5003E-02
"06/15/1992" "11:14:25" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 and <0.8, >8 " -273.276 12.53 7 8.3861E-02 .0000 .0000
.0000 .0000 7.6795E-03 .0000 3.4904E-03 .0000 6.0160E-02 .3190 .0000 .2732 .3365 2.4465E-02 3.7891E-02
"06/15/1992" "11:16:10" "SC PCM <3, 3-10, 10-20, 20-30, 30-40, 40-50, >50 and <0.3, >8 " -272.209 10.93 7 .1412 .0000 .0000
3.3972E-04 .0000 4.1296E-03 .0000 .0000 .0000 .0000 4.2215E-02 .4837 .0000 .1544 2.5667E-02 9.9115E-02
"06/15/1992" "11:18:03" "SC PCM <5, 5-8, 8-20, 20-30, 30-40, 40-50, >50 and <0.3, >8 " -272.224 11.04 6 8.6318E-02 .0000 6.2016E-07
3.2317E-04 .0000 2.2255E-03 .0000 .0000 .0000 .0000 6.5672E-02 .3431 .0000 8.4681E-02 2.5656E-02 .1429
"06/15/1992" "12:16:10" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 with AR>=200 or W>=8 (14 cat.) " -285.792 53.75 4 .0000 8.7093E-02 8.7093E-02
8.7093E-02 .0000 8.7093E-02 .0000 .1419 .0000 .0000 .2037 8.7093E-02 .0000 .1092 5.5273E-02 .1341
"06/15/1992" "12:16:21" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 with AR>=100 or W>=8 (14 cat.) " -272.200 11.02 5 5.0335E-02 4.9881E-02 4.9881E-02
5.6553E-02 .0000 .2414 .0000 .0000 .0000 .0000 .2577 .0000 .2205 2.2922E-02 2.5260E-02 9.4228E-02
"06/15/1992" "12:16:44" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 with AR>=50 or W>=8 (14 cat.) " -273.057 12.26 6 5.5674E-02 .0000 1.3179E-07
.0000 .0000 1.3801E-02 .0000 3.7693E-02 .0000 5.3310E-02 .3375 .0000 .3226 .2351 2.3665E-02 4.4856E-02

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 "06/15/1992" "12:18:06" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 with AR>=30 or W>=8 (14 cat.)  "  -273.632       13.16       7  6.7616E-02   .0000       .0000
.0000       .0000      4.9098E-03   .0000      1.9981E-02   .0000      6.4082E-03   .2060       .0000       .6920      7.0740E-02  2.3745E-02  6.6264E-02
 "06/15/1992" "12:19:28" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 with AR>=20 or W>=8 (14 cat.)  "  -273.360       12.73       8   .1208       .0000       .0000
.0000       .0000      6.9703E-03   .0000       .0000       .0000      3.0064E-02   .2439       .0000       .5410       .1781      2.4490E-02  5.1541E-02
 "06/15/1992" "12:20:57" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 with AR>=10 or W>=8 (14 cat.)  "  -273.866       13.72       8  8.8611E-02   .0000       .0000
.0000       .0000      8.1095E-03   .0000       .0000       .0000      2.5890E-02   .2019       .0000       .4075       .3565      2.5024E-02  3.8497E-02
 "06/15/1992" "12:22:28" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 with AR>=5 or W>=8 (14 cat.)   "  -274.167       14.40       8  7.1042E-02   .0000       .0000
.0000       .0000      5.0759E-03   .0000      4.7770E-03   .0000       .0000       .1090       .0000       .7382       .1430      2.5059E-02  5.8887E-02
 "06/15/1992" "12:24:05" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 with AR>=3 or W>=8 (14 cat.)   "  -274.231       14.54       7  4.1630E-02   .0000       .0000
.0000       .0000      5.8288E-03   .0000      7.2078E-04   .0000      1.0573E-02   .1299       .0000       .6530       .2000      2.5215E-02  5.1238E-02
 "06/15/1992" "15:17:15" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 and >8, <0.3                   "  -272.198       10.89       7   .1430       .0000       .0000
.0000      6.4848E-04   .0000      3.2479E-03   .0000       .0000      4.9158E-02   .0000       .0000       .4088       .4276      2.5808E-02   .1227

 "06/16/1992" "15:57:13" "SC PCM <5, 5-30, >30 and >8, <0.3                                               "  -275.834       18.83      10  4.1618E-02   .0000       .0000
.0000      4.7435E-03   .5686      2.5768E-02  2.5232E-02
 "06/16/1992" "15:57:21" "SC PCM <5, 5-40, >40 and >8, <0.3                                               "  -272.871       12.51      10   .2515       .0000       .0000
.0000      2.0072E-03   .7917      2.7267E-02  6.5788E-02
 "06/16/1992" "15:57:28" "SC PCM <8, 8-40, >40 and >8, <0.3                                               "  -272.805       12.41       9   .1906       .0000       .0000
1.0688E-02  8.2511E-03   .7160      2.5565E-02  5.4117E-02
 "06/16/1992" "16:20:15" "SC PCM <10, 10-40, >40 and <0.3, >8                                             "  -272.895       12.21       8   .1414      1.5538E-05   .0000
1.1243E-02  5.4704E-02   .2171      2.4137E-02  5.6716E-02
 "06/16/1992" "16:20:42" "SC PCM <15, 15-40, >40 and <0.3, >8                                             "  -272.886       12.13       8   .1446      2.1089E-05   .0000
7.3058E-02   .1151       .3195      2.3806E-02  3.7739E-02
 "06/16/1992" "15:58:04" "SC PCM <10, 10-30, >30 and >8, <0.3                                             "  -274.890       15.82       9  7.0146E-02   .0000       .0000
.1135      4.1740E-02   .2284      2.3632E-02  1.8589E-02
 "06/16/1992" "15:58:14" "SC PCM <10, 10-50, >50 and >8, <0.3                                             "  -274.641       15.42       9  7.9344E-02   .0000       .0000
9.8803E-02  3.6726E-02  1.3111E-11  2.4535E-02  2.2019E-02
 "06/16/1992" "16:37:21" "SC PCM >50, 20-50, <20 and >8, <0.3                                             "  -275.523       16.03       8  4.1166E-02   .6671       .0000
.1482       .1710      1.8609E-04  2.3804E-02  2.4382E-02
 "06/16/1992" "15:58:39" "SC PCM <10, 10-40, >40 and AR>=100 or W>=8 (6 categories)                       "  -274.361       15.16       9  8.5993E-02   .2858       .0000
.2372       .1225       .3545      2.4533E-02  3.6979E-02
 "06/16/1992" "15:58:46" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 and AR>=150 or W>=8 (14 cat.)  "  -272.330       11.22       1  5.8425E-05  5.6473E-02  5.6473E-02
9.3549E-02  2.4707E-02   .2394       .0000       .0000      2.3420E-02  8.5612E-02  7.6892E-02   .1257      8.5612E-02   .1054      2.7771E-02   .1274
 "06/16/1992" "15:58:54" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 and >8, <0.3 (with AR>=3)      "  -272.197       10.83       8   .2109       .0000       .0000
.0000      4.5497E-04   .0000      2.2876E-03   .0000       .0000       .0000       .0000       .0000       .2874       .5971      2.6318E-02   .1745
 "06/16/1992" "15:59:39" "SC PCM <10, 10-40, >40 and >8, <0.3 (with AR>=3)                                "  -272.968       11.90       9   .2183       .0000      3.9534E-05
.0000      7.6856E-03   .7128      2.6190E-02  6.5721E-02

 "06/17/1992" "14:24:32" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 and >8, <0.3 and AR>=10        "  -272.198       10.89       7   .1430       .0000       .0000
.0000      6.4848E-04   .0000      3.2479E-03   .0000       .0000      4.9158E-02   .0000       .0000       .4088       .4276      2.5808E-02   .1227
 "06/17/1992" "14:25:51" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 and >8, <0.3 and AR>=3         "  -272.198       10.89       7   .1430       .0000       .0000
.0000      6.4849E-04   .0000      3.2479E-03   .0000       .0000      4.9158E-02   .0000       .0000       .4088       .4276      2.5808E-02   .1227
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"06/17/1992" "14:28:12" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 and >8, <0.3 (chrysotile) " -199.146 8.429 2 1.3952E-02 .0000 .0000
.0000 .0000 .2027 .0000 .0000 .0000 .3859 .2964 .0000 .0000 1.1885E-11 3.2157E-02 7.5085E-02
"06/17/1992" "14:32:50" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 and >8, <0.3 (amphiboles) " -100.336 1.656 1 .1976 .0000 .0000
.0000 .0000 .0000 .0000 9.3260E-02 .0000 .0000 5.5979E-02 .0000 .7515 7.0580E-11 2.3542E-02 .1025
"06/17/1992" "14:33:09" "SC PCM <40, >40 and <0.2, 0.2-0.3, 0.3-0.4, 0.4-2, 2-5, 5-8, >8 (chrysotile) " -199.147 8.432 3 3.7153E-02 .0000 .0000
.0000 .0000 7.7411E-03 .0000 .4238 .0000 .0000 .0000 6.5665E-02 .0000 .5028 3.2162E-02 2.7220E-02
"06/17/1992" "14:33:41" "SC PCM <40, >40 and <0.2, 0.2-0.3, 0.3-0.4, 0.4-2, 2-5, 5-8, >8 (amphiboles) " -100.379 1.697 3 .6374 .0000 .0000
.0000 .0000 .0000 .0000 3.1406E-02 .0000 .8748 .0000 .0000 .0000 9.3811E-02 2.3351E-02 8.8094E-02
"06/17/1992" "14:33:51" "SC PCM <10, 10-40, >40 and <0.3, >8 (chrysotile) " -231.202 165.7 3 .0000 .1906 .0000
2.0354E-02 .2327 .5564 3.6817E-02 4.5930E-05
"06/17/1992" "14:34:07" "SC PCM <10, 10-40, >40 and <0.3, >8 (amphiboles) " -100.344 1.655 3 .6468 .0000 .0000
.0000 3.9432E-02 8.5786E-02 2.3356E-02 8.8092E-02
"06/17/1992" "14:34:13" "SC PCM <10, 10-40, >40 and >8, <0.4 " -273.352 13.00 9 .1619 .0000 .0000
.1034 1.4351E-02 .6578 2.4091E-02 3.4458E-02
"06/17/1992" "14:45:23" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 and <0.3, >8 (with AR>=10) " -275.830 18.52 7 9.0747E-03 .0000 .0000
3.7724E-04 .0000 6.8825E-04 .0000 7.1379E-03 .0000 .0000 .0000 .2738 .0000 -1.0060E-10 2.5949E-02 .3142
"06/17/1992" "15:45:33" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 and >8, <0.3 (2 studies) " -301.025 12.62 8 .1249 .0000 .0000
.0000 1.5961E-03 .0000 4.1331E-02 .0000 .0000 .0000 .0000 -2.1416E-05 3.1086E-02 1.8208E-02
"06/17/1992" "15:45:33" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 and >8, <0.3 (2 studies) " -301.025 12.62 8 .1249 .0000 .0000
.0000 1.5961E-03 .0000 4.1331E-02 .0000 .0000 .0000 .0000 -2.1416E-05 2.1682E-02 2.9493E-02
"06/17/1992" "15:45:50" "SC PCM <40, >40 and <0.2, 0.2-0.3, 0.3-0.4, 0.4-2, 2-5, 5-8, >8 (2 studies) " -300.792 12.06 6 5.9787E-02 2.6205E-05 .0000
.0000 .0000 7.8049E-04 .0000 4.1073E-02 .0000 .8914 .0000 4.1637E-02 3.2830E-02 .1416
"06/17/1992" "15:45:50" "SC PCM <40, >40 and <0.2, 0.2-0.3, 0.3-0.4, 0.4-2, 2-5, 5-8, >8 (2 studies) " -300.792 12.06 6 5.9787E-02 2.6205E-05 .0000
.0000 .0000 7.8049E-04 .0000 4.1073E-02 .0000 .8914 .0000 4.1637E-02 2.0805E-02 8.7989E-02
"06/17/1992" "15:47:24" "SC PCM <10, 10-40, >40 and <0.3, >8 (2 studies) " -300.139 11.32 8 .1837 .0000 .0000
.1094 3.2465E-02 8.7587E-02
"06/17/1992" "15:47:24" "SC PCM <10, 10-40, >40 and <0.3, >8 (2 studies) " -300.139 11.32 8 .1837 .0000 .0000
.1094 2.0771E-02 6.6119E-02

"06/22/1992" "15:33:41" "SC M(14) <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 and <0.3, >8 " -277.733 20.96 9 1.2108E-02 .0000 .0000
9.7750E-04 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .2541 .7450 1.9854E-10 2.1741E-02 .4278
"06/22/1992" "15:35:19" "PS M(14) <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 and <0.3, >8 " -277.324 19.37 9 2.1452E-02 .0000 .0000
3.3816E-03 .0000 .0000 .0000 1.6148E-02 .0000 .0000 .0000 .0000 .9455 3.4942E-02 2.2094E-02 .3327
"06/22/1992" "15:36:20" "FBC M(14) <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 and <0.3, >8 " -282.927 31.48 9 .0000 2.0191E-06 2.8155E-04
.0000 .0000 .0000 .8194 2.2740E-02 1.290
"06/22/1992" "15:37:36" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 and <0.3 and AR>=20, >8 " -272.197 10.92 5 5.2268E-02 1.7829E-05 1.3304E-09
6.0850E-04 .0000 3.1381E-03 .0000 .0000 .0000 .0000 5.6291E-02 .3825 .0000 9.9690E-02 2.5851E-02 .1301
"06/22/1992" "15:40:55" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 and <0.3 and AR>=30, >8 " -272.256 11.12 5 4.8301E-02 8.7621E-05 1.3116E-06
8.4954E-04 .0000 2.3397E-03 .0000 .0000 .0000 .0000 7.1845E-02 .3003 .0000 5.9915E-02 2.5516E-02 .1679
"06/22/1992" "15:43:58" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 and <0.3, >8 (chrysotile) " -174.591 3.392 2 .1827 .0000 .0000
.0000 .0000 .0000 .1688 .0000 .0000 .2492 .5106 .0000 .0000 7.1357E-02 3.0137E-02 9.0414E-02
"06/22/1992" "15:46:08" "SC PCM <40, >40 and <0.2, 0.2-0.3, 0.3-0.4, 0.4-2, 2-5, 5-8, >8 (chrysotile) " -174.591 3.395 2 .1825 .0000 .0000

.0000 .0000 5.5468E-03 .0000 .3469 .0000 .0000 .0000 .0000 .0000 .3974 3.0140E-02 3.8470E-02
"06/22/1992" "15:55:24" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 and <0.3, >8 (chrysotile) (avg)" -126.207 1.2755E-15 0 .0000 .0000 .0000
3.9108E-03 .0000 1.7452E-02 .0000 1.0756E-02 .0000 .0000 .0000 .0000 .0000 .9679 2.6668E-02 2.1269E-02
"06/22/1992" "16:30:35" "SC PCM <40, >40 and <0.2, 0.2-0.3, 0.3-0.4, 0.4-2, 2-5, 5-8, >8 (chrysotile) (avg)" -126.207 2.9177E-13 -1 .0000 .0000 2.8851E-04
.0000 .0000 1.4347E-02 .0000 .0000 .0000 .0000 .0000 .8395 .1459 -1.9596E-10 2.6668E-02 1.3955E-02
"06/22/1992" "15:49:00" "PS PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 and <0.3, >8 " -272.711 12.25 8 .1395 .0000 .0000
8.6521E-03 .1246 .0000 .0000 .0000 .0000 .1227 .4444 .0000 .0000 .2996 2.5616E-02 3.4242E-02
"06/22/1992" "15:50:08" "FBC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 and <0.3, >8 " -275.871 18.62 8 1.6231E-02 .0000 3.7774E-04
7.0798E-04 7.2592E-03 .0000 .7180 2.5916E-02 .3137

"06/23/1992" "14:32:26" "SC PCM <20, >20 (chrysotile only - averaged K013) " -127.858 3.449 3 .3270 1.000 2.9297E-02
2.0218E-03
"06/23/1992" "15:20:51" "SC PCM <5,5-10,10-20,20-30,30-40,40-50,>50 with AR>=100 or W>=8 (14 CAT.)(no discharged)" -247.715 6.231 5 .2839 .1653 .1653
5.3902E-02 .0000 .2203 .0000 .0000 .0000 .0000 .2507 .0000 .0000 6.1001E-02 2.4264E-02 .1097
"06/23/1992" "15:21:06" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 with <0.3, >8 (no discharged) " -247.916 6.347 5 .2733 .0000 .0000
7.7664E-04 .0000 3.3297E-03 .0000 1.1683E-02 .0000 .0000 .1023 .3292 .0000 .1214 2.3640E-02 .1100
"06/23/1992" "15:21:59" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 with <0.4, >8 (no discharged) " -247.977 6.302 6 .3897 .0000 .0000
9.2037E-04 .0000 5.3676E-03 .0000 2.3489E-02 .0000 .0000 .2528 .5300 .0000 .1875 2.3356E-02 5.1364E-02
"06/23/1992" "15:22:39" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 with <0.5, >8 (no discharged) " -248.237 6.697 7 .4607 .0000 .0000
.0000 .0000 4.4608E-03 .0000 7.6930E-02 .0000 3.6633E-02 .4443 .0000 .0000 .4377 2.2722E-02 3.3184E-02
"06/23/1992" "15:43:52" "SC PCM <5,5-10,10-20,20-30,30-40,40-50,>50 with <0.5 and AR>=3,>8(no discharged)" -248.237 6.697 7 .4607 .0000 .0000
.0000 .0000 4.4608E-03 .0000 7.6930E-02 .0000 3.6633E-02 .4443 .0000 .0000 .4377 2.2722E-02 3.3184E-02
"06/23/1992" "15:50:53" "SC PCM <5,5-10,10-20,20-30,30-40,40-50,>50 with >8,<0.5and AR>=10(no discharged)" -248.223 6.690 6 .3499 .0000 1.0298E-04
.0000 .0000 .0000 .0000 .0000 .1014 .4356 6.4002E-03 .0000 .0000 -3.7956E-06 2.2698E-02 3.2980E-02
"06/23/1992" "15:45:06" "SC PCM <5,5-10,10-20,20-30,30-40,40-50,>50 with <0.5and AR>=20,>8(no discharged)" -248.139 6.630 8 .5767 4.1766E-04 .0000
.0000 .0000 .0000 .0000 .1019 .0000 .0000 .4509 .0000 .0000 .4468 2.2774E-02 3.3466E-02
"06/23/1992" "16:04:30" "SC PCM <20, >20 with <0.3, >8 (no discharged) " -250.437 9.979 9 .3517 3.1512E-04 .0000
.6923 2.1630E-02 1.6030E-02
"06/23/1992" "16:04:37" "SC PCM <40, >40 with <0.3, >8 (no discharged) " -251.384 12.81 8 .1178 9.4338E-05 3.9873E-03
.1952 2.8847E-02 7.4959E-02
"06/23/1992" "16:04:49" "SC PCM <40, >40 with <0.3, >5 (no discharged) " -250.175 9.585 8 .2948 7.0228E-05 1.5561E-02
.1310 2.4517E-02 7.8915E-02
"06/23/1992" "16:39:42" "SC PCM >10 (all with AR >= 3) (no WDC chrysotile or tremolite) " -220.082 16.49 9 5.6634E-02 .9283 2.5391E-02
4.4491E-03
"06/23/1992" "16:39:44" "SC PCM <10, 10-20, >20 (all with AR >= 3) (no WDC chrysotile or tremolite) " -219.772 16.07 9 6.4832E-02 .0000 3.9618E-12
2.5926E-02 3.8301E-04
"06/23/1992" "16:39:46" "PS PCM >10 (all with AR >= 3) (no WDC chrysotile or tremolite) " -220.532 17.26 9 4.4107E-02 .9300 2.5829E-02
4.6048E-03
"06/23/1992" "16:40:17" "PS PCM <10, 10-20, >20 (all with AR >= 3) (no WDC chrysotile or tremolite) " -220.468 17.36 9 4.2634E-02 .0000 .1894
2.6163E-02 4.7643E-04
"06/23/1992" "16:39:49" "SC(no C,CS,M,or MS) PCM >10 (all with AR >= 3) (no WDC chrysotile or tremolite) " -220.925 18.92 9 2.5190E-02 .6933 2.6422E-02
1.1936E-03

