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FINAL

METHODOLOGY FOR CONDUCTING RISK ASSESSMENTS AT ASBESTOS SUPERFUND SITES PART 1: PROTOCOL

INTERIM VERSION

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DISCLAIMER

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1.0 INTRODUCTION

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

The protocol presented in this document was developed based on a detailed, critical review of the literature and additional studies conducted to fill important knowledge gaps in the record. Considerations addressed during the development of this protocol are documented in Part 2 of this report (the Technical Background Document), under separate cover.

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

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

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

Importantly, if the risk models or risk table presented in this document are applied to exposure estimates derived using methods different from those defined herein, the resulting risk estimates may not be valid.

The models employed for assessing asbestos-related risks in this protocol are adapted from those proposed in the Airborne Asbestos Health Assessment Update (U.S. EPA 1986). The approach has been modified, however, to better account for the limitations imposed by asbestos analytical techniques. Studies published since the appearance of

the Update have also provided new insights into the relationship between asbestos measurement and biological activity. Consequently, a review and evaluation of the new studies and key studies published earlier are presented in the companion Technical Background Document (Part 2 of this report).

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

2.0 PROTOCOL FOR ASSESSING ASBESTOS-RELATED RISKS

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

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

Because the hazard from asbestos exposure derives primarily from inhalation, the protocol provided in this document is designed specifically to be applied to estimates of airborne asbestos concentrations to which populations of interest are potentially exposed. Such estimates can be derived either by extrapolation from a well-designed air sampling array or from release and transport modeling of asbestos concentrations measured in representative samples of soils or bulk material, which may serve as sources of airborne asbestos.

Depending on the specific scenario of interest, either estimates of long-term average exposure concentrations or detailed estimates of time-dependent exposure may be required. The latter can be used as inputs to the risk models described in this document (Section 2.1) to assess risk. Risks associated with time-averaged exposure can be derived using the risk table (Section 2.2).

As indicated previously, exposure estimates to be used with this protocol to assess risk need to be representative of the exposure settings of interest and need to be expressed in terms of a specific exposure index. Requirements for developing exposure estimates are therefore highlighted in Section 2.3.

2.1 ESTIMATING RISK USING RISK MODELS

Models to be used for estimating lung cancer and mesothelioma risks are presented below along with a description of the types of data required as inputs and a procedure for evaluating the models.

2.1.1 Lung Cancer

The Airborne Health Effects Assessment Update (U.S. EPA 1986) utilizes a model for lung cancer in which the asbestos-related age-specific mortality from lung cancer at age t is proportional to cumulative asbestos exposure at time t-10 years (i.e., cumulative exposure lagged 10 years), multiplied by the age- and calendar year-specific background mortality rate of lung cancer in the absence of asbestos exposure (Equation 6.1 in Part 2 of this document). The same model is employed here except that it has been modified to incorporate the recommended exposure index, C_{opt}, rather than the more traditional C_{PCM}, which was employed in the original model.

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

$$I_L = I_E[1+K_L C_{opt} d_{(t-10)}] \qquad (2.1)$$

where:

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

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

"C_{opt}" is the concentration of asbestos expressed as the weighted sum of two size categories of asbestos structures defined in Equation 2.2;

"t" is age;

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

"K_L" is the proportionality constant between dose and response. This is the risk coefficient that represents the potency of asbestos. Appropriate values shall be selected as described below.

The above model is a relative risk model in that it assumes that the excess mortality of lung cancer from asbestos is proportional to the mortality in an unexposed population. Since smokers have a much higher mortality from lung cancer, if smoking-specific mortality rates are applied, the model predicts a higher excess mortality from asbestos-related lung cancer in smokers than in non-smokers. This is consistent with the multiplicative relationships between smoking and asbestos that have been observed in epidemiological studies. Note that the K_L in the model pertains to an occupational

pattern of exposure (e.g., 8 hours per day, 240 days per year) and must be modified before application to environmental exposure patterns.

To apply the model described in Equation 2.1 for estimating lung cancer risks to a specific population, the following data are required:

- annualized (age-specific) smoking- and sex-specific mortality rates (both for total mortality and mortality from respiratory cancer) for the specific population of interest;
- time-dependent (rather than time-averaged) exposure estimates that can be integrated to produce annualized (time-dependent) cumulative exposure; and
- an appropriate value to use for the risk coefficient, K_L.

As applied in this protocol, all exposure estimates to be used as inputs to the above model must be expressed specifically in terms of C_{opt}, which is the concentration of asbestos expressed as a weighted sum of two size categories of asbestos structures that are separately enumerated during analysis:

$$C_{opt} = 0.003C_S + 0.997C_L \qquad (2.2)$$

where:

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

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

IMPORTANTLY, THE CONCENTRATIONS OF STRUCTURES REQUIRED FOR DERIVING C_{OPT} MUST BE OBTAINED FROM APPROPRIATE ANALYSES OF ASBESTOS SAMPLES OR THE RESULTING RISK ESTIMATES DERIVED USING THIS PROTOCOL MAY NOT BE VALID. THIS PROTOCOL SHOULD NOT BE APPLIED TO ASBESTOS MEASUREMENTS OBTAINED USING METHODS OTHER THAN THOSE SPECIFIED IN SECTION 2.3.

The value to be employed for K_L in the above model shall be selected from the following table, depending on whether the type of asbestos to which the population of interest is exposed is chrysotile (serpentine asbestos) or one of the asbestiform amphiboles (i.e. crocidolite, amosite, anthophyllite, tremolite, or actinolite):

TABLE 2-1: RECOMMENDED RISK COEFFICIENTS[1]

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

[1] Coefficients derived as described in Chapter 6 of the Technical Background Document (Part 2 of this report).

IMPORTANTLY, THE RISK COEFFICIENTS PROVIDED IN TABLE 2-1 ARE ONLY VALID WHEN USED IN CONJUNCTION WITH ASBESTOS EXPOSURE ESTIMATES EXPRESSED AS DEFINED BY C_{OPT} (EQUATION 2.2).

The recommended procedure for incorporating the data listed above and applying the lung cancer model is described in Appendix A, which describes a lifetable analysis.

2.1.2 Mesothelioma

The model used here to describe mesothelioma mortality in relation to asbestos exposure is the same model proposed in the Airborne Health Assessment Update (U.S. EPA 1986 and Equation 6.7 of Part 2 of this report) except that it has been modified to incorporate the recommended exposure index, C_{opt}, in an identical manner to that described for the lung cancer model (Section 2.1.1). This model assumes that asbestos-induced mesothelioma mortality is independent of age at first exposure and increases according to a power of time from onset of exposure, as described in the following relationship:

$$I_M = K_M \cdot C_{opt} \cdot [(T-10