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 "06/23/1992" "16:39:51" "SC(no C,CS,M,or MS) PCM <10,10-20,>20 (all with AR >= 3) (no WDC or tremolite)  "  -220.428       17.89       9  3.5777E-02   .0000      5.4710E-11
2.6733E-02  4.2818E-04

 "06/24/1992" "14:59:32" "SC PCM >10 (all with AR>=3 and W>=0.2) (no tremolite or WDC chrysotile)         "  -219.932       16.02       9  6.5704E-02   .9655      2.5115E-02
1.0459E-02
 "06/24/1992" "14:59:34" "SC PCM <10,10-20,>20(all with AR>=3 and W>=0.2)(no tremolite or WDC chrysotile) "  -219.402       15.14       9  8.6504E-02   .0000      2.4662E-11
2.5513E-02  4.4249E-04
 "06/24/1992" "14:59:36" "FBC PCM >10 (all with AR>=3 and W>=0.2) (no tremolite or WDC chrysotile)        "  -220.855       18.70       9  2.7090E-02   .9594      2.6243E-02
1.0404E-02
 "06/24/1992" "14:59:38" "FBC PCM <10,10-20,>20(all with AR>=3 and W>=0.2)(no tremolite or WDC chrysotile)"  -220.072       16.90       8  3.0312E-02  1.9053E-03  1.9158E-12
2.6426E-02  4.8211E-04
 "06/24/1992" "14:59:41" "SC PCM <5, 5-40, >40, with W <0.5, >5                                          "  -279.469       27.19      10  1.5875E-03   .0000       .0000
4.6480E-03   .0000       .8946      2.9880E-02  1.5430E-02
 "06/30/1992" "10:00:07" "SC PCM  5-40, >40, with W >5, <0.3                                             "  -272.935       12.19      10   .2716       .0000      1.7176E-03
.8530      2.5612E-02  7.0424E-02
 "06/24/1992" "14:59:58" "SC PCM  5-40, >40, with W <0.5, >5                                             "  -279.469       27.19      10  1.5875E-03  4.6480E-03   .0000
.8946      2.9880E-02  1.5430E-02
 "06/24/1992" "15:00:08" "SC PCM  5-40, >40, with W <0.3, >5 (and all structures AR>=3)                  "  -273.227       12.61      10   .2459      1.4845E-03   .0000
.1517      2.5388E-02  7.8347E-02
 "06/24/1992" "15:00:17" "SC PCM  5-40, >40, with W <0.3, >5 (and all structures AR>=5)                  "  -274.576       15.49      10   .1144      1.4548E-03   .0000
.1902      2.5505E-02  8.6887E-02
 "06/30/1992" "10:00:12" "SC PCM  5-40, >40, with W >5, <0.3 and AR>=3                                   "  -272.935       12.19      10   .2716       .0000      1.7176E-03
.8530      2.5612E-02  7.0424E-02
 "06/30/1992" "10:00:17" "SC PCM  5-40, >40, with W >5, <0.3 and AR>=5                                   "  -272.935       12.19      10   .2716       .0000      1.7176E-03
.8530      2.5612E-02  7.0424E-02
 "06/24/1992" "15:00:35" "SC PCM  5-40, >40, with W <0.5 and AR>=5, >5                                   "  -279.469       27.19      10  1.5875E-03  4.6480E-03   .0000
.8946      2.9880E-02  1.5430E-02
 "06/24/1992" "15:00:46" "SC PCM  5-40, >40, with W <0.5 and AR>=10, >5                                  "  -279.469       27.19      10  1.5875E-03  4.6480E-03   .0000
.8946      2.9880E-02  1.5430E-02
 "06/24/1992" "15:00:56" "SC PCM  5-40, >40, with W <0.5 and AR>=20, >5                                  "  -278.500       24.89      10  4.7281E-03  6.8172E-03   .0000
.9347      2.8885E-02  1.5186E-02
 "06/24/1992" "15:01:00" "SC PCM  5-40, >40, with W <0.5 and AR>=30, >5                                  "  -277.782       22.81      10  1.0646E-02  1.2458E-02   .0000
.9274      2.7747E-02  1.5152E-02
 "06/24/1992" "15:01:03" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50 (no discharged chrysotile)    "  -255.492       20.01       8  9.4712E-03   .0000       .0000
2.3031E-02  9.2428E-02  4.8158E-02   .8364      2.4594E-02  7.7840E-03
 "06/24/1992" "15:01:13" "SC PCM  5-40, >40, with W <0.3, >5 (and all structures AR>=3) (no discharged)  "  -248.899       8.027       9   .5311      1.7527E-03   .0000
.2102      2.4254E-02  7.1338E-02
 "06/24/1992" "15:01:18" "SC PCM  5-40, >40, with W <0.5 and AR>=20, >5 (no discharged chrysotile)       "  -253.154       18.13      10  5.2069E-02  7.4254E-03   .0000
.9926      2.6968E-02  1.6049E-02

 "06/25/1992" "10:28:00" "SC M(16) 5-40, >40 and <0.3, >5                                                "  -320.420       65.65      12   .0000      1.2664E-03   .0000
5.5987E-02  2.9951E-02   .2335
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"06/25/1992" "10:28:07" "SC M(14) 5-40, >40 and <0.3, >5 " -286.209 40.07 10 .0000 1.1853E-03 .0000
7.1229E-02 2.3175E-02 .2276
"06/25/1992" "10:28:13" "SC M(16) 5-40, >40 and <0.3, >5 (no discharged chrysotile) " -294.603 56.81 11 .0000 1.6400E-03 .0000
.1014 2.6934E-02 .2021
"06/25/1992" "10:28:17" "SC M(14) 5-40, >40 and <0.3, >5 (no discharged chrysotile) " -260.648 32.11 9 .0000 1.4970E-03 .0000
.1164 2.1490E-02 .1998
"06/25/1992" "10:28:21" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, 40-50, >50, and <0.3, >5 " -272.188 10.78 7 .1480 .0000 .0000
4.2994E-04 .0000 1.7850E-03 .0000 .0000 .0000 .0000 3.3391E-02 .2812 .0000 4.0372E-02 2.5783E-02 .1943
"06/25/1992" "10:30:25" "SC PCM 5-40, >40 and 0.1-0.3, >5 " -272.938 12.17 10 .2734 1.8856E-03 .0000
.1407 2.5473E-02 7.0764E-02
"06/25/1992" "10:30:30" "SC PCM 5-40, >40 and 0.2-0.3, >5 " -272.985 12.21 10 .2706 3.4336E-03 .0000
.1429 2.5396E-02 6.8760E-02
"06/25/1992" "10:53:03" "SC PCM 5-40, >40 with >5, <0.3 and AR>=10 " -272.935 12.19 10 .2716 .0000 1.7176E-03
.8530 2.5612E-02 7.0424E-02
"06/25/1992" "10:30:41" "SC PCM 5-40, >40 with <0.3 and AR>=20, >5 " -272.902 12.14 10 .2751 1.8812E-03 .0000
.1478 2.5544E-02 6.9820E-02
"06/25/1992" "10:30:47" "SC PCM 5-40, >40 with <0.4 and AR>=5, >5 " -274.247 14.82 9 9.5423E-02 2.2016E-03 1.5835E-02
.1005 2.5652E-02 4.2275E-02
"06/25/1992" "10:30:58" "SC PCM 5-40, >40 with <0.4 and AR>=20, >5 " -274.223 14.82 9 9.5218E-02 2.8966E-03 1.3154E-02
.1296 2.5808E-02 4.0611E-02
"06/25/1992" "10:31:15" "SC PCM 5-40, >40 with <0.3 " -277.690 22.79 11 1.8207E-02 .9986 2.8284E-02
.1140
"06/25/1992" "10:31:18" "SC PCM 5-40, >40 with >5 " -299.923 81.71 11 .0000 .7287 5.5902E-02
1.5134E-02
"06/25/1992" "10:53:08" "PS PCM 5-40, >40 and <0.3, >5 " -276.320 19.51 10 3.3427E-02 2.1545E-02 2.1116E-02
.9573 2.7270E-02 1.2536E-02
"06/25/1992" "10:32:46" "FBC PCM 5-40, >40 and <0.3 (there are no fibers >5) " -277.767 22.97 11 1.7084E-02 .9986 2.8292E-02
.1139
"06/25/1992" "10:32:49" "SC PCM 5-40, >40 and <0.3, >5 (no discharged chrysotile) " -248.966 8.273 8 .4067 1.9186E-03 4.6766E-03
.1770 2.4251E-02 6.5809E-02
"06/25/1992" "10:32:56" "PS PCM 5-40, >40 and <0.3, >5 (no discharged chrysotile) " -252.063 14.90 9 9.3166E-02 1.7562E-02 5.3984E-02
.9285 2.4971E-02 1.2388E-02
"06/25/1992" "10:32:58" "FBC PCM 5-40, >40 and <0.3 (there are no fibers >5) (no discharged chrysotile) " -255.100 21.82 10 1.5245E-02 .9985 2.7767E-02
.1133
"06/25/1992" "10:33:01" "SC PCM(16) 5-40, >40 and <0.3, >5 " -309.395 49.04 12 .0000 1.7750E-03 .0000
.1332 3.9379E-02 6.9539E-02
"06/25/1992" "10:53:11" "SC PCM(16) 5-40, >40 with >5, <0.3 (no discharged chrysotile) " -285.380 45.29 11 .0000 .0000 2.1511E-03
.8193 3.7799E-02 6.2884E-02

"06/26/1992" "15:45:42" "SC PCM <5, >5 with W <0.3, >5 " -294.370 61.95 11 .0000 .0000 .0000
.9799 3.5380E-02 4.1829E-03
"06/26/1992" "15:45:47" "SC PCM <5, >5 with W <0.3 and AR>=20, >5 " -294.170 61.28 11 .0000 .0000 .0000

.9779 3.4927E-02 4.1831E-03
"06/26/1992" "15:45:49" "SC PCM 5-40, >40 with AR>=20, >5 (4 categories) " -277.958 23.15 11 1.6070E-02 7.1418E-03 .0000
.9929 2.7947E-02 1.4448E-02
"06/26/1992" "15:45:52" "SC PCM 5-40, >40 with <0.3, 0.3-5, >5 " -272.935 12.19 10 .2716 1.7176E-03 .0000
.0000 .8530 .1453 2.5612E-02 7.0424E-02
"06/26/1992" "15:46:03" "SC PCM 5-40, >40 with <0.3, >5 (but exclude all M and MS) " -272.935 12.19 10 .2716 1.7176E-03 .0000
.1453 2.5612E-02 7.0424E-02
"06/26/1992" "15:46:08" "SC PCM 5-40, >40 with <0.3, >5 (2 studies) " -300.312 11.46 9 .2451 .1256 3.3596E-02
7.8526E-02
"06/26/1992" "15:46:08" "SC PCM 5-40, >40 with <0.3, >5 (2 studies) " -300.312 11.46 9 .2451 .1256 2.1933E-02
7.2764E-02
"06/26/1992" "15:46:20" "SC PCM 5-40, >40 with <0.3, >5 (chrysostile only) " -199.150 8.438 3 3.7044E-02 7.3631E-04 1.5232E-02
2.7287E-02 3.2171E-02 .1319
"06/26/1992" "15:46:30" "SC PCM 5-40, >40 with <0.3, >5 (amphiboles only) " -100.725 2.344 3 .5038 2.2569E-04 .0000
.1014 2.4772E-02 8.5164E-02
"06/26/1992" "15:46:32" "SC PCM 5-40, >40 with <0.3 and AR>=20, >5 (2 studies) " -300.286 11.41 9 .2481 .1283 3.3499E-02
7.7677E-02
"06/26/1992" "15:46:32" "SC PCM 5-40, >40 with <0.3 and AR>=20, >5 (2 studies) " -300.286 11.41 9 .2481 .1283 2.1909E-02
7.2156E-02
"06/26/1992" "15:46:42" "SC PCM 5-40, >40 with <0.3 and AR>=20, >5 (chrysotile only) " -199.150 8.438 3 3.7048E-02 8.5321E-04 1.4942E-02
3.3975E-02 3.2170E-02 .1252
"06/26/1992" "15:46:50" "SC PCM 5-40, >40 with <0.3 and AR>=20, >5 (amphiboles only) " -100.723 2.337 3 .5051 2.6046E-04 .0000
.1018 2.4718E-02 8.4964E-02
"06/26/1992" "17:18:46" "SC PCM 5-40, >40 with >5 (C and CS only), <0.3 (FBC only) (2 studies) " -300.289 11.34 8 .1824 .8903 3.3130E-02
8.6976E-02
"06/26/1992" "17:18:46" "SC PCM 5-40, >40 with >5 (C and CS only), <0.3 (FBC only) (2 studies) " -300.289 11.34 8 .1824 .8903 2.1784E-02
7.5613E-02
"06/26/1992" "17:19:12" "SC PCM 5-40, >40 with >5 (C and CS only), <0.3 (FBC only) (chrysotile only) " -199.150 8.438 3 3.7044E-02 1.5135E-02 7.5254E-04
.9546 3.2171E-02 .1304
"06/26/1992" "17:19:48" "SC PCM 5-40, >40 with >5 (C and CS only), <0.3 (FBC only) (amphiboles only) " -100.724 2.341 3 .5043 .0000 2.3382E-04
.8983 2.4743E-02 8.5096E-02
"06/26/1992" "17:19:51" "SC PCM 5-40, >40 with >5, <0.3 (no discharged) (2 studies) " -276.253 7.248 7 .4031 .8852 3.1198E-02
9.5056E-02
"06/26/1992" "17:19:51" "SC PCM 5-40, >40 with >5, <0.3 (no discharged) (2 studies) " -276.253 7.248 7 .4031 .8852 2.1220E-02
7.3280E-02
"06/26/1992" "17:20:27" "SC PCM 5-40, >40 with >5, <0.3 (chrysotile only - no discharged) " -174.593 3.399 2 .1821 3.4305E-02 1.5901E-03
.7876 3.0145E-02 6.0929E-02
"06/26/1992" "15:47:32" "SC PCM 5-40, >40 with <0.3 and AR>=20, >5 (no discharged) (2 studies) " -276.253 7.262 7 .4017 .1027 3.1189E-02
9.3412E-02
"06/26/1992" "15:47:32" "SC PCM 5-40, >40 with <0.3 and AR>=20, >5 (no discharged) (2 studies) " -276.253 7.262 7 .4017 .1027 2.1218E-02
7.2605E-02
"06/26/1992" "15:47:47" "SC PCM 5-40, >40 with <0.3 and AR>=20, >5 (chrysotile only - no discharged) " -174.593 3.397 2 .1823 2.0719E-03 3.6781E-02

.2255 3.0158E-02 5.1641E-02
"06/26/1992" "15:48:06" "SC PCM 5-40, >40 with AR>=20, >5 (4 categories) (no discharged) (2 studies) " -279.340 13.11 9 .1571 .9916 3.1665E-02
1.3384E-02
"06/26/1992" "15:48:06" "SC PCM 5-40, >40 with AR>=20, >5 (4 categories) (no discharged) (2 studies) " -279.340 13.11 9 .1571 .9916 2.1102E-02
1.9317E-02
"06/26/1992" "15:48:13" "SC PCM 5-40, >40 with AR>=20, >5 (4 categories)(chrysotile only - no discharged)" -174.600 3.396 2 .1823 1.1242E-03 .3689
2.1254E-11 3.0232E-02 1.2891E-02
"06/26/1992" "15:48:16" "SC PCM 5-40, >40 with AR>=20, >5 (4 categories) (amphiboles only) " -103.580 6.615 4 .1569 1.3691E-02 .0000
.9863 1.9872E-02 1.5860E-02
"06/26/1992" "15:48:17" "SC PCM 5-40, >40 with AR>=3, >5 (4 categories) (amphiboles only) " -105.610 10.10 4 3.7986E-02 8.0680E-03 .0000
.9919 2.0367E-02 1.3821E-02
"06/26/1992" "15:48:19" "SC PCM 5-40, >40 with AR>=5, >5 (4 categories) (amphiboles only) " -105.251 9.464 4 4.9692E-02 8.4672E-03 .0000
.9915 2.0225E-02 1.3745E-02
"06/26/1992" "15:48:21" "SC PCM 5-40, >40 with AR>=10, >5 (4 categories) (amphiboles only) " -104.569 8.284 4 8.0934E-02 9.2017E-03 .0000
.9908 2.0025E-02 1.4364E-02
"06/26/1992" "15:48:23" "SC PCM 5-40, >40 with AR>=30, >5 (4 categories) (amphiboles only) " -103.778 6.865 4 .1425 2.3034E-02 .0000
.9770 2.0138E-02 1.6260E-02
"06/26/1992" "15:48:24" "SC PCM 5-40, >40 with AR>=50, >5 (4 categories) (amphiboles only) " -103.554 6.499 4 .1641 5.9731E-02 .0000
.9403 2.0684E-02 1.7099E-02
"06/26/1992" "15:48:26" "SC PCM <5, 5-40, >40 with <0.3, >5 (no discharged chrysotile) " -248.966 8.273 8 .4067 .0000 .0000
1.9186E-03 4.6766E-03 .1770 2.4251E-02 6.5809E-02
"06/26/1992" "15:48:36" "SC PCM 5-40, >40 with <0.3, 0.3-5, >5 (no discharged chrysotile) " -248.966 8.273 8 .4067 1.9186E-03 .0000
4.6766E-03 .8164 .1770 2.4251E-02 6.5809E-02
"06/26/1992" "18:00:06" "SC PCMQ >10 (all structures AR>=3,W>0.2) (no WDC chrysotile or tremolite) " -223.907 24.09 9 3.4107E-03 .9521 2.3551E-02
1.0063E-02
"06/26/1992" "18:10:08" "SC PCMQ <10,10-20,>20 (all structures AR>=3,W>0.2) (no WDC chrysotile/tremolite)" -221.562 19.60 8 1.1142E-02 .1793 3.3351E-13
2.3184E-02 4.3772E-04
"06/30/1992" "10:44:26" "PS PCM, USING SUM OF SURFACE AREA INSTEAD OF THE SUM OF THE NUMBER OF STRUCTURES" -285.826 39.16 11 .0000 .5002 2.9496E-02
1.0475E-06
"06/30/1992" "10:44:27" "PS PCM, USING SUM OF VOLUME INSTEAD OF THE SUM OF THE NUMBER OF STRUCTURES " -291.704 55.77 11 .0000 .5002 4.7021E-02
1.0362E-06

"07/01/1992" "15:49:07" "SC PCM 5-40, >50 and W >5, <0.3 (all structures AR>=20) (no discharged) " -253.886 19.50 9 2.0509E-02 .0000 7.6482E-04
.3941 2.7504E-02 .2366

"07/02/1992" "11:56:05" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, >=40 and W <0.3, >=5 " -272.586 11.47 8 .1757 .0000 .0000
1.1629E-03 .0000 5.3055E-03 .0000 .0000 .0000 .0000 6.1057E-02 .1258 2.4594E-02 6.9386E-02
"07/02/1992" "11:57:25" "SC PCM <5, 5-10, 10-20, 20-30, 30-40, >=40 and W <0.3, >=5 (no discharged) " -248.218 6.779 6 .3412 .0000 .0000
9.5393E-04 .0000 6.7145E-03 1.9149E-02 .0000 .0000 .0000 8.2033E-02 .1382 2.2930E-02 6.7034E-02
"07/02/1992" "13:14:24" "SC PCM >=5 and W <0.3, >=5 (no discharged chrysotile) " -267.012 49.63 10 .0000 .9815 3.0991E-02
5.0646E-03
"07/02/1992" "13:14:26" "SC PCM 5-40, >=40 (no discharged chrysotile) " -261.069 31.75 10 .0000 .9907 2.8947E-02

5.4757E-03
"07/02/1992" "13:14:29" "SC PCM >=5 (no discharged chrysotile) " -285.450 103.2 10 .0000 .9875 5.7855E-02
7.0975E-03
"07/02/1992" "13:14:31" "SC PCM 5-40 and W <0.3, >=5 (no discharged chrysotile) " -283.414 99.33 10 .0000 .9753 5.5205E-02
4.4280E-03
"07/02/1992" "13:14:33" "SC PCM 5-40 (no discharged chrysotile) " -286.783 107.2 10 .0000 .9671 6.2602E-02
2.6253E-03
"07/02/1992" "13:14:50" "SC PCM <5, 5-40, >=40 and W <0.3, >=5 (no discharged chrysotile) " -248.966 8.273 8 .4067 .0000 .0000
1.9186E-03 4.6766E-03 .1770 2.4251E-02 6.5809E-02
"07/02/1992" "13:15:02" "SC PCM <5, 5-40, >=40 (no discharged chrysotile) " -261.069 31.75 10 .0000 .0000 .9907
2.8947E-02 5.4757E-03
"07/02/1992" "13:14:35" "SC PCM <5, >=5 and W <0.3, >=5 (no discharged chrysotile) " -267.012 49.63 10 .0000 .0000 .0000
.9815 3.0991E-02 5.0646E-03
"07/02/1992" "13:14:39" "SC PCM <5 and W <0.3 (there are no fibers W >= 5) (no discharged chrysotile) " -301.986 132.5 10 .0000 .6775 .1194
2.0883E-05
"07/02/1992" "13:14:41" "SC PCM <5, >=5 (no discharged chrysotile) " -285.450 103.2 11 .0000 1.000 5.7855E-02
8.8654E-05
"07/02/1992" "13:14:43" "SC PCM <5 (no discharged chrysotile) " -301.288 132.0 10 .0000 .6657 .1169
1.6960E-05
"07/02/1992" "13:14:45" "SC PCM 5-40, >=40 and W >=5 (no discharged chrysotile) " -267.213 60.09 10 .0000 .9371 5.1633E-02
1.6962E-02
"07/02/1992" "13:14:46" "SC PCM 5-40, >=40 and W <0.3 (no discharged chrysotile) " -260.510 33.58 10 .0000 .9982 3.3808E-02
.1069
"07/02/1992" "14:50:19" "SC PCM <5,5-10,10-20,20-40,>=40 and <0.15,0.15-0.3,0.3-1,1-5,>=5 (no discharged)" -248.178 6.674 6 .3515 .0000 .0000
.0000 .0000 .0000 .0000 2.5839E-03 .0000 .0000 .0000 .1706 .0000 .0000 .0000 .0000 2.5171E-02 .0000
.0000 .0000 6.0103E-02 .0000 .5370 .0000 .2046 2.2673E-02 5.5023E-02
"07/02/1992" "15:42:07" "SC M(14) <5,5-10,10-20,20-40,>=40 and <0.15,0.15-0.3,0.3-1,1-5,>=5 " -279.614 23.57 9 4.2818E-03 .0000 .0000
.0000 .0000 .0000 1.5838E-02 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000
.0000 .0000 .0000 .0000 .8857 2.5155E-02 7.3297E-02 2.1648E-02 .2244
"07/02/1992" "15:43:31" "SC PCM <5,5-10,10-20,20-40,>=40 and <0.15,0.15-0.3,0.3-1,1-5,>=5 " -272.616 11.60 7 .1137 .0000 .0000
.0000 .0000 .0000 .0000 1.8178E-03 .0000 .0000 .0000 3.3464E-02 .0000 .0000 .0000 .0000 .1020 .0000
.0000 .0000 1.7003E-02 .0000 .7188 .0000 .1269 2.4549E-02 7.7920E-02
"07/02/1992" "16:13:33" "SC M(14) <5, 5-10, 10-20, 20-40, >=40 and >=5, 1-5, 0.3-1, 0.15-0.3, <0.15 " -279.614 23.57 8 1.8615E-03 .0000 .0000
.0000 .0000 .0000 .0000 .0000 .0000 .0000 1.5838E-02 .0000 .0000 .0000 .0000 .0000 .0000 .0000
.0000 .0000 .0000 7.3297E-02 .0000 2.5155E-02 -1.2727E-09 2.1648E-02 .2244
"07/02/1992" "16:30:29" "SC PCM <5, 5-10, 10-20, 20-40, >=40 and >=5, 1-5, 0.3-1, 0.15-0.3, <0.15 " -272.616 11.60 6 7.0614E-02 .0000 .0000
.0000 .0000 .0000 .0000 .0000 .0000 1.8178E-03 .0000 .0000 .0000 .0000 .0000 3.3464E-02 1.7003E-02 .0000
.0000 .0000 .1020 .1269 .0000 .0000 -1.9608E-09 2.4549E-02 7.7920E-02
"07/02/1992" "17:20:59" "SC PCM <5, 5-10, 10-20, 20-40, >=40 and <0.3, 0.3-1, 1-5, >=5 " -272.680 11.64 8 .1674 .0000 .0000
.0000 .0000 1.2014E-03 .0000 .0000 .0000 5.4344E-03 .0000 .0000 .0000 .0000 .0000 .0000 1.1976E-02 .8382
.0000 .1431 2.4572E-02 6.7829E-02
"07/02/1992" "17:18:45" "SC PCM <5, 5-10, 10-20, 20-40, >=40 and <0.3, 0.3-1, 1-5, >=5 (with CI) " -272.680 11.64 8 .1674 .0000 .0000

.0000 .0000 1.2014E-03 .0000 .0000 .0000 5.4344E-03 .0000 .0000 .0000 .0000 .0000 .0000 1.1976E-02 .8382
.0000 .1431 2.4572E-02 6.7829E-02

"07/06/1992" "09:32:37" "SC PCM >=40 and W <0.3, >=5 " -310.173 118.6 11 .0000 .2645 9.1781E-02
5.7162E-02
"07/06/1992" "10:57:33" "SC PCM (no length or width categories) " -322.668 131.4 11 .0000 .6354 .1125
1.3791E-05
"07/06/1992" "10:57:42" "SC PCM length >= 5 " -309.474 107.2 11 .0000 .9691 6.3273E-02
2.5174E-03
"07/06/1992" "11:18:57" "SC PCM (no length or width categories) " -322.668 131.4 11 .0000 .6354 .1125
1.3791E-05
"07/06/1992" "11:19:00" "SC PCM length >= 5 " -309.474 107.2 11 .0000 .9691 6.3273E-02
2.5174E-03
"07/06/1992" "11:33:31" "PS PCM <5, 5-10, 10-20, 20-40, >=40 and W <0.15, 0.15-0.3, 0.3-1, 1-5, >=5 " -273.275 12.67 7 7.9868E-02 .0000 .0000
.0000 .0000 .0000 5.4514E-03 .0000 .0000 .0000 .0000 .4190 3.9527E-02 .0000 .0000 4.3412E-02 .0000 .0000
.0000 .0000 7.3795E-02 .0000 .0000 .0000 .4188 2.3729E-02 2.3807E-02
"07/06/1992" "13:44:41" "PS M(14) <5, 5-10, 10-20, 20-40, >=40 and W <0.15, 0.15-0.3, 0.3-1, 1-5, >=5 " -275.607 15.73 8 4.5597E-02 .0000 .0000
.0000 .0000 .0000 7.9976E-02 .0000 .0000 .0000 .0000 .3587 5.1851E-03 .0000 .0000 .0000 .0000 .0000
.0000 .0000 .0000 .0000 .0000 .2160 .3401 2.1931E-02 8.7607E-02
"07/06/1992" "15:20:12" "SC PCM <5, 5-10, 10-20, 20-40, >=40 and W <0.1, 0.1-0.3, 0.3-1, 1-5, >=5 " -272.609 11.58 7 .1146 .0000 .0000
.0000 .0000 .0000 .0000 1.7628E-03 .0000 .0000 .0000 3.8041E-02 .0000 .0000 .0000 .0000 9.6416E-02 .0000
.0000 .0000 1.2887E-02 .0000 .7253 .0000 .1256 2.4639E-02 7.9469E-02

"07/07/1992" "13:28:40" "SC PCM <5, 5-10, 10-20, 20-40, >=40 and Complex, >=1, 0.3-1, 0.15-0.3, <0.15 " -274.051 14.09 6 2.7817E-02 .0000 .0000
.0000 .0000 .0000 .0000 .0000 .0000 1.2681E-03 .0000 .0000 7.6933E-03 .0000 .0000 .0000 .0000 .0000
.0000 .0000 .1038 4.4982E-02 .0000 6.8896E-03 -1.8720E-10 2.3811E-02 9.7120E-02
"07/07/1992" "14:46:55" "PS PCM <5, 5-10, 10-20, 20-40, >=40 and Complex, >=1, 0.3-1, 0.15-0.3, <0.15 " -294.903 61.42 10 .0000 .0000 .0000
.0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .2615 .0000 .0000 .7385 .0000
.0000 .0000 .0000 .0000 .0000 .0000 -1.0440E-08 3.4370E-02 2.4421E-03
"07/07/1992" "15:06:25" "PS PCM <5, 5-10, 10-20, 20-40, >=40 and W <0.15, 0.15-0.3, 0.3-1, >=1, Complex " -274.044 14.95 6 1.9811E-02 .0000 .0000
.0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .4217 .0000 .0000 .2071 2.8387E-03 2.8200E-04 .0000
.0000 .0000 1.0417E-02 .0000 .0000 .3577 -1.1622E-08 2.4136E-02 4.6418E-02
"07/07/1992" "15:24:54" "PS PCM 5-10, 10-20, 20-40, >=40 and W <0.15, 0.15-0.3, 0.3-1, >=1, Complex " -275.101 17.10 6 8.0952E-03 .0000 .0000
.0000 .0000 .0000 .2655 .0000 .0000 .2317 4.4614E-04 .0000 .0000 2.5093E-02 .0000 2.7684E-02 .0000 .0000
.4496 -1.8055E-07 2.6883E-02 3.3488E-02
"07/07/1992" "15:30:50" "PS PCM 5-10, 10-20, 20-40, >=40 and Complex, >=1, 0.3-1, 0.15-0.3, <0.15 " -274.044 14.95 7 3.5898E-02 .0000 .0000
.0000 .0000 .0000 2.8399E-03 .2072 .0000 .0000 .4218 1.0419E-02 .0000 .0000 .0000 .0000 .0000 .0000
.3578 -7.4710E-09 2.4136E-02 4.6405E-02
"07/07/1992" "15:50:02" "PS PCM 5-10, 10-20, 20-40, >=40 and Complex, >=1, 0.4-1, 0.2-0.4, <0.2 " -273.078 12.73 8 .1208 .0000 .0000
.0000 .0000 .0000 3.1200E-03 5.6519E-02 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .2888 .0000 .0000
.0000 1.4806E-10 2.4043E-02 .1039
"07/07/1992" "16:31:01" "SC PCM 5-10, 10-20, 20-40, >=40 and Complex, >=1, 0.4-1, 0.2-0.4, <0.2 " -272.998 12.43 6 5.2239E-02 .0000 .0000

.0000 1.5795E-03 .0000 .0000 4.9393E-02 .0000 1.1903E-02 .0000 .0000 .0000 .0000 2.1272E-03 .0000 3.0210E-02 .0000
.0000 1.5002E-10 2.4148E-02 3.9445E-02
"07/07/1992" "16:56:39" "PS PCM 5-10, 10-20, 20-40, >=40 and Complex, >=1, 0.4-1, <0.4 " -278.198 21.79 9 8.8203E-03 .0000 .0000
.0000 .0000 .0000 .4346 .0000 .0000 .0000 .0000 .0000 .1909 .3745 .0000 -1.0420E-06 2.2334E-02 1.3918E-02

"07/08/1992" "08:36:46" "PS PCM <5, 5-10, 10-20, 20-40, >=40 and W <0.4, 0.4-1, >=1, Complex " -274.519 14.77 6 2.1279E-02 .0000 .0000
.0000 .0000 .0000 .0000 .0000 .0000 .0000 6.1242E-02 8.8340E-04 2.0129E-02 5.4116E-02 .0000 1.2797E-02 .8508
.0000 -7.3093E-07 2.5732E-02 7.1660E-02
"07/08/1992" "08:42:38" "PS PCM <5, 5-10, 10-20, 20-40, >=40 and Complex, >=1, 0.4-1, <0.4 " -273.814 14.11 9 .1177 .0000 .0000
.0000 .0000 .0000 .0000 .0000 .0000 3.9837E-03 3.0906E-02 .0000 .0000 .0000 .0000 .0000 3.2175E-02 .0000
.0000 .9329 2.4067E-02 9.1268E-02
"07/08/1992" "09:04:18" "PS PCM >=40, 20-40, 10-20, 5-10, <5 and Complex, >=1, 0.4-1, <0.4 " -292.314 55.42 10 .0000 .0000 .0000
.0000 .0000 .6995 .0000 .0000 .0000 .0000 .0000 .0000 .3005 .0000 .0000 .0000 .0000 .0000
.0000 -4.5399E-07 3.0207E-02 2.7264E-03
"07/08/1992" "09:09:10" "PS PCM >=40, 20-40, 10-20, 5-10, <5 and W <0.4, 0.4-1, >=1, Complex " -298.842 69.62 10 .0000 .0000 .0000
.0000 .0000 .0000 .0000 .0000 .9993 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 6.9620E-04
.0000 -2.5203E-07 4.4540E-02 2.2204E-03
"07/08/1992" "09:16:06" "PS PCM <5, 5-10, 10-20, 20-40, >=40 and Complex, <0.4, 0.4-1, >=1 " -273.814 14.11 8 7.8127E-02 .0000 .0000
.0000 .0000 .0000 .0000 .0000 .0000 3.9837E-03 .0000 .0000 3.0906E-02 .0000 3.2175E-02 .0000 .0000 .0000
.9329 2.6822E-10 2.4067E-02 9.1268E-02
"07/08/1992" "09:24:17" "PS PCM <5, 5-10, 10-20, 20-40, >=40 and Complex, <0.4, >=1, 0.4-1 " -292.314 55.42 10 .0000 .0000 .0000
.0000 .0000 .0000 .0000 .0000 .0000 .0000 .3006 .0000 .0000 .6994 .0000 .0000 .0000 .0000
.0000 -1.2442E-06 3.0200E-02 2.7271E-03
"07/08/1992" "09:27:24" "PS PCM 5-10, 10-20, 20-40, >=40 and Complex, <0.4, 0.4-1, >=1 " -273.814 14.11 8 7.8127E-02 .0000 .0000
.0000 .0000 3.9837E-03 .0000 .0000 3.0906E-02 .0000 3.2175E-02 .0000 .0000 .0000 .9329 1.4118E-10 2.4067E-02 9.1268E-02
"07/08/1992" "09:57:02" "PS PCM <5, 5-10, 10-20, 20-40,>=40 and W <0.4, 0.4-1, >=1(no complex structures)" -275.298 16.34 7 2.1478E-02 .0000 1.2928E-03
.0000 .0000 .0000 .0000 .0000 .0000 4.5807E-02 1.8949E-02 3.3914E-02 .0000 .9000 -1.1481E-05 2.7020E-02 8.8065E-02
"07/08/1992" "10:17:31" "PS PCM <5, 5-10, 10-20, 20-40,>=40 and W >=1, 0.4-1, <0.4(no complex structures)" -275.298 16.34 8 3.6935E-02 .0000 1.2930E-03
.0000 .0000 .0000 .0000 4.5810E-02 .0000 .0000 .0000 3.3927E-02 1.8952E-02 .0000 .9000 2.6966E-02 8.8070E-02
"07/08/1992" "13:34:26" "PS PCM <5,5-10,10-20,20-40,>=40 and >=1, 0.4-1, <0.4 and Complex with 6 lengths " -273.774 14.04 7 4.9819E-02 .0000 .0000
.0000 .0000 .0000 .0000 3.7007E-02 .0000 .0000 .0000 .0000 3.4493E-02 .0000 .0000 .9198 .0000 2.8166E-03
5.9101E-03 .0000 5.3636E-10 2.3957E-02 8.8626E-02
"07/08/1992" "14:44:47" "SC PCM <5,5-10,10-20,20-40,>=40 and >=1, 0.4-1, <0.4 and Complex with 6 lengths " -311.176 143.3 10 .0000 .0000 .0000
.0000 .0000 .0000 .0000 .0000 5.4027E-05 .9999 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000
.0000 .0000 -9.9125E-08 1.4853E-02 9.5085E-04
"07/08/1992" "14:48:02" "SC PCM Complex with 6 lengths and <5,5-10,10-20,20-40,>=40 and >=1, 0.4-1, <0.4 " -293.905 58.17 9 .0000 .0000 .0000
.0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 1.5413E-05 .1811 .0000 .8189
.0000 .0000 -1.8353E-07 4.1522E-02 3.4939E-03
"07/08/1992" "14:58:17" "SC PCM <5,5-10,10-20,20-40,>=40 and <0.4, 0.4-1, >=1 and Complex with 6 lengths " -272.749 11.85 7 .1049 .0000 .0000
.0000 6.5666E-04 .0000 .0000 6.0087E-03 .0000 5.8557E-02 2.6025E-02 .0000 .0000 .8173 .0000 .0000 .0000 .0000
.0000 .0000 9.1494E-02 2.4199E-02 3.6281E-02
"07/08/1992" "15:13:14" "SC PCM <5,5-10,10-20,20-30,>30 for<.3 and 5-10,10-20,20-30,30-40,40-50,>50 for>5" -274.867 15.39 8 5.1113E-02 .0000 3.3674E-03

.0000 7.4658E-02 .4261 .0000 .0000 .0000 .2326 .2633 2.3275E-02 3.2685E-02
"07/08/1992" "15:45:37" "SC PCM <5,5-10,10-20,20-40,>=40 and <0.3, 0.3-1, >=1 and Complex with 6 lengths " -272.964 12.11 7 9.6267E-02 .0000 .0000
.0000 6.3774E-04 .0000 .0000 4.1770E-03 .0000 1.8608E-02 .0000 .0000 .0000 .8789 2.3299E-02 .0000 .0000 .0000
.0000 .0000 7.4421E-02 2.4148E-02 7.5365E-02

"07/09/1992" "09:11:08" "SC PCM <5,5-10,10-20,20-40,>=40 and <0.4, 0.4-1, >=1 and C and CS with 6 lengths" -272.749 11.85 7 .1049 .0000 .0000
.0000 6.5666E-04 .0000 .0000 6.0087E-03 .0000 5.8557E-02 2.6025E-02 .0000 .0000 .8173 .0000 .0000 .0000 .0000
.0000 .0000 9.1494E-02 2.4199E-02 3.6281E-02
"07/09/1992" "11:30:24" "SC PCM 5-40, >=40 and W <0.3 " -277.690 22.79 11 1.8207E-02 .9986 2.8284E-02
.1140
"07/09/1992" "11:30:28" "SC PCM 5-40, >=40 and W >5 " -299.923 81.71 11 .0000 .7287 5.5902E-02
1.5134E-02
"07/09/1992" "11:30:29" "SC PCM 5-40 and W <0.3, >5 " -309.212 107.4 11 .0000 .9697 6.2884E-02
3.3178E-03
"07/09/1992" "11:30:31" "SC PCM 5-40, >=40 and W <0.3, >5 and Length < 5 (no widths) (with 95% CI) " -318.153 159.1 9 .0000 8.1546E-02 .0000
.6999 -1.6245E-07 1.5694E-02 2.9785E-03
"07/09/1992" "12:05:26" "SC PCM <8, 8-15, 15-25, 25-40, >=40 and W <0.3, >=5 " -272.701 11.78 9 .2254 .0000 .0000
5.6375E-03 .0000 .0000 3.8505E-02 .0000 .0000 .1430 2.3986E-02 7.0573E-02
"07/09/1992" "12:05:47" "SC PCM 10-20, 20-40, >=40 and W <0.3, >=5 " -273.565 13.25 9 .1508 1.4457E-02 .0000
.0000 8.5144E-03 .1634 2.3902E-02 5.9924E-02
"07/09/1992" "14:31:48" "SC PCM <5, 5-10, 10-20, 20-40, >=40 and <0.4, 0.4-1 and Complex with 6 lengths " -273.213 12.51 8 .1290 .0000 .0000
.0000 .0000 1.0729E-02 3.2242E-03 .0000 .0000 .8210 .0000 .0000 .0000 .0000 7.6252E-02 8.8839E-02 2.4809E-02 3.9978E-02
"07/09/1992" "14:55:48" "SC PCM 5-40, >=40 and W <0.3, >5 (multipy control animals/response by 10^6) " -2.774611E+07 12.11 10 .2770 1.7130E-03 .0000
.1450 2.6668E-02 7.0300E-02
"07/09/1992" "15:18:32" "SC PCM 5-40,>=40 and W<0.3,>5 (2 studies) (control animals/response * 10^6) " -5.549198E+07 12.10 9 .2074 .1240 2.6668E-02
8.1133E-02
"07/09/1992" "15:18:32" "SC PCM 5-40,>=40 and W<0.3,>5 (2 studies) (control animals/response * 10^6) " -5.549198E+07 12.10 9 .2074 .1240 2.6668E-02
7.1689E-02
"07/09/1992" "15:46:24" "SC M(16) <5, 5-10, 10-20, 20-40, >=40 and <0.15, 0.15-0.3, 0.3-1, 1-5, >=5 " -310.198 37.43 11 .0000 .0000 .0000
.0000 .0000 .0000 1.7778E-02 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000
.0000 .0000 .0000 .0000 .9076 1.9604E-02 5.5023E-02 2.2577E-02 .2350
"07/09/1992" "15:47:33" "PS M(16) <5, 5-10, 10-20, 20-40, >=40 and <0.15, 0.15-0.3, 0.3-1, 1-5, >=5 " -304.903 25.27 10 4.0203E-03 .0000 .0000
.0000 .0000 .0000 .1318 .0000 .0000 .0000 .0000 .1955 .0000 .0000 .0000 .0000 .0000 8.3400E-02
.0000 .0000 .0000 .0000 .0000 .1961 .3931 2.1022E-02 7.2003E-02
"07/09/1992" "16:06:08" "SC PCM Length < 5 (no widths) and 5-40, >=40 and W <0.3, >5 (with 95% CI) " -272.935 12.19 10 .2716 .0000 1.7176E-03
.0000 .1453 2.5612E-02 7.0424E-02
"07/09/1992" "17:22:46" "PS PCM(F&B)5-10,10-20,20-40,>40 and<.4,.4-1,>1 C only and CS with 6 length cat." -272.433 11.32 6 7.8319E-02 .0000 .0000
.0000 .0000 2.1747E-03 7.1876E-02 5.3176E-02 .0000 .0000 .7673 .0000 .0000 .0000 .0000 .0000 .0000 .0000
.1045 9.8618E-04 .0000 .0000 .0000 -5.1981E-08 2.4947E-02 6.3726E-02

"07/10/1992" "09:34:47" "SC PCM Length < 5 (no widths) and 5-40, >=40 and W >5, <0.3 (with 95% CI) " -272.935 12.19 10 .2716 .0000 .0000
1.7176E-03 .8530 2.5612E-02 7.0424E-02

"07/10/1992" "10:28:12" "SC PCM <5,5-10,10-20,20-40,>=40 and <0.15,0.15-0.3,0.3-1,1-5,>=5 (Mesotheliomas)" -60.6932 14.64 9 .1005 .0000 .0000
.0000 1.5443E-03 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000
.4446 .0000 .5538 .0000 .0000 .0000 -5.0341E-08 4.6448E-03 6.0542E-04
"07/10/1992" "11:30:52" "SC PCM <5,5-10,10-20,20-40,>=40 and >=5,1-5,0.3-1,0.15-0.3,<0.15 (Mesotheliomas)" -59.0535 12.20 9 .2015 .0000 .0000
.0000 .0000 7.4663E-05 7.7508E-02 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000
.0000 .0000 .0000 .0000 .0000 .0000 4.2322E-10 1.4830E-03 1.1808E-02
"07/10/1992" "12:20:58" "SC PCM <5,5-10,10-20,20-40,>=40 & >=.3,.15-.3,<.15 & Complex w/6 lengths (Meso.)" -60.6227 14.73 9 9.7866E-02 .0000 .0000
.0000 .0000 .0000 .0000 5.4696E-02 .0000 .8768 6.8520E-02 .0000 .0000 .0000 .0000 .0000 .0000 .0000
.0000 .0000 .0000 -1.9458E-08 4.3684E-03 7.3528E-04
"07/10/1992" "12:15:35" "SC PCM <5,5-10,10-20,20-40,>=40 & <.15,.15-.3,>=.3 & Complex w/6 lengths (Meso.)" -60.6067 14.72 8 6.4088E-02 .0000 .0000
.0000 .0000 .0000 .0000 .8618 .0000 3.1225E-02 .0000 .0000 9.6821E-02 .0000 .0000 .0000 .0000 .0000
.0000 1.0111E-02 .0000 -5.4691E-08 4.2054E-03 9.5365E-04
"07/10/1992" "12:29:04" "SC PCM Complex w/6 lengths & <5,5-10,10-20,20-40,>=40 & <.15,.15-.3,>=.3 (Meso.)" -59.3875 11.93 9 .2167 .0000 .0000
.0000 .0000 .0000 .0000 9.2717E-05 .0000 .0000 .0000 .0000 .0000 2.9416E-03 .0000 .0000 .0000 .0000
.0000 .0000 .9970 -1.6111E-06 4.7046E-03 1.0201E-02
"07/10/1992" "12:32:22" "SC PCM Complex w/6 lengths & <5,5-10,10-20,20-40,>=40 & >=.3,.15-.3,<.15 (Meso.)" -60.7657 15.50 9 7.7300E-02 .0000 .0000
.0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .1489 .0000 .5814 .2697 .0000
.0000 .0000 .0000 -1.5832E-08 4.6132E-03 2.6062E-04
"07/10/1992" "13:46:21" "SC PCM Complex w/6 lengths & <5,5-10,10-20,20-40,>=40 & <.15,>=.3,.15-.3 (Meso.)" -59.3238 12.04 10 .2815 .0000 .0000
.0000 .0000 .0000 .0000 7.8080E-05 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .1022 .0000
.0000 .0000 .0000 .8977 4.6447E-03 1.1447E-02
"07/10/1992" "14:23:02" "SC PCM >= 20 " -282.315 28.39 11 2.0676E-03 .2055 .7945
2.5406E-02 1.0021E-02
"07/10/1992" "15:20:11" "SC PCM >= 20 and < 0.4 " -285.310 39.84 11 .0000 .4983 .5017
2.6927E-02 1.2277E-02

"07/16/1992" "09:13:25" "SC PCM <5, 5-10, 10-20, 20-40, >=40 & <0.4 and Complex only with 6 lengths " -273.250 12.63 7 8.0924E-02 .0000 1.5099E-04
1.0898E-02 4.2320E-03 .8006 .0000 .0000 .0000 .1114 .0000 7.2753E-02 2.4602E-02 4.1308E-02
"07/16/1992" "09:14:13" "SC PCM <5, 5-10, 10-20, 20-40, >=40 & <0.2, 0.2-0.4 and Complex only w/6 lengths" -273.150 12.42 8 .1328 .0000 .0000
.0000 6.5172E-04 .0000 1.4206E-02 .0000 .0000 .0000 .8095 .0000 .0000 .0000 .1250 .0000 5.0575E-02 2.4376E-02
4.2294E-02
"07/16/1992" "16:17:33" "SC PCM <5, 5-10, 10-20, 20-40, >=40 & >=1, 0.4-1, <0.4 (no complex structures) " -273.681 13.88 7 5.2712E-02 .0000 2.4004E-04
.0000 .0000 .0000 .0000 5.0739E-02 .0000 1.1999E-02 2.7987E-02 .0000 6.2087E-04 .0000 .0000 .9084 2.4677E-02 4.0742E-02

"07/20/1992" "11:16:23" "SC PCM Length >=20 and Width <0.2 " -313.069 137.2 11 .0000 .5000 .5000
7.8262E-02 8.3237E-02
"07/20/1992" "11:16:24" "SC PCM Length >=30 " -287.475 40.36 11 .0000 .4976 .5024
3.6883E-02 9.8082E-03
"07/20/1992" "11:16:25" "SC PCM Length >=30 and Width <0.4 " -316.358 110.2 11 .0000 .5702 .4298
.1132 2.6895E-02
"07/20/1992" "11:16:26" "SC PCM Length >=30 and Width <0.2 " -331.356 132.3 11 .0000 .5175 .4825
.1544 .1622

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 "07/20/1992" "11:16:27" "SC PCM  Length >=20 and  Width >=0.4                                          "  -285.590       34.13      11   .0000       .3007       .6993
2.9009E-02  1.0020E-02
 "07/20/1992" "11:16:28" "SC PCM  Length >=10                                                           "  -292.283       56.96      11   .0000      3.6654E-02   .9633
3.0399E-02  1.0603E-02
 "07/20/1992" "16:59:38" "SC PCM  F&B with 5-40,<0.3, F&B with >=40,<0.3, and Complex only with >=40,>=5  "  -272.933       12.20      10   .2712      1.7376E-03   .8516
.1467      2.5581E-02  7.0175E-02
 "07/20/1992" "17:02:26" "SC PCM  F=>40,<.3,  B=>40,<.3,  Complex=>40,>5,  F=5-40,<.3,  B=5-40,<.3        "  -272.537       11.55       8   .1718       .4988       .4405
5.9873E-02  8.8266E-06  8.3673E-04  2.9366E-02   .1525

 "07/21/1992" "13:14:11" "SC PCM  5-40 & <0.3,  >=40 &<0.3,  and >=40 & >=5                             "  -272.935       12.19      10   .2716      1.7176E-03   .8530
.1453      2.5612E-02  7.0424E-02
 "07/21/1992" "13:19:20" "SC PCM  >=40 & >=5,  5-40 & <0.3, and >=40 &<0.3                              "  -272.935       12.19      10   .2716       .1453      1.7176E-03
.8530      2.5612E-02  7.0424E-02

 "08/06/1992" "15:38:36" "SC PCM  length >= 8 and width < 0.25                                          "  -306.530       100.2      11   .0000       .3319       .6681
5.4171E-02  4.4551E-03

 "12/14/1992" "16:30:46" "SC PCM  Length < 5 (no widths) and 5-40, >=40  and  W <0.3, >5  (with 95% CI)   "  -272.935       12.19      10   .2716       .0000      1.7176E-03
.0000       .8530       .1453      2.5612E-02  7.0424E-02

 "12/15/1992" "10:16:36" "(all except chrysotile) SC PCM <5,5-10,10-20,20-40,>=40 and <0.15,0.15-0.3,0.3-1,1-5,>=5                "  -100.359       1.685       3   .6399
.0000       .0000       .0000       .0000       .0000       .0000       .0000       .0000       .0000       .0000       .0000       .0000       .0000       .0000       .0000
.0000       .0000       .0000       .0000      7.6546E-02   .0000       .9027       .0000       .0000      2.0714E-02  2.2772E-02  8.6916E-02
 "12/15/1992" "10:17:47" "(chrysotile only) SC PCM <5,5-10,10-20,20-40,>=40 and <0.15,0.15-0.3,0.3-1,1-5,>=5                "  -199.146       8.430       1  2.9414E-03  1.9054E-08
.0000       .0000       .0000       .0000       .0000       .0000       .0000       .0000       .1719       .0000       .0000       .0000       .0000       .0000       .0000
.0000      2.0494E-02   .0000       .5626       .0000       .0000       .2450       .0000     -6.1822E-05  3.2157E-02  3.7205E-02

 "12/17/1992" "14:09:01" "(chrysotile only) SC PCM <5,5-10,10-20,20-40,>=40 and >=5,1-5,0.3-1,0.15-0.3,<0.15                "  -224.122       109.7       3   .0000       .0000
.0000       .0000       .1402      9.5597E-03   .0000       .0000       .0000       .0000       .0000       .0000       .0000       .0000       .0000       .0000       .8502
.0000       .0000       .0000       .0000       .0000       .0000       .0000       .0000      1.2193E-07  5.9591E-02  1.1295E-04

 "12/18/1992" "09:34:18" "(chrysotile only) SC PCM >=40,<5,5-10,10-20,20-40 and <0.15,0.15-0.3,0.3-1,1-5,>=5                "  -199.146       8.430       3  3.7196E-02   .0000
.0000       .2450       .0000       .0000       .0000       .0000       .0000       .0000       .0000       .0000       .0000       .0000       .1719       .0000
.0000       .0000       .0000       .0000       .0000       .0000      2.0501E-02   .0000       .5625      3.2158E-02  3.7206E-02

 "10/08/1993" "16:02:37" "SC PCM 5-40, >=40 with >=5, < 0.3 (All except chrysotile)                       " -2.774594E+07   2.321       3   .5082       .0000      7.1027E-05
9.8000E-02   .9019      2.6668E-02  8.6399E-02

 "10/12/1993" "17:03:34" "SC PCM >=40, 5-40 with <0.3, >=5 (Chrysotile only) (d1*1000,d2*100,d4*30)       " -2.774604E+07   8.826       3  3.0963E-02   .3958      9.4552E-02
.2883       .2214      2.6668E-02  3.3475E-04

 "03/23/1994" "14:46:29" "SC - Length: <5, 5-40; Width:  <.3, >5                                        "  -271.156       8.005      10  0.6280      2.5270E-03  0.0000E+00
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0.9161 8.1337E-02 2.3018E-02 8.4603E-02
"03/23/1994" "14:52:42" "SC - Length: 5-20, >20; Width: <.3, >5 " -276.444 17.53 10 6.2729E-02 1.5736E-02 0.0000E+00
0.3639 0.6204 2.1557E-02 1.0547E-02
"03/23/1994" "15:13:12" "SC - Length: 5-40, >40; Width: >5 " -303.315 90.11 11 0.0000E+00 0.3142 0.6858
6.1680E-02 1.6153E-02
"03/23/1994" "15:13:26" "SC - Length: 5-20, >20; Width: <.3 " -284.330 35.14 11 0.0000E+00 1.5189E-02 0.9848
2.2466E-02 1.0049E-02
"03/23/1994" "15:35:48" "SC - Length: 5-20, >20; Width: <.3 and Length: 5-40, >40; Width: >5 " -275.192 15.27 10 0.1217 1.1560E-02 0.2105
0.0000E+00 0.7780 2.2547E-02 1.5203E-02

"06/28/1994" "15:56:48" "SC (smooth): L: 5-10, 10-20, 20-40, >40; W: 0-.15, .15-.3, .3-1, 1-5, >5 " -274.350 13.01 8 0.1108 0.0000E+00 0.0000E+00
0.0000E+00 0.0000E+00 0.0000E+00 9.3741E-02 0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 1.7745E-02 0.0000E+00 2.8592E-02 0.0000E+00 0.0000E+00 0.5198 0.0000E+00
0.0000E+00 0.0000E+00 0.3401
2.1446E-02 6.0462E-02

"06/30/1994" "08:40:56" "SC (smooth): L: <5, 5-10, 10-20, 20-40, >40; W: 0-.15, .15-.3, .3-1, 1-5, >5 " -285.085 51.34 9 0.0000E+00 2.0498E-04 7.1561E-05
0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00
0.0000E+00 0.0000E+00 0.0000E+00
0.7434 0.0000E+00 0.0000E+00 0.0000E+00 0.2563 4.5062E-02 6.3313E-02

"06/30/1994" "09:27:22" "SC (smooth): L: <5, 5-10, 10-20, 20-40, >40; W: 0-.15, .15-.3, .3-1, 1-5, >5 " -272.652 10.23 9 0.3313 0.0000E+00 0.0000E+00
0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 0.3393 0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00
2.2450E-02 0.0000E+00 0.0000E+00
0.0000E+00 0.1061 0.0000E+00 0.0000E+00 0.5322 2.1610E-02 2.6262E-02

"07/05/1994" "12:25:40" "SC (smooth): L: <5, 5-10, 10-20, 20-40, >40; W: 0-.15, .15-.3, .3-1, 1-5, >5 " -274.379 14.21 8 7.5695E-02 0.0000E+00 0.0000E+00
0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 8.6406E-04 0.0000E+00 0.0000E+00 0.0000E+00 9.4722E-02 0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00
1.8899E-02 0.0000E+00 0.0000E+00
0.0000E+00 0.4309 0.0000E+00 0.0000E+00 0.4546 2.3140E-02 2.9659E-02

"07/05/1994" "13:42:25" "SC (smooth) - Length: 5-40, >40; Width: <.3, >5 " -273.849 12.39 10 0.2589 5.4909E-03 0.0000E+00
0.6729 0.3216 2.1457E-02 3.1507E-02
"07/05/1994" "13:46:50" "SC (smooth) - Length: 5-40, >40; Width: <.3, >5 " -274.767 14.82 10 0.1382 3.1150E-03 0.0000E+00
0.6166 0.3803 2.2734E-02 3.0645E-02

"07/11/1994" "09:30:21" "Davis Studies - Using mass to calculate the constant for the dose " -271.857 9.198 7 0.2382 0.0000E+00 0.0000E+00
0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 5.9335E-02 0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 7.7491E-02 0.0000E+00 0.0000E+00 0.0000E+00
0.0000E+00 0.3107 0.0000E+00
0.0000E+00 0.0000E+00 0.5525 0.0000E+00 -7.1447E-05 2.1965E-02 2.1994E-02

"07/11/1994" "09:48:26" "PS (smooth) L: <5, 5-10, 10-20, 20-40, >40; W: <.15, .15-.3, .3-1, 1-5, >5 " -274.561 15.30 8 5.2770E-02 0.0000E+00 0.0000E+00
0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 0.2206 0.0000E+00 0.0000E+00 1.5167E-03 0.1926 0.0000E+00 0.0000E+00 0.0000E+00

```
0.0000E+00  0.0000E+00  0.0000E+00
  0.0000E+00  0.0000E+00  0.5853      0.0000E+00 -2.9093E-07  2.3400E-02  1.7669E-02

 "09/06/1994" "14:33:11" " SC - Length: <5, 5-10, 10-20 20-40, >40; F&B, C&M                            "  -275.569       16.15       9  6.3160E-02  0.0000E+00  0.0000E+00
0.0000E+00  0.0000E+00  5.2769E-02  2.5228E-02  0.0000E+00  0.0000E+00  0.8311      9.0947E-02  2.2160E-02  1.5963E-02
 "09/06/1994" "14:44:46" " PS - Length: <5, 5-10, 10-20 20-40, >40; F&B, C&M                            "  -276.055       16.35       9  5.9294E-02  0.0000E+00  0.0000E+00
0.0000E+00  0.0000E+00  6.4922E-02  1.4464E-02  0.0000E+00  0.0000E+00  0.7031      0.2175      2.2220E-02  1.4475E-02

 "09/08/1994" "09:59:21" "(Indirect) PS - Length: <5, 5-10, 10-20 20-40, >40; F&B, C&M                  "  -281.736       33.23      11  0.0000E+00  0.0000E+00  0.0000E+00
0.0000E+00  1.9526E-02  0.0000E+00  0.0000E+00  0.0000E+00  0.0000E+00  0.0000E+00  0.9805      2.7743E-02  0.1171
 "09/08/1994" "10:40:42" "(Indirect) PS - Length: <5, 5-10, 10-20 20-40, >40; F&B, C&M                  "  -281.698       33.16      11  0.0000E+00  0.0000E+00  0.0000E+00
0.0000E+00  2.0334E-02  0.0000E+00  0.0000E+00  0.0000E+00  0.0000E+00  0.0000E+00  0.9797      2.7748E-02  0.1125
 "09/08/1994" "10:40:54" "(Indirect) SC - Length: <5, 5-10, 10-20 20-40, >40; F&B, C&M                  "  -301.014       90.67       9  0.0000E+00  0.0000E+00  0.0000E+00
1.1306E-03  0.6515      0.0000E+00  0.3474      0.0000E+00  0.0000E+00  0.0000E+00  0.0000E+00  6.7921E-02  2.4401E-02

 "09/09/1994" "15:25:33" "(Indirect) SC - Length: <5, 5-10, 10-20 20-40, >40; F&B (w<.3), C&M            "  -301.014       90.67       9  0.0000E+00  0.0000E+00  0.0000E+00
1.1306E-03  0.6515      0.0000E+00  0.3474      0.0000E+00  0.0000E+00  0.0000E+00  0.0000E+00  6.7921E-02  2.4401E-02
 "09/09/1994" "15:25:54" "(Indirect) PS - Length: <5, 5-10, 10-20 20-40, >40; F&B (w<.3), C&M            "  -281.698       33.16      11  0.0000E+00  0.0000E+00  0.0000E+00
0.0000E+00  2.0334E-02  0.0000E+00  0.0000E+00  0.0000E+00  0.0000E+00  0.0000E+00  0.9797      2.7748E-02  0.1125

 "09/09/1994" "15:28:54" " (Direct) PS - Length: <5, 5-10, 10-20 20-40, >40; F&B (w<.3), C&M             "  -277.173       17.54       8  2.4088E-02  0.0000E+00  0.0000E+00
0.0000E+00  0.0000E+00  2.0403E-02  9.0581E-04  0.0000E+00  4.6108E-03  0.9375      3.6547E-02  2.2579E-02  0.1224
 "09/09/1994" "15:29:19" " (Direct) SC - Length: <5, 5-10, 10-20 20-40, >40; F&B (w<.3), C&M             "  -272.162       9.944       9  0.3545      0.0000E+00  0.0000E+00
1.7669E-03  0.0000E+00  3.8221E-03  0.0000E+00  0.0000E+00  0.0000E+00  0.9790      1.5448E-02  2.2709E-02  0.1088

 "09/15/1994" "15:28:41" "(Indirect) PS - Length: <5, 5-10, 10-20 20-40, >40; width: <.3, >= .3          "  -282.522       33.70      10  0.0000E+00  0.0000E+00  0.0000E+00
1.6818E-04  5.2736E-02  0.0000E+00  0.0000E+00  0.0000E+00  0.0000E+00  0.0000E+00  0.9471      2.6545E-02  0.1388
 "09/15/1994" "15:29:00" "(Indirect) PS - Length: <5, 5-10, 10-20 20-40, >40; F&B (w<.3), C&M (w>=.3)     "  -281.698       33.16      11  0.0000E+00  0.0000E+00  0.0000E+00
0.0000E+00  2.0334E-02  0.0000E+00  0.0000E+00  0.0000E+00  0.0000E+00  0.0000E+00  0.9797      2.7748E-02  0.1125
 "09/15/1994" "15:29:18" "(Indirect) SC - Length: <5, 5-10, 10-20 20-40, >40; width: <.3, >= .3          "  -312.657       116.4       9  0.0000E+00  1.1927E-04  0.0000E+00
1.3661E-03  0.0000E+00  0.0000E+00  0.9985      0.0000E+00  0.0000E+00  0.0000E+00  0.0000E+00  8.5000E-02  1.2810E-02
 "09/15/1994" "15:29:34" "(Indirect) SC - Length: <5, 5-10, 10-20 20-40, >40; F&B (w<.3), C&M (w>=.3)     "  -304.851       103.5       8  0.0000E+00  2.1660E-07  0.0000E+00
8.6262E-04  0.6668      0.0000E+00  0.3324      0.0000E+00  0.0000E+00  0.0000E+00  0.0000E+00  8.1093E-02  2.5418E-02

 "09/29/1994" "15:14:20" "(Indirect) PS - Length: <5, 5-10, 10-20 20-40, >40; width: <.3, >= 1           "  -278.476       26.59      10  2.1803E-03  0.0000E+00  0.0000E+00
0.0000E+00  0.1713      0.0000E+00  0.1244      0.0000E+00  0.0000E+00  0.0000E+00  0.7044      2.8964E-02  1.1187E-02
 "09/29/1994" "15:14:30" "(Indirect) PS - Length: <5, 5-10, 10-20 20-40, >40; width: <1, >= 1            "  -278.476       26.59      10  2.1803E-03  0.0000E+00  0.0000E+00
0.0000E+00  0.1713      0.0000E+00  0.1244      0.0000E+00  0.0000E+00  0.0000E+00  0.7044      2.8964E-02  1.1187E-02
 "09/29/1994" "15:14:38" "(Indirect) SC - Length: <5, 5-10, 10-20 20-40, >40; width: <.3, >= 1           "  -273.829       15.15       8  5.5433E-02  5.3701E-05  2.6475E-03
0.0000E+00  0.0000E+00  0.0000E+00  0.9859      1.1353E-02  0.0000E+00  0.0000E+00 -6.8408E-09  2.5704E-02  1.2676E-02
 "09/29/1994" "15:14:46" "(Indirect) SC - Length: <5, 5-10, 10-20 20-40, >40; width: <1, >= 1            "  -273.637       14.50       8  6.8763E-02  5.1098E-05  2.3654E-03
0.0000E+00  0.0000E+00  0.0000E+00  0.9855      1.2036E-02  0.0000E+00  0.0000E+00  7.0771E-10  2.5422E-02  1.2459E-02
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 "10/08/1994" "13:35:28" " (Direct) PS - Length: 5-35, >35; width: <.4, >=.4                                  "  -273.526       12.55       9  0.1832      3.6855E-02  1.0638E-02
0.9525     -4.4052E-13  2.2537E-02  4.9013E-02
 "10/08/1994" "13:35:30" " (Direct) SC - Length: 5-35, >35; width: <.4, >=.4                                  "  -274.549       13.85      10  0.1792      6.7383E-03  0.0000E+00
0.9933      1.9299E-13  2.2452E-02  2.6220E-02
 "10/08/1994" "13:35:33" " (Direct) PS - Length: 10-35, >35; width: <.4, >=.4                                 "  -278.769       21.65       9  9.3099E-03  0.3404      4.9499E-02
0.3818      0.2283      2.4778E-02  1.6989E-02
 "10/08/1994" "13:35:35" " (Direct) SC - Length: 10-35, >35; width: <.4, >=.4                                 "  -274.577       13.29       9  0.1492      2.7992E-02  1.8079E-02
0.9539      1.1028E-13  2.1312E-02  2.0133E-02
 "10/08/1994" "13:35:38" " (Direct) PS - Length: 10-30, >30; width: <.4, >=.4                                 "  -278.770       21.61       9  9.4643E-03  0.1124      5.9273E-02
0.7112      0.1171      2.2471E-02  2.1357E-02
 "10/08/1994" "13:35:41" " (Direct) SC - Length: 10-30, >30; width: <.4, >=.4                                 "  -275.485       15.94       9  6.7477E-02  3.2623E-02  2.3444E-02
0.9238      2.0145E-02  2.1867E-02  1.4365E-02
 "10/08/1994" "13:35:43" " (Direct) PS - Length: 5-30, >30; width: <.4, >=.4                                  "  -273.993       12.89       9  0.1669      1.9502E-02  2.1946E-02
0.9586     -2.2348E-10  2.0451E-02  3.4136E-02
 "10/08/1994" "13:35:46" " (Direct) SC - Length: 5-30, >30; width: <.4, >=.4                                  "  -277.242       19.78      10  3.0632E-02  8.8853E-03  0.0000E+00
0.9062      8.4893E-02  2.3156E-02  1.5083E-02
 "10/08/1994" "13:35:48" " (Direct) PS - Length: >40; width: <.4, >=.4                                        "  -331.352       132.3      11  0.0000E+00   1.000      3.8068E-14
0.1544      0.1680
 "10/08/1994" "13:35:51" " (Direct) SC - Length: >40; width: <.4, >=.4                                        "  -300.376       70.55      11  0.0000E+00  0.7468      0.2532
5.6862E-02  3.1167E-02
 "10/08/1994" "15:07:24" " (Direct) PS - Length: 5-35, >35; width: <.4, >=.4                                  "  -273.526       12.55       9  0.1832      3.6855E-02  1.0638E-02
0.9525     -4.4052E-13  2.2537E-02  4.9013E-02
 "10/08/1994" "15:07:27" " (Direct) SC - Length: 5-35, >35; width: <.4, >=.4                                  "  -274.549       13.85      10  0.1792      6.7383E-03  0.0000E+00
0.9933      1.9299E-13  2.2452E-02  2.6220E-02
 "10/08/1994" "15:07:29" " (Direct) PS - Length: 10-35, >35; width: <.4, >=.4                                 "  -278.769       21.65       9  9.3099E-03  0.3404      4.9499E-02
0.3818      0.2283      2.4778E-02  1.6989E-02
 "10/08/1994" "15:07:32" " (Direct) SC - Length: 10-35, >35; width: <.4, >=.4                                 "  -274.577       13.29       9  0.1492      2.7992E-02  1.8079E-02
0.9539      1.1028E-13  2.1312E-02  2.0133E-02
 "10/08/1994" "15:07:35" " (Direct) PS - Length: 10-30, >30; width: <.4, >=.4                                 "  -278.770       21.61       9  9.4643E-03  0.1124      5.9273E-02
0.7112      0.1171      2.2471E-02  2.1357E-02
 "10/08/1994" "15:07:38" " (Direct) SC - Length: 10-30, >30; width: <.4, >=.4                                 "  -275.485       15.94       9  6.7477E-02  3.2623E-02  2.3444E-02
0.9238      2.0145E-02  2.1867E-02  1.4365E-02
 "10/08/1994" "15:07:41" " (Direct) PS - Length: 5-30, >30; width: <.4, >=.4                                  "  -273.993       12.89       9  0.1669      1.9502E-02  2.1946E-02
0.9586     -2.2348E-10  2.0451E-02  3.4136E-02
 "10/08/1994" "15:07:44" " (Direct) SC - Length: 5-30, >30; width: <.4, >=.4                                  "  -277.242       19.78      10  3.0632E-02  8.8853E-03  0.0000E+00
0.9062      8.4893E-02  2.3156E-02  1.5083E-02
 "10/08/1994" "15:07:47" " (Direct) PS - Length: >40; width: <.4, >=.4                                        "  -331.352       132.3      11  0.0000E+00   1.000      3.8068E-14
0.1544      0.1680
 "10/08/1994" "15:07:49" " (Direct) SC - Length: >40; width: <.4, >=.4                                        "  -300.376       70.55      11  0.0000E+00  0.7468      0.2532
5.6862E-02  3.1167E-02

 "10/10/1994" "08:00:28" " (Direct) PS - Length: 5-35, >35; width: <.4, >=.4                                  "  -273.526       12.55       9  0.1832      3.6855E-02  1.0638E-02
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0.9525      1.1095E-13  2.2538E-02  4.9012E-02
 "10/10/1994" "08:00:31" " (Direct) SC - Length: 5-35, >35; width: <.4, >=.4                          "  -274.549       13.85      10  0.1793      6.7384E-03  0.0000E+00
0.9933      1.9284E-13  2.2454E-02  2.6220E-02
 "10/10/1994" "08:00:33" " (Direct) PS - Length: 10-35, >35; width: <.4, >=.4                          "  -278.768       21.65       9  9.3202E-03  0.3404      4.9500E-02
0.3817      0.2283      2.4778E-02  1.6987E-02
 "10/10/1994" "08:00:36" " (Direct) SC - Length: 10-35, >35; width: <.4, >=.4                          "  -274.577       13.29       9  0.1493      2.7991E-02  1.8080E-02
0.9539      1.0979E-13  2.1314E-02  2.0134E-02
 "10/10/1994" "08:00:38" " (Direct) PS - Length: 10-30, >30; width: <.4, >=.4                          "  -278.771       21.61       9  9.4607E-03  0.1123      5.9294E-02
0.7113      0.1171      2.2472E-02  2.1356E-02
 "10/10/1994" "08:00:41" " (Direct) SC - Length: 10-30, >30; width: <.4, >=.4                          "  -275.485       15.94       9  6.7504E-02  3.2620E-02  2.3446E-02
0.9238      2.0172E-02  2.1869E-02  1.4365E-02
 "10/10/1994" "08:00:44" " (Direct) PS - Length: 5-30, >30; width: <.4, >=.4                          "  -273.992       12.89       9  0.1670      1.9478E-02  2.1954E-02
0.9586      2.7876E-13  2.0451E-02  3.4131E-02
 "10/10/1994" "08:00:47" " (Direct) SC - Length: 5-30, >30; width: <.4, >=.4                          "  -277.241       19.77      10  3.0658E-02  8.8850E-03  0.0000E+00
0.9062      8.4873E-02  2.3157E-02  1.5084E-02
 "10/10/1994" "08:00:49" " (Direct) PS - Length: >40; width: <.4, >=.4                                "  -331.357       132.3      11  0.0000E+00   1.000      3.8065E-14
0.1544      0.1680
 "10/10/1994" "08:00:52" " (Direct) SC - Length: >40; width: <.4, >=.4                                "  -300.376       70.55      11  0.0000E+00  0.7468      0.2532
5.6857E-02  3.1165E-02
 "10/18/1994" "10:52:04" " (Direct) SC - Length: 5-40, >40; width: <.4, >=.4 (not adjusted)            "  -275.345       17.84      10  5.6943E-02  2.4333E-03  0.0000E+00
0.9963      1.2560E-03  2.7391E-02  4.7399E-02
 "10/18/1994" "10:52:22" " (Direct) SC - Length: 5-40, >40; width: <.3, >=.3 (not adjusted)            "  -275.510       17.22      10  6.8761E-02  1.3829E-03  0.0000E+00
0.9684      3.0243E-02  2.5583E-02  8.5973E-02
 "11/10/1994" "13:06:25" " (Direct) SC - L: 5, W: <.4; L:5, W: >=.4; L: >40, w: <.4 (not adjusted)      "  -275.346       17.86      11  8.4167E-02  2.4379E-03  0.0000E+00
0.9976      2.7465E-02  4.7575E-02

                                                                                                          Log-Like       Chi-S      DF  p-value     coefficients for each
length-width category followed by 2 equation coefficients
 "10/22/1996" "19:32:55" "PS PCM  lengths <10, >=10                                                    "  -296.320       69.01      12  0.0000E+00  0.0000E+00   1.000
3.4161e-02  3.5653e-04
 "10/22/1996" "19:32:56" "PS PCM  lengths >=10                                                         "  -296.320       69.01      12  0.0000E+00   1.000      3.4161e-02
3.5653e-04
 "10/22/1996" "19:32:56" "PS PCM  lengths >=10 and widths < 0.3                                        "  -325.595       129.6      12  0.0000E+00   1.000      0.1064
2.6484e-03
 "10/22/1996" "19:32:56" "PS PCM  lengths >=10 and widths < 0.4                                        "  -312.334       110.2      12  0.0000E+00   1.000      6.6970e-02
1.9852e-03
 "10/22/1996" "19:32:57" "PS PCM  lengths >=10 and widths < 0.5                                        "  -306.968       96.93      12  0.0000E+00   1.000      5.5436e-02
1.4187e-03
 "10/22/1996" "19:32:57" "PS PCM  lengths >=10 and widths >=0.3                                        "  -297.031       70.29      12  0.0000E+00   1.000      3.5080e-02
3.8243e-04
 "10/22/1996" "19:32:57" "PS PCM  lengths >=10 and widths >=0.4                                        "  -298.067       72.82      12  0.0000E+00   1.000      3.6791e-02
4.0886e-04
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 "10/22/1996" "19:32:57" "PS PCM  lengths >=10 and widths >=0.5                                  "  -298.522       73.82      12  0.0000E+00   1.000      3.7227e-02
4.4693e-04
 "10/22/1996" "19:32:58" "PS PCM  lengths <10, >=10 and widths <0.3, >=0.3                       "  -296.228       68.97      11  0.0000E+00  0.0000E+00  0.0000E+00
0.6171      0.3829      3.4084e-02  8.9173e-04
 "10/22/1996" "19:32:58" "PS PCM  lengths <10, >=10 and widths <0.4, >=0.4                       "  -296.124       68.75      11  0.0000E+00  0.0000E+00  0.0000E+00
0.6218      0.3782      3.3966e-02  8.6454e-04
 "10/22/1996" "19:32:58" "PS PCM  lengths <10, >=10 and widths <0.5, >=0.5                       "  -296.226       68.95      11  0.0000E+00  0.0000E+00  0.0000E+00
0.5800      0.4200      3.4167e-02  7.8386e-04
 "10/22/1996" "19:32:59" "PS PCM  lengths <5, 5-10, >=10 and widths <0.3, >=0.3                  "  -296.228       68.97      11  0.0000E+00  0.0000E+00  0.0000E+00
0.0000E+00  0.0000E+00  0.6171      0.3829      3.4084e-02  8.9173e-04
 "10/22/1996" "19:32:59" "PS PCM  lengths <5, 5-10, >=10 and widths <0.4, >=0.4                  "  -296.124       68.75      11  0.0000E+00  0.0000E+00  0.0000E+00
0.0000E+00  0.0000E+00  0.6218      0.3782      3.3966e-02  8.6454e-04
 "10/22/1996" "19:32:59" "PS PCM  lengths <5, 5-10, >=10 and widths <0.5, >=0.5                  "  -296.226       68.95      11  0.0000E+00  0.0000E+00  0.0000E+00
0.0000E+00  0.0000E+00  0.5800      0.4200      3.4167e-02  7.8386e-04

 "10/22/1996" "19:33:00" "SC PCM  lengths <10, >=10                                              "  -292.283       56.96      12  0.0000E+00  0.0000E+00   1.000
3.0399e-02  3.8864e-04
 "10/22/1996" "19:33:01" "SC PCM  lengths >=10                                                   "  -292.283       56.96      12  0.0000E+00   1.000      3.0399e-02
3.8864e-04
 "10/22/1996" "19:33:01" "SC PCM  lengths >=10 and widths < 0.3                                  "  -301.778       90.24      12  0.0000E+00   1.000      4.3548e-02
1.2887e-03
 "10/22/1996" "19:33:01" "SC PCM  lengths >=10 and widths < 0.4                                  "  -300.564       87.30      12  0.0000E+00   1.000      4.2830e-02
8.0126e-04
 "10/22/1996" "19:33:02" "SC PCM  lengths >=10 and widths < 0.5                                  "  -299.230       80.93      12  0.0000E+00   1.000      4.0893e-02
5.9682e-04
 "10/22/1996" "19:33:02" "SC PCM  lengths >=10 and widths >=0.3                                  "  -291.282       53.08      12  0.0000E+00   1.000      3.0016e-02
5.3901e-04
 "10/22/1996" "19:33:02" "SC PCM  lengths >=10 and widths >=0.4                                  "  -291.615       53.13      12  0.0000E+00   1.000      3.0601e-02
7.0335e-04
 "10/22/1996" "19:33:03" "SC PCM  lengths >=10 and widths >=0.5                                  "  -289.538       47.01      12  0.0000E+00   1.000      2.8679e-02
1.0040e-03
 "10/22/1996" "19:33:03" "SC PCM  lengths <10, >=10 and widths <0.3, >=0.3                       "  -291.282       53.08      12  0.0000E+00  0.0000E+00  0.0000E+00
0.0000E+00   1.000      3.0016e-02  5.3901e-04
 "10/22/1996" "19:33:03" "SC PCM  lengths <10, >=10 and widths <0.4, >=0.4                       "  -291.297       53.07      11  0.0000E+00  0.0000E+00  0.0000E+00
0.1906      0.8094      2.9857e-02  7.3280e-04
 "10/22/1996" "19:33:03" "SC PCM  lengths <10, >=10 and widths <0.5, >=0.5                       "  -289.410       47.20      11  0.0000E+00  0.0000E+00  0.0000E+00
6.8701e-02  0.9313      2.8234e-02  9.6970e-04
 "10/22/1996" "19:33:04" "SC PCM  lengths <5, 5-10, >=10 and widths <0.3, >=0.3                  "  -291.282       53.08      12  0.0000E+00  0.0000E+00  0.0000E+00
0.0000E+00  0.0000E+00  0.0000E+00   1.000      3.0016e-02  5.3901e-04
 "10/22/1996" "19:33:04" "SC PCM  lengths <5, 5-10, >=10 and widths <0.4, >=0.4                  "  -291.297       53.07      11  0.0000E+00  0.0000E+00  0.0000E+00
0.0000E+00  0.0000E+00  0.1906      0.8094      2.9857e-02  7.3280e-04
 "10/22/1996" "19:33:05" "SC PCM  lengths <5, 5-10, >=10 and widths <0.5, >=0.5                  "  -289.410       47.20      11  0.0000E+00  0.0000E+00  0.0000E+00
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0.0000E+00  0.0000E+00  6.8701e-02  0.9313      2.8234e-02  9.6970e-04

 "10/28/1996" "12:44:57" "DPS PCM  lengths <10, >=10                                                  "  -287.949       44.46      12  0.0000E+00  0.0000E+00   1.000
2.5235e-02  5.1220e-04
 "10/28/1996" "12:44:57" "DPS PCM  lengths >=10                                                       "  -287.949       44.46      12  0.0000E+00   1.000      2.5235e-02
5.1220e-04
 "10/28/1996" "12:44:58" "DPS PCM  lengths >=10 and widths < 0.3                                      "  -316.503       110.2      12  0.0000E+00   1.000      7.3622e-02
5.6629e-03
 "10/28/1996" "12:44:58" "DPS PCM  lengths >=10 and widths < 0.4                                      "  -300.922       82.23      12  0.0000E+00   1.000      4.4147e-02
3.4464e-03
 "10/28/1996" "12:44:58" "DPS PCM  lengths >=10 and widths < 0.5                                      "  -293.750       61.78      12  0.0000E+00   1.000      3.5229e-02
2.3840e-03
 "10/28/1996" "12:44:58" "DPS PCM  lengths >=10 and widths >=0.3                                      "  -289.658       48.05      12  0.0000E+00   1.000      2.6465e-02
5.4368e-04
 "10/28/1996" "12:44:59" "DPS PCM  lengths >=10 and widths >=0.4                                      "  -291.088       51.44      12  0.0000E+00   1.000      2.7837e-02
5.8117e-04
 "10/28/1996" "12:44:59" "DPS PCM  lengths >=10 and widths >=0.5                                      "  -292.360       54.33      12  0.0000E+00   1.000      2.8690e-02
6.2912e-04
 "10/28/1996" "12:44:59" "DPS PCM  lengths <10, >=10 and widths <0.3, >=0.3                           "  -286.566       41.86      11  0.0000E+00  0.0000E+00  0.0000E+00
0.7938      0.2062      2.4631e-02  2.1051e-03
 "10/28/1996" "12:45:00" "DPS PCM  lengths <10, >=10 and widths <0.4, >=0.4                           "  -286.586       41.99      11  0.0000E+00  0.0000E+00  0.0000E+00
0.7526      0.2474      2.4604e-02  1.6363e-03
 "10/28/1996" "12:45:00" "DPS PCM  lengths <10, >=10 and widths <0.5, >=0.5                           "  -286.449       41.81      11  0.0000E+00  0.0000E+00  0.0000E+00
0.7528      0.2472      2.4906e-02  1.4683e-03
 "10/28/1996" "12:45:01" "DPS PCM  lengths <5, 5-10, >=10 and widths <0.3, >=0.3                      "  -286.566       41.86      11  0.0000E+00  0.0000E+00  0.0000E+00
0.0000E+00  0.0000E+00  0.7938      0.2062      2.4631e-02  2.1051e-03
 "10/28/1996" "12:45:01" "DPS PCM  lengths <5, 5-10, >=10 and widths <0.4, >=0.4                      "  -286.586       41.99      11  0.0000E+00  0.0000E+00  0.0000E+00
0.0000E+00  0.0000E+00  0.7526      0.2474      2.4604e-02  1.6363e-03
 "10/28/1996" "12:45:01" "DPS PCM  lengths <5, 5-10, >=10 and widths <0.5, >=0.5                      "  -286.449       41.81      11  0.0000E+00  0.0000E+00  0.0000E+00
0.0000E+00  0.0000E+00  0.7528      0.2472      2.4906e-02  1.4683e-03

 "10/28/1996" "12:45:03" "DSC PCM  lengths <10, >=10                                                  "  -283.543       33.35      12  1.1074e-05  0.0000E+00   1.000
2.3313e-02  5.5129e-04
 "10/28/1996" "12:45:03" "DSC PCM  lengths >=10                                                       "  -283.543       33.35      12  1.1074e-05   1.000      2.3313e-02
5.5129e-04
 "10/28/1996" "12:45:03" "DSC PCM  lengths >=10 and widths < 0.3                                      "  -292.585       62.75      12  0.0000E+00   1.000      2.9350e-02
1.9603e-03
 "10/28/1996" "12:45:04" "DSC PCM  lengths >=10 and widths < 0.4                                      "  -291.994       61.26      12  0.0000E+00   1.000      2.9669e-02
1.2027e-03
 "10/28/1996" "12:45:04" "DSC PCM  lengths >=10 and widths < 0.5                                      "  -288.758       50.76      12  0.0000E+00   1.000      2.7648e-02
9.0725e-04
 "10/28/1996" "12:45:04" "DSC PCM  lengths >=10 and widths >=0.3                                      "  -283.168       31.45      12  8.3897e-04   1.000      2.3906e-02
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7.5397e-04
 "10/28/1996" "12:45:05" "DSC PCM  lengths >=10 and widths >=0.4                                    "  -283.756       32.11      12  4.9080e-04   1.000      2.4780e-02
9.7866e-04
 "10/28/1996" "12:45:05" "DSC PCM  lengths >=10 and widths >=0.5                                    "  -284.839       33.82      12  0.0000E+00   1.000      2.5206e-02
1.3372e-03
 "10/28/1996" "12:45:05" "DSC PCM  lengths <10, >=10 and widths <0.3, >=0.3                         "  -283.115       31.57      11  1.4270e-04  0.0000E+00  0.0000E+00
0.1662      0.8338      2.3616e-02  8.4322e-04
 "10/28/1996" "12:45:06" "DSC PCM  lengths <10, >=10 and widths <0.4, >=0.4                         "  -283.015       31.25      11  2.5114e-04  0.0000E+00  0.0000E+00
0.2851      0.7149      2.3447e-02  1.0489e-03
 "10/28/1996" "12:45:06" "DSC PCM  lengths <10, >=10 and widths <0.5, >=0.5                         "  -283.016       31.11      11  3.0503e-04  0.0000E+00  0.0000E+00
0.3050      0.6950      2.3103e-02  1.1895e-03
 "10/28/1996" "12:45:06" "DSC PCM  lengths <5, 5-10, >=10 and widths <0.3, >=0.3                    "  -283.115       31.57      11  1.4270e-04  0.0000E+00  0.0000E+00
0.0000E+00  0.0000E+00  0.1662      0.8338      2.3616e-02  8.4322e-04
 "10/28/1996" "12:45:07" "DSC PCM  lengths <5, 5-10, >=10 and widths <0.4, >=0.4                    "  -283.015       31.25      11  2.5114e-04  0.0000E+00  0.0000E+00
0.0000E+00  0.0000E+00  0.2851      0.7149      2.3447e-02  1.0489e-03
 "10/28/1996" "12:45:07" "DSC PCM  lengths <5, 5-10, >=10 and widths <0.5, >=0.5                    "  -283.016       31.11      11  3.0503e-04  0.0000E+00  0.0000E+00
0.0000E+00  0.0000E+00  0.3050      0.6950      2.3103e-02  1.1895e-03
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APPENDIX D:
THE VARIATION IN K_L VALUES DERIVED FOR CHRYSOTILE MINERS AND CHRYSOTILE TEXTILE WORKERS

The difference between the observed risk of lung cancer for comparable levels of chrysotile exposure among Quebec miners (most recent followup: Liddell et al. 1997) and South Carolina textile workers (Dement et al. 1994; McDonald et al. 1983a) has been the focus of much attention. Reasonably good agreement between results from the Quebec studies and another study of chrysotile miners in Italy (Piolatto et al. 1990) coupled with reasonably good agreement between results from the South Carolina Plant and results from textile plants in Mannheim, Pennsylvania (McDonald et al. 1983b) and in Roachdale, England (Peto 1980a,b; Peto et al. 1985) suggest that the difference between Quebec and South Carolina may reflect a general difference between the two industries (see Table 7-6 and Section 7.2.2). This appears true despite the fact, for example, that cohorts at two of the textile plants were apparently exposed to significant amounts of amphibole in addition to chrysotile (see Appendix A and Section 7.2.2).

Three main hypotheses have been advanced to explain the difference in the risk per unit exposure observed among miners and textile workers (see, for example, Sebastien et al. 1989). These are:

(1) the low reliability of exposure estimates in the various studies;

(2) differences in fiber size distributions in the two industries (with textile-related exposures presumably involving greater fractions of longer fibers); or

(3) simultaneous exposure to a co-carcinogen (i.e., oil that may have been sprayed on the asbestos fibers) in the textile industry.

It has also been proposed that differences in the concentration of long tremolite (amphibole) fibers in dusts from each of the two industries might represent an explanatory factor (see, for example, McDonald 1998b). However, this would also require a large relative difference between the potencies of tremolite (amphiboles) and chrysotile toward the induction of lung cancer. This latter issue is addressed further in Sections 7.4–7.6. McDonald (1998b) also presents an overview of the current status of each of the hypotheses described above.

In an attempt to distinguish among the above-listed hypotheses, Sebastien et al. (1989) conducted a study to determine lung fiber concentrations in tissue samples from deceased members of the cohorts studied from both the Quebec mines (specifically, from the Thetford mine) and the South Carolina textile plant. These researchers ultimately analyzed tissue samples from 72 members of the South Carolina cohort and 89 members of the Thetford (Quebec) cohort. Because the tissue samples came from cohort members, they could be matched with estimates of the exposure experienced by each of the individuals as well as details concerning the age at first employment, the age at death, the years of employment, and the number of years following employment until death.

In the Sebastien et al. (1989) study, tissue samples were obtained in formalin-fixed or paraffin blocks, which were then digested in bleach, filtered, and analyzed by TEM. Tissue samples were apparently "opportunistic." Only fibers longer than 5 μm with an aspect ratio >3:1 were included in the count. For consideration of the limitations associated with such preparations, see Section 5.2.

Results from matching of tissue samples with the histories of corresponding cohort members indicate that tissue samples obtained from each cohort covered a broad range of exposure levels, duration of exposure, and years since the end of exposure. They also indicate that South Carolina cohort members included in the Sebastien et al. (1989) study experienced, on average, 13.5 years of exposure with 18.1 years between the end of exposure and death. In contrast, Thetford workers included in this study experienced an average of 32.6 years of exposure with only 11.6 years between the end of exposure and death. Corresponding to differences in exposure levels observed across the two cohorts in the original epidemiology studies, mean exposure levels experienced by Thetford cohort members included in this study were about 10 times mean exposure levels experienced by South Carolina workers (19.5 mpcf vs. 1.9 mpcf).

Because Sebastien and coworkers recognized the general lack of a good model describing the retention and clearance of asbestos fibers in the lungs at the time their study was conducted, they performed most of their analyses either on pairs of members (one from each cohort) matched for duration of exposure and time since end of exposure or on groups of members from each cohort similarly stratified by duration of exposure and time since end of exposure.

Results from their study indicate that, overall, lung burdens observed among Thetford cohort members are substantially higher than those observed among South Carolina cohort members. Geometric mean lung chrysotile concentrations are reported to be 5.3 and 0.63 fibers/μg dry lung tissue in Thetford workers and South Carolina workers, respectively. Furthermore, despite tremolite representing only a minor contaminant in the chrysotile from Quebec and the dusts to which the miners were exposed (Sebastien et al. 1986), the majority of fibers observed in the lungs of Thetford miners were in fact tremolite (mean concentration 18.4 f/μg dry lung). Since the raw material used in the South Carolina plant came largely from Quebec, tremolite was also expected to be a minor contaminant in the dusts to which textile workers were exposed. Yet among these workers also, tremolite represented a substantial fraction of the lung fibers observed (mean concentration 0.36 f/μg). Thus, the ratio of tremolite concentrations observed among Thetford miners and that observed among South Carolina workers (18.4:0.36, or 51) is even more extreme than the ratio observed for chrysotile (8.4).

To evaluate the first of the above-listed hypotheses, it is instructive to compare the ratios of chrysotile or tremolite fibers observed in the lungs of deceased workers from Thetford and South Carolina, respectively, with the overall exposures that each received. A rough estimate of cumulative exposure for each set of workers in the Sebastien et al. (1989) study representing each cohort can be derived as the product of the mean duration of exposure and the mean intensity of exposure. Thus, for example, mean cumulative exposure in Thetford was 32.6 yearsx19.5 mpcf or 635.7 mpcf-yrs. Similarly, for South Carolina, mean cumulative exposure was 25.65 mpcf-yrs, which gives a Thetford/South Carolina ratio of 24.8. This presumably represents the relative cumulative exposure to chrysotile. For tremolite, Sebastien and coworkers report that, based on a regression analysis, the fraction of tremolite fibers among total

asbestos fibers were likely only 0.4 times as much in South Carolina as in Thetford (where they likely averaged 1% of total fibers). Therefore, the ratio of cumulative exposures to tremolite for the sets of cohort members studied by Sebastien and coworkers is likely 62.

Comparing the ratio of Thetford:South Carolina lung burden estimates with the ratios of the corresponding cumulative exposures, it appears that the chrysotile lung burden ratio (8.4) is only a third of the ratio predicted based on cumulative exposure (24.8). However, the ratio of lung tremolite concentrations (51) is much closer to the corresponding cumulative exposure ratio (62). It thus appears that, although, airborne concentrations may not closely track the exposures that led to the observed lung burdens for individuals (see below), the overall trend in exposures predicted by airborne measurements is approximately correct. It is therefore likely that overall exposure concentrations in Thetford were in fact substantially higher than in South Carolina (in agreement with airborne measurements). Thus, we concur with Sebastien et al. that the unreliability of exposure estimates in these two cohorts is unlikely to explain the observed difference in the risk per unit of exposure observed for each cohort.

Importantly, although the general trend in relative overall exposure levels predicted by airborne measurements between Thetford and South Carolina appear to have been confirmed by mean lung fiber concentrations in the Sebastien et al. (1989) study, the estimated exposures correlate poorly with lung burdens for any particular individual. To demonstrate this, we analyzed the Thetford:South Carolina ratios of lung chrysotile concentrations and, separately, lung tremolite concentrations reported by Sebastien et al. for their set of 32 matched pairs of cohort workers to determine whether trends in these ratios adequately matched trends in the corresponding estimated airborne exposure level ratios for the same matched pairs. To do this, we subjected the ratios presented in Table 7 of the Sebastien et al. (1989) study to a Rank Von Neuman test (Gilbert 1987). Results indicate that trends in neither lung chrysotile concentration ratios nor lung tremolite concentration ratios can be predicted by the observed trend in the estimated airborne concentration ratios among these 32 matched pairs.

There are numerous sources of potential uncertainty that may mask the relationship between airborne exposure estimates and resulting lung burdens (Section 5.2). Potentially the largest of these is the variation expected among lung burden estimates derived from use of “opportunistic” tissue samples, which are not controlled for the portion of the respiratory tree represented by the sample. Even for samples collected from adjacent locations in lung parenchyma, observed fiber concentrations may vary substantially and such variation is magnified between samples taken from different individuals at locations in the lung that may not in any way correspond to their relative position in the respiratory tree.

Other potentially important sources of variation that may mask the relationship between airborne exposure concentrations and resulting lung burden estimates may primarily involve limitations in the degree to which the airborne estimates from an epidemiology study represent actual exposures to the individual members of a study cohort (Section 5.1). The following factors may all contribute to the uncertainty of exposure estimates:potential differences between individual exposures versus area concentrations (which are what is typically measured), the adequacy of extrapolation to the earliest exposures in a cohort (when measurements were generally not available), or the adequacy of estimating job x time matrices for individual workers that can then be integrated with work area exposure estimates to derive individual exposure estimates.

The second of the above-listed hypotheses, involves potential differences in the size of structures that may have been present in the airborne concentrations in Thetford and South Carolina, which may not have been adequately represented by the exposure measurements. More generally, this is a question of the degree to which measured exposures in the two environments adequately reflect potential differences in the character of exposure that relate to biological activity.

Sebastien et al. (1989) considered this second hypothesis by generating and comparing size distributions for the fibers observed in the lungs of workers from Thetford and, separately, South Carolina. Importantly, the size distributions for each cohort were generated by including the first five fibers observed from every member of that cohort, without regard to the duration of exposure, level of exposure, or time since exposure experienced by each cohort member. Therefore, the size distributions obtained are "averaged" over very different time frames during which differing degrees of fiber retention and clearance will have taken place, each of which potentially alters the distributions of fiber sizes (Section 6.2). Thus, the two distributions generated are each actually collections of samples from multiple, varied size distributions (rather than single distributions) and this likely masks distinctions between the two work environments. It is therefore not surprising that the authors found relatively little differences in the two size distributions.

The portion of the generated size distributions that are least likely to have been affected by the limitations due to the manner in which they are generated (as Sebastien et al. suggest) is the fraction of tremolite (amphibole) fibers longer than 20 μm. This is because (1) tremolite fibers (unlike chrysotile) are biodurable and (2) biodurable fibers longer than approximately 20 μm have been shown to clear from the lung only very slowly, if at all (Section 6.2). Thus, the Thetford:South Carolina ratio of long tremolite fibers may provide the best indication of the relative exposures to long fibers in the two environments.

Table D-1 presents the estimated, relative concentrations of specific lengths of fibers observed in lung tissue among Thetford miners and South Carolina workers, respectively. The length category for various fibers is presented in the last column of the table. The estimated concentrations, presented in Columns 2 (for Thetford) and 3 (for South Carolina) of this table were derived as follows. For the first length category (L>5 μm), concentrations are taken directly from Table 5 of the Sebastien et al. (1989) paper (the geometric means are presented). Concentrations for the remaining length categories were estimated by multiplying the concentrations for this first length category by the fraction of the size distribution represented by each succeeding length category (as provided in Table 4 of the Sebastien et al. paper). So that the relative precision of these concentration estimates can be evaluated, an estimate of the numbers of fibers included in each length category (from the total used to derive the size distribution in Table 4 of Sebastien et al.) are provided in Columns 6 (for Thetford) and 7 (for South Carolina), respectively. The Thetford:South Carolina ratios of the concentrations of fibers in each length category (for each fiber type) are provided in Column 5 of the table.

Table D-1. Estimated Concentrations of Sized Fibers Observed in the Lungs of Thetford Miners and South Carolina Textile Workers[a]

	MEAN LUNG CONCENTRATION				NUMBER OF FIBERS		
Fiber Type	Thetford	South Carolina	Units	Ratio: Th/SC	Thetford	South Carolina	Size Range of Fibers[b]
Chrys	5.3	0.63	f/µg lung	8.41	371	226	Length>5 µm
Trem	18.4	0.38	f/µg lung	48.42	405	175	
Chrys	1.73	0.17	f/µg lung	10.00	121	62	Length>8 µm
Trem	3.90	0.091	f/µg lung	42.95	86	42	
Chrys	0.59	0.070	f/µg lung	8.41	41	25	Length>13µm
Trem	0.72	0.024	f/µg lung	30.46	16	11	
Chrys	0.16	0.031	f/µg lung	5.15	11	11	Length>20µm
Trem	0.037	0.008	f/µg lung	4.40	1	4	

[a]Derived from data presented in Tables 4 and 5 of Sebastien et al. (1989)
[b]Geometric mean

It is instructive to compare the ratios presented in Table D-1 to the Thetford:South Carolina ratios of mean cumulative exposures estimated above for chrysotile and tremolite among the cohort members included in the Sebastien et al. (1989) study (24.8 and 62, respectively). As indicated in Table D-1, for chrysotile, the ratio remains approximately constant at about 9 (varying only between 8.4 and 10) for all of the size ranges reported except the longest. For the longest category (L>20), however, the ratio drops to 5. Because fibers longer than 20 µm are expected to be the most persistent in the body (Section 6.2), it may be that the ratio of 5 best represents the relative concentration of long chrysotile structures among the two sets of cohort members.

Because this ratio (for the long fibers found in the lung) is only approximately 1/5 of the estimated ratio for the cumulative exposure to chrysotile (24.8), this suggests that the South Carolina cohort may indeed have been exposed to dusts enriched in long fibers relative to dusts experienced at Thetford. Because the estimate of this ratio is based on counts of at least 11 fibers from Thetford and South Carolina, respectively, it is unlikely that this ratio will vary by more than a factor of 2 or 3 (the 95% CI around 11 fibers, based on a Poisson distribution is 6–19).

The trend with tremolite is even more striking. Moreover, as previously indicated, because tremolite fibers are biodurable, it is the tremolite fibers longer than 20 µm that may best represent the ratio of long fibers to which these two groups of cohort members were exposed. The ratios observed among tremolite fibers steadily decrease from approximately 50 for fibers longer than 5 µm to 4.4 for fibers longer than 20 µm, although this last value is uncertain (due to it being based on only 1 fiber observed among Thetford-derived lungs and only 4 fibers among South Carolina-derived lungs). In fact these data are statistically consistent even with a ratio considerably less than 1, (i.e., with a considerably higher concentration of long tremolite fibers in South Carolina than in Quebec). Given that the ratio of the original cumulative exposures for tremolite was estimated to be 62, that the ratio of long tremolite fibers is only 4.4 suggests that dusts in South Carolina may have been highly enriched in long fibers.

Observations that the fibers to which textile workers were exposed were longer and thinner than those found in mining are further supported by various published size distributions of fibers determined in air samples collected in these environments (see, for example, Gibbs and Hwang 1975, 1980). Also, as noted in Crump (1986), the raw fiber purchased by textile plants was commonly described as the longest grade of product (see Table 22 of Crump). Size issues are addressed further in Section 7.4.

The data in a more recent study by Case et al. (2000) demonstrates even more strongly that South Carolina textile workers were exposed to fibers that were substantially longer than those inhaled by Quebec miners and millers. In this study, lung fiber contents were determined for 64 deceased textile workers and 43 deceased chrysotile miners and millers, respectively, which represent randomly selected subsets of the workers, miners, and millers for whom lung burdens were previously described by Sebastien et al. (1989), as discussed above.

In the Case et al. (2000) study, analyses were conducted on sets of TEM specimen grids that had originally been prepared in the Sebastien et al. (1989) study, thus selection of subjects and the preparation of samples in this study is the same as described above for the Sebastien et al. study. However, Case et al. focused specifically on the counting of fibers longer than 18 μm.

Results from the Case et al. (2000) study are summarized in Table D-2. As indicated in the second column of Table D-2, the mean cumulative exposure to which the selected cohort members from Quebec and South Carolina were exposed in this study was 186 and 3.63 mpcf-y (millions of particles per cubic ft-years), respectively. This gives a Quebec/South Carolina ratio of approximately 51. In contrast the Quebec/South Carolina ratios of the concentrations of asbestos fibers observed in lungs among these selected cohort members are substantially smaller (4.28 for long chrysotile, 12.04 for long tremolite, and 5.45 for long amphibole). This implies that the lungs of South Carolina workers are substantially enriched in these long fibers relative to the lungs of Quebec miners and millers. Moreover, because substantial numbers of long fibers were counted in these analyses, the uncertainty of these ratios is relatively small.

TABLE D-2. ESTIMATED MEAN AIRBORNE EXPOSURE CONCENTRATIONS AND ASSOCIATED LUNG FIBER BURDENS FOR A SELECTED SET OF TEXTILE WORKERS, MINERS, AND MILLERS[a]

Location	Mean Airborne Exposure Concentration (mpcfy)	Lung Chrysotile Content (long fibers) (f/μg)	Lung Tremolite Content (long fibers) (f/μg)	Lung Total Amphibole Content (long fibers) (f/μg)
Quebec Mining	186	0.231	0.325	0.349
SC Textiles	3.63	0.054	0.027	0.064
Ratio	**51.24**	**4.28**	**12.04**	**5.45**

[a]Derived from data presented in Table 2 of Case et al. (2000)

If the estimated K_L's derived for Quebec miners (0.00029) and South Carolina textile workers (0.021), as reported in Table 7-6, are adjusted to account for the relative concentrations of long fibers reported by Case et al. the disparity in these K_L estimates effectively disappears. If adjusted as described in Section 7.4.2, the new K_{L*}'s for Quebec (0.234) and for South Carolina (1.21) now differ by only a factor of 5 (rather than the original factor of 72). Thus, accounting for long structures appears to reconcile these potency estimates.

The data presented by Case et al. (2000) also indicates that the lungs of textile workers in South Carolina (but not those of Quebec miners) contain substantial concentrations of commercial amphibole asbestos fibers (amosite and crocidolite) in addition to tremolite. In fact, the majority of the amphibole fibers observed in lungs from South Carolina workers were composed of the commercial amphibole types. This suggests, among other things, that the exposure environment in South Carolina should actually be characterized as a mixed exposure environment rather than a chrysotile exposure environment. As indicated in the following two paragraphs, however, conclusions concerning the nature of the general exposure environments in Quebec mines or the South Carolina textile mill that are based only on observations among the small subsets of these cohorts examined by Case et al. may not be robust.

Importantly, Case et al. indicate in their paper that, because they observed substantially greater absolute numbers of long fibers in the lungs of Quebec miners than in the lungs of South Carolina workers, they conclude that (regardless of the above analysis), Quebec miners were still exposed to a greater absolute number of long fibers than South Carolina workers. However, this does not appear to be a valid conclusion that can be derived from the data provided in the paper.

We compared the mean exposure concentrations reported for the subset of Quebec miners and South Carolina textile workers that Case et al. (2000) examined (Table D-2) to the distribution of exposures reported among the entire cohorts in Quebec (Table A-2) and South Carolina (Table A-8), respectively. Results suggest that, exposures for the subset of Quebec cohort members included in the Case et al. study are higher than approximately 75% of the exposures experienced by the overall cohort. In contrast, exposures for the subset of the textile worker cohort examined by Case et al. are lower than approximately 50% of exposures experienced in the overall cohort. Thus, given that the mean exposures experienced by the subsets of each cohort examined by Case et al. do not reflect mean exposures for the respective cohorts as a whole, it is not reasonable to compare absolute numbers of structures observed in the lungs of these workers and draw general conclusions about the relative, absolute exposures among the entire, respective cohorts.

At this point it is worth mentioning some of the potential differences in the characteristics of mining dusts and textile mill dusts that may affect biological activity, but that may not be adequately delineated when measuring exposures by PCM (in f/ml) and almost certainly not delineated when exposures are measured by midget impinger (in mpcf), see Section 4.3. During the mining of asbestos, only a small fraction of the rock (generally no more than 10%) that is mined is typically composed of the fibers of interest.

While the host rock in a mine may be of similar chemical composition, it generally represents an entirely different crystalline habit. Nevertheless, a large fraction of the dust that is created during mining is likely composed of fragments from the host rock and many of these fragments

will be of a size that would be included in the particles counted by midget impinger. Furthermore, at least some fraction of the fragments created by the crushing and cutting of the host rock will be elongated "cleavage" fragments (Section 4.0) so that at least some fraction of these may be included even in PCM counts, despite many of them being either too thick to be respirable, or too short or thick to be biologically active (see Section 6.2). Note, although Sebastien et al. (1989) employed TEM to characterize fibers in the study, they apparently employed a fiber definition that was sufficiently broad that they too would have counted large numbers of structures that may be too short or too thick to contribute to biological activity.

In comparison, the dusts created in a textile factory are likely composed almost exclusively of true asbestos fibers. The raw material received by the factory will already have been milled and beneficiated to remove the vast majority of non-fibrous material. It is therefore, much less likely that extraneous fragments (even cleavage fragments) exist that might be counted either by midget impinger or PCM. We make this point because, if this represents the true situation, it would be expected that risk per unit exposure estimates (i.e., exposure-response factors) derived from any mining site, may be smaller than estimates derived for the same fiber type in occupational environments where only finished fiber is used. Thus, another interpretation of the variation observed among estimated K_L values for amphiboles (reported in Section 7.2.2) is that mining values are somewhat low. As later described (Section 7.3.2), the same may be true for amphibole K_M values. The implications of this possibility are discussed further in each respective section.

Note, although the Sebastien et al. (1989) paper suggests that (mpcf) exposure estimates from Thetford and South Carolina grossly suggest the relative range of lung burdens observed, there is too much scatter in the data to determine how closely the air ratios track the lung burden ratios. For example, ratios derived from arithmetic means (rather than the geometric means) for the Sebastien et al. data are substantially different. Moreover, as indicated above, there may be substantially different size distributions in the two environments, which might at least in part be explained by the inclusion of large numbers of cleavage fragments (with dimensions inappropriate for biological activity) in the mining environment.

Although the third of the above-listed hypotheses was not addressed by Sebastien and coworkers, the question of whether a co-carcinogen contributes to the overall observed lung cancer rate among textile workers has been considered by several other researchers. To test the hypothesis of whether oils potentially contributed to disease in South Carolina, Dement and Brown (1994) performed a nested case-control study among a subset of the cohort members previously studied by Dement et al. (most recent update, 1994). In this analysis, Dement and Brown qualitatively assessed the probability of mineral oil exposure for cases and controls based on knowledge of historic descriptions of mineral oil use. The extent of such exposure was then further categorized into three strata: none or little, moderate, or heavy, based on where each worker was longest employed. Cases and controls were then further categorized based on years at risk and level of asbestos exposure. Results from this nested analysis indicated no significant change in the estimated exposure-response slope for asbestos after adjusting for mineral oil exposure.

Additional, albeit qualitative, evidence that oils may not represent an adequate explanation for the relative lung cancer risks observed in mining and textiles is provided by McDonald (1998b).

McDonald suggests that oils were not used in the Roachdale plant until 1974. Therefore, due to latency, it is unlikely that the use of such oils would have had a substantial impact on the observed lung cancer cases at the point in time that the study was conducted (Peto 1980a,b; Peto et al. 1985).

Taken as a whole, the evidence presented in this section suggests that the relative distribution of fiber sizes found in dusts in the textile industry and the mining industry, respectively, may be the leading hypothesis for explaining the observed differences in lung cancer risk per unit of exposure between these two industries.

REFERENCES

Case BW; Dufresne A; McDonald AD; McDonald JC; Sebastien P. Asbestos Fiber Type and Length in Lungs of Chrysotile Textile and Production Workers: Fibers Longer than 18 µm. *Inhalation Toxicology*. 1(Suppl 1):411–418. 2000.

Crump KS. Asbestos Potency Assessment for EPA Hearing. Prepared for Asbestos Information Association/North America. 116 pp. 1986.

Dement JM; Brown DP. Lung Cancer Mortality Among Asbestos Textile Workers: A Review and Update. *Annals of Occupational Hygiene*. 38(4):525–532. 1994.

Dement JM; Brown DP; Okun A. Follow-up Study of Chrysotile Asbestos Textile Workers: Cohort Mortality and Case-Control Analysis. *American Journal of Industrial Medicine*. 26:431–447. 1994.

Gibbs GW; Hwang CY. Physical Parameters of Airborne Asbestos Fibres in Various Work Environments - Preliminary Findings. *American Industrial Hygiene Association Journal*. 36(6):459–466. 1975.

Gibbs GW; Hwang CY. Dimensions of Airborne Asbestos Fibers. In *Biological Effects of Mineral Fibers*. Wagner JC (ed.). IARC Scientific Publication. pp. 69–78. 1980.

Gilbert O. *Statistical Method for Environmental Pollution Monitoring*. Van Nostrand Reinhold, New York. 1987.

Liddell FDK; McDonald AD; McDonald JC. The 1891–1920 Birth Cohort of Quebec Chrysotile Miners and Millers: Development From 1904 and Mortality to 1992. *Annals of Occupational Hygiene*. 41:13–36. 1997.

McDonald AD; Fry JS; Wooley AJ; McDonald JC. Dust Exposure and Mortality in an American Chrysotile Textile Plant. *British Journal of Industrial Medicine*. 39:361–367. 1983a.

McDonald AD; Fry JS; Woolley AJ; McDonald JC. Dust Exposure and Mortality in an American Factory Using Chrysotile, Amosite, and Crocidolite in Mainly Textile Manufacture. *British Journal of Industrial Medicine*. 40:368–374. 1983b.

McDonald JC. Invited Editorial: Unfinished Business - The Asbestos Textiles Mystery. *Annals of Occupational Hygiene*. 42(1):3–5. 1998b.

Peto J. Lung Cancer Mortality in Relation to Measured Dust Levels in an Asbestos Textile Factory. In *Biological Effects of Mineral Fibres*. Wagner JC (ed.). IARC Scientific Publications. pp. 829–836. 1980a.

Peto J. The Incidence of Pleural Mesothelioma in Chrysotile Asbestos Textile Workers. In *Biological Effects of Mineral Fibres*. Wagner JC (ed.). IARC Scientific Publications. pp. 703–711. 1980b.

Peto J; Doll R; Hermon C; Binns W; Clayton R; Goffe T. Relationship of Mortality to Measures of Environmental Asbestos Pollution in an Asbestos Textile Factory. *Annals of Occupational Hygiene*. 29(3):305–355. 1985.

Piolatto G; Negri E; LaVecchia C; Pira E; Decarli A; Peto J. An Update of Cancer Mortality Among Chrysotile Asbestos Miners in Balangero, Northern Italy. *British Journal of Industrial Medicine.* 47:810–814. 1990.

Sebastien P; Plourde M; Robb R; Ross M; Nadon B; Wypruk T. Ambient Air Asbestos Survey in Quebec Mining Towns. Part II: Main Study. Environmental Protection Service, Environment Canada. EPS 5/AP/RQ/2E. July. 1986.

Sebastien P; McDonald JC; McDonald AD; Case B; Harley R. Respiratory Cancer in Chrysotile Textile and Mining Industries: Exposure Inferences from Lung Analysis. *British Journal of Industrial Medicine*. 46:180–187. 1989.

APPENDIX E:
CALCULATION OF LIFETIME RISKS OF DYING OF LUNG CANCER OR MESOTHELIOMA FROM ASBESTOS EXPOSURE

This appendix describes how additional lifetime risk of lung cancer and mesothelioma are calculated from the estimated K_L, the potency for lung cancer, and K_M, the potency for mesothelioma. Let $S_E(t \mid x)$ be the probability of surviving to age t, given survival to age x <t, under some pattern E of asbestos exposure, let $M_E(t)$ be the mortality rate at age t for a given cause (i.e., lung cancer or mesothelioma) under exposure pattern E. For a small age increment, Δt, the probability of dying of the given cause between age t and $t+\Delta t$, given survival to age t, is $M_E(t)*\Delta t$. The corresponding probability of dying given survival to age x_1 is the probability, $S_E(t \mid x_1)$, of surviving to age t given survival to age x_1, times the probability of dying from the given cause given survival to age t, or

$$S_E(t \mid x_1) * M_E(t) * \Delta t \qquad \text{(Eq. E-1)}$$

The probability of dying of the given cause between ages x_1 and x_2 given survival to age x_1 is therefore given by the integral

(Eq. E-2)

$$P_E(x_1, x_2) = \int_{x_1}^{x_2} S_E(t \mid x_1) * M_E(t)\, dt$$

and the additional probability of dying from the given cause as a result of exposure pattern E is

$$P_E(x_1, x_2) - P_O(x_1, x_2) \qquad \text{(Eq. E-3)}$$

where the subscript 0 indicates no asbestos exposure.

The lung cancer and mesothelioma models in Sections A.1 and A.2 model the mortality rate, $M_E(t)$. It is shown below how expressions (Eq. E-2 and E-3) are implemented to convert estimates of mortality rate obtained from the lung cancer and mesothelioma models into estimates of additional risk defined by equation (Eq. E-3).

Let b_i, i=1 to n, represent the mortality rate from all causes for persons in the age interval (t_i-1, t_i), where ti-1 <ti and t_0=0, and let a_i be the corresponding mortality rate for lung cancer. Typically, mortality rates are reported for 5-year age-intervals as the number of deaths in a given calendar year per 100,000 persons alive at the beginning of the year, in which case Δ_i=5 and b_i is the reported value for all-cause mortality divided by 100,000. Let Δ_i be the width of the interval (termed the "i^{th} observational interval") formed by the intersection of the age-interval (t_i-1, t_i) and the interval (x_1, x_2) representing the age-interval over which we wish to calculate the probability of dying of lung cancer. For an unexposed person, the probability of dying of lung cancer in the

i^{th} observational interval, given survival to the beginning of the interval, is calculated as $a_i*\Delta_i$ (risk per person-year times years of observation), and the probability of surviving this age interval, given survival to the beginning of the interval, is calculated as $S_i=1-b_i*\Delta_i$. The probability of surviving to the beginning of the ith interval given survival to age x_1 is calculated recursively as

$$\prod_{j=0}^{i-1} S_j \qquad \text{(Eq. E-4)}$$

where, by definition, $S_0 \equiv 1$. The probability $P_0(x_1, x_2)$ of dying of lung cancer between x_1 and x_2, given survival to x_1, is the sum over each observational interval of the probability of surviving to the beginning of the age-interval times the probability of dying of lung cancer in the interval given survival to the beginning of the interval, or

$$P_0(x_1, x_2) = \sum_{i=1}^{n} \left(\prod_{j=0}^{i-1} S_j \right) * a_i * \Delta_i \qquad \text{(Eq. E-5)}$$

This expression represents a discrete approximation to the integral (Eq. E-2).

We now indicate how this expression is modified to account for exposure. First suppose the exposure pattern E is a step function defined by constant exposure to f (in units of the optimal exposure index) between ages e_1 and e_2, with no exposure at other ages. According to the lung cancer model (Eq. A-1), in the presence of exposure the mortality rate ai for the ith observational interval is increased to $ai*(1+KL*d_i)$, where di is the cumulative exposure lagged 10 years for this interval. In the implementation of this algorithm, d_i is calculated as

$$d_i = \begin{cases} 0, & \text{if } m_i < e_1 + 10 \\ f * (m_i - e_1 - 10), & \text{if } e_1 + 10 \le m_i < e_2 + 10 \\ f * (e_2 - e_1,) & \text{if } e_2 + 10 \le m_i \end{cases} \qquad \text{(Eq. E-6)}$$

where m_i is the midpoint of the ith observational interval.

Thus, to account for exposure, a_i in expression (Eq. E-5) is replaced by $a_i*(1+K_L*d_i)$. The survival probabilities, S_i, in (Eq. E-5) must be modified to account for the affect of exposure upon both mesothelioma and lung cancer. Applying the mesothelioma model (Eq. A-3), the mesothelioma mortality rate in the ith observational interval is K_M*Q_i, where K_M is the mesothelioma potency factor, and

$$Q_i = \begin{cases} 0, & \text{if } m_i < e_1 + 10 \\ f * (m_i - e_1 - 10)^3, & \text{if } e_1 + 10 \le m_i < e_2 + 10 \\ f * \left[(m_i - e_1 - 10)^3 - (m_i - e_2 - 10)^3 \right], & \text{if } e_2 + 10 < m_i \end{cases} \qquad \text{(Eq. E-7)}$$

Thus, to

account for the dose-related effects of both lung cancer and mesothelioma upon survival, $S_i=1-b_i*\Delta$ i is replaced by

$$S_i(E)=1-(b_i-a_i*K_L*d_i-K_M*Q_i)*\Delta_i \qquad \text{(Eq. E-8)}$$

Similarly, the probability of dying of mesothelioma from exposure pattern E between the ages of x_1 and x_2, given survival to x_1, is calculated as

$$K_M*f*\sum_{i=1}^{n}\prod_{j=0}^{i-1}S_j(E)*Q_i*\Delta_i \qquad \text{(Eq. E-9)}$$

The oldest (n^{th}) age-interval is unbounded above. In the implementation of the algorithm, a width of 1/bn is assigned to this interval, which is an estimate of the average survival time in this age-interval. When, as is typical, the oldest interval is for ages $\geq$85 years, this assignment only affects the calculation when the followup period extends past 85 years (x_2>85), and then only minimally.

When used to estimate risk from continuous exposure (24 hours/day, 7 days/week), K_L and K_M were adjusted upward by multiplying by 365/240 (to adjust from an assumed occupational exposure of 240 days/year to 365 days/year) and by 2.0 (to adjust from an assumed exposure during work hours to 24 hours/day, assuming that the amount of air breathed during 24 hours is roughly double the amount breathed during a single work shift.

This algorithm is expanded to handle dose patterns composed of any linear combination of step functions simply by replacing d_i and Q_i by the sum of the corresponding terms resulting from each step function that composes the linear combination. Since any exposure pattern of interest can be approximated to any degree or accuracy by a linear combination of step functions, the algorithm can consequently estimate risk from any exposure pattern of interest.

Age-specific mortality rates for both lung cancer (a_i) and all-causes (b_i) are needed to calculate asbestos-related risk using the above approach. In order to account for differences in asbestos-related risk between males and females and—particularly for lung cancer—between smokers and non-smokers, it is necessary to apply sex- and smoking-specific mortality rates. Lung cancer and all-cause mortality rates for U.S. males and females for the year 2000 (CDC 2003) are provided in Table E-1. Also provided in this table are corresponding rates for never-smokers and current smokers, which were calculated from the U.S. 2000 rates, data on the effect of smoking obtained from the Cancer Prevention Study II (CPS-II) of the American Cancer Society (Thun et al. 1997a), and information on the prevalence of smoking obtained from the National Health Interview Survey (NHIS) (Trosclair et al. 2002). The following paragraphs describe how these smoking-specific rates were calculated.

Table E-1. Mortality Rates for All Causes and Lung Cancer per 100,000 Population per Year

	All Causes			Lung Cancer		
Age	**U.S. 2000**	**Non-smokers**	**Smokers**	**U.S. 2000**	**Non-smokers**	**Smokers**
Males						
1	799.9	799.9	799.9	0	0	0
5	36.5	36.5	36.5	0	0	0
130	18.3	18.3	18.3	0	0	0
288	25.0	25.0	25.0	0	0	0
15-20	94.9	94.9	94.9	0	0	0
20-25	142.0	93.8	281.4	0	0	0
25-30	141.9	93.7	281.2	0.3	0.1	0.9
30-35	157.3	103.9	311.7	0.8	0.2	2.5
35-40	209.8	138.4	416.3	3.3	0.9	10.4
40-45	303.3	192.5	623.7	10.4	2.7	32.6
45-50	461.7	314.9	886.0	26.0	5.8	84.4
50-55	658.3	430.1	1318.1	54.6	8.1	189.1
55-60	1007.5	671.4	1979.1	118	15.7	413.8
60-65	1565.5	1087.1	2948.5	206.2	23.6	734.2
65-70	2399.3	1690.8	4447.7	327.5	42.6	1151.3
70-75	3705.4	2661.6	6723.1	444.0	59.7	1555
75-80	5591.2	4334.9	9223.2	507.3	80.9	1740
80-85	8956.9	7257.3	13870.5	549.6	128.4	1767.3
85+	16605.4	15651.1	19364.3	499.0	144.1	1525.2
Females						
1	654.3	654.3	654.3	0	0	0
5	29.1	29.1	29.1	0	0	0
130	14.5	14.5	14.5	0	0	0
288	16.6	16.6	16.6	0	0	0
15-20	40.0	40.0	40.0	0	0	0
20-25	48.2	48.2	48.2	0	0	0
25-30	56.5	56.5	56.5	0	0	0
30-35	76.0	76.0	76.0	0.9	0.3	3.2
35-40	115.1	112.7	124.2	2.6	0.8	9.3
40-45	172.2	171.7	174.2	8.1	2.6	29.0
45-50	254.0	207.6	428.5	16.6	3.2	67.2
50-55	386.3	324.1	620.3	35.1	11.2	125.0
55-60	611.8	486.0	1085.1	70.9	16.5	275.4
60-65	982.0	774.5	1762.6	122.3	32.1	461.5
65-70	1527.5	1199.7	2760.7	181.6	41.4	709.2
70-75	2381.8	1943.6	4030.4	238.7	81.6	829.6
75-80	3812.6	3230.0	6004.2	268.6	79.6	979.6
80-85	6444.8	5753.4	9045.8	272.8	118.0	855.3
85+	14768.6	13829.2	18302.3	213.5	84.7	698.2

CPS-II (Thun et al. 1997a) prospectively followed more than one million persons in the U.S.

beginning in 1982. Subjects were recruited by volunteers and were ≥30 years of age at the time of enrollment. Smoking status was determined by a questionnaire administered at the time of enrollment. Never smokers were defined as persons who had never smoked any tobacco product, and current smokers as persons who were cigarette smokers at the time of enrollment. Although follow-up has now been extended, following a recommendation of Dr. Thun (Thun 2003), the present calculations are based upon follow-up through 1988 (Thun et al. 1997a). There are two reasons for this: (1) follow-up past 1988 mostly involves older ages for which sufficient numbers of deaths had already occurred prior to 1988 to insure adequate statistical stability of mortality rates; and (2) more importantly, since smoking histories were not updated, with longer follow-up there is greater misclassification of persons who were classified as current smokers at time of enrollment, but who may have quit smoking during the follow-up.

Based on follow-up of the CPS-II cohort through 1988, Thun et al. (1997a) present age-specific mortality rates for a number of causes of death, including lung cancer and all-cause mortality, by 5-year age-intervals beginning at age 30. Separate tabulations are provided for never smokers and for current smokers in both males and females (reproduced in Table E-2). These rates are not necessarily representative of the general U.S. population. For example, a member of the CPS-II cohort is more likely to be college-educated, married, middle-class, and white (Thun et al. 1997b). Note also, that, despite the fact that smoking is a well-documented health risk, female smokers in CPS-II (Table E-2) had lower all-cause mortality than U.S. women in general (Table E-1). Consequently, rather than applying the CPS-II rates directly to the U.S. population, they are used only to estimate age- and sex-specific relative risks resulting from smoking. These relative risks are used in conjunction with estimates of the current fraction of smokers to partition the U.S. 2000 mortality rates between non-smokers and smokers. For a given age, sex and mortality cause (lung cancer or all-cause mortality), we write

(Eq. E-10)

$$r_{2000} \quad r_{NS} * \left(1 - p_{SM}\right) + r_{NS} * RR_{SM} * p_{SM}$$

where r_{2000} is the U.S. 2000 mortality rate for the age, sex and cause category, p_{SM} is the proportion of smokers in the U.S. population, and RR_{SM} is the relative risk for smoking obtained from the CPS-II data (mortality rate in current smokers divided by mortality rate in non-smokers). The U.S. mortality rate for non-smokers, r_{NS}, is estimated by solving this equation. The corresponding U.S. rate for smokers is then estimated as the product of the rate in non-smokers and the relative risk for smoking, $r_{NS}*RR_{SM}$.

Table E-2. CPS-II Mortality Rates for All Causes and Lung Cancer per 100,000 Population per Year[a]

	All Causes		Lung Cancer[b]	
Age	**Non-smokers**	**Smokers**	**Non-smokers (adj)**	**Smokers (adj)**
Males				
25-30	—	—	(0.02)	(0.3)
30-35	—	—	(0.2)	(2.2)
35-40	72.9	219.3	4.6(0.6)	5.9(7.4)
40-45	93.7	303.6	0.0(1.5)	18.7(17.5)
45-50	151.8	427.1	6.0(2.8)	41.4
50-55	221.4	678.5	5.5(4.9)	115.3
55-60	367.7	1083.8	5.3(7.8)	206.1
60-65	672.6	1824.2	11.6	361.1
65-70	1096.7	2884.9	21.5	581.6
70-75	1846.6	4664.5	34.9	909
75-80	3441.2	7321.7	52	1118.3
80-85	5466.5	10447.8	89.2	1227.7
85+	11141.6	13784.9	86.8	919
Females				
30-35	—	—	(0.03)	(0.4)
35-40	80.6	88.8	2.0(0.2)	4.0(2.8)
40-45	109.3	110.9	0.0(0.8)	8.9(9.5)
45-50	122.4	252.6	1.9(2.0)	42.4
50-55	182.1	348.5	5.8	64.7
55-60	268.2	598.8	7.2	119.9
60-65	411.4	936.3	12.3	176.6
65-70	666.5	1533.7	16.7	286.3
70-75	1073.9	2227	30.5	310
75-80	1838.7	3417.9	32.5	400
80-85	3154.2	4959.2	57.6	417.6
85+	8069.2	10679.2	60.6	499.6

[a]Thun et al. (1997a).
[b]Adjusted rates (in parentheses) were used to calculate the rates in Table E-1.
See text for adjustment method.

To implement this approach an estimate is needed for p_{SM}, the proportion of smokers in the U.S. population. Based on the NHIS administered in 2000 to a nationally representative sample of the U.S. non-institutionalized population over 18 years of age, the proportion of current smokers was 0.257 among men and 0.210 among women. Smoking prevalence was fairly age-independent, except among persons greater than 65 years of age. Among men the proportions of current smokers was 0.285, 0.297, 0.264, and 0.102 among men aged 18–24, 25–44, 45–64 and ≥65, respectively. The corresponding proportions for women were 0.251, 0.245, 0.216, and 0.093 (Trosclair et al. 2002). The oldest category likely includes a sizable percentage of former smokers whose mortality rates are influenced by their former smoking habits. Because of this and related problems, it was decided not to age-adjust smoking rates, but simply to apply the overall rates from the NHIS survey. Consequently, the proportion of smokers was assume to be p_{SM}=0.257 in men and p_{SM}=0.210 in women.

Smoking-specific mortality rates were not available from CPS-II below the age of 35. Additionally, in both males and females the CPS-II lung cancer rates in the lowest age categories were based on fewer than 10 deaths, and consequently quite uncertain. In these age categories, the lung cancer rates were adjusted using a cubic function of (age less the oldest age at which the 2000 U.S. rate was zero), keeping the total expected number of lung cancer deaths in these categories equal to the observed number. The resulting adjusted rates are shown in parentheses in Table E-2. Equation E-10 was applied to these adjusted rates.

Turning now to all-cause mortality, for males between the ages of 35 and 60, the CPS-II all-cause mortality rates in smokers were approximately three times the rates in non-smokers (RR≈3). Consequently, to estimate smoking-specific rates below the age of 35, equation E-10 was applied using RR=3 between the ages of 20 and 35 and RR=1 for earlier ages. For women, since the all-cause mortality rates in smokers and non-smokers differed by less than 10% between the ages of 35 and 45, the rates in smokers and non-smokers were assumed to be equal below the age of 35. The resulting smoking-specific rates are shown in Table E-1. The difference in estimated rates between smokers and non-smokers is not necessarily solely due to smoking; other differences in lifestyle between smoker and non-smokers likely contributed, particularly among males.

REFERENCES

Center for Disease Control National Center for Health Statistics (CDC). GMWK210. Death Rates for 113 Selected Causes, by 5-year Age Groups, Race, and Sex: United States, 1999-2000. http://www.cdc.gov/nchs/datawh/statab/unpubd/mortabs/gmwk210_10.htm. 2003.

Thun MJ. Personal Communication to Dr. Kenny Crump. 2003.

Thun MJ; Day-Lally C; Myers DG; Calle EE; Flanders WD; Zhu BP; Namboodiri MM; Heath CW. Trends in Tobacco Smoking and Mortality from Cigarette Use in Cancer Prevention Studies, I (1959 through 1965) and II (1982 through 1988). In *Changes in Cigarette-Related Disease Risks and Their Implication for Prevention and Control*. Burns D; Garfinkel L; Samet J; (eds.). Smoking and Tobacco Control Monograph, No. 8, National Institutes of Health, National Cancer Institute. Government Printing Office. Bethesda, MD. 1997a.

Thun MJ; Peto R; Lopez AD; Monaco JH; Henley SJ; Heath CW; Doll R. Alcohol Consumption and Mortality among Middle-aged and Elderly U.D. Adults. *The New England Journal of Medicine*. 337(24):1705–1714. 1997b.

Trosclair A; Husten C; Pederson L; Dhillon I. Cigarette Smoking among Adults – United States, 2000. *Morbidity and Mortality Weekly Report. Surveillance Summaries*. 51(29):642–645. 2002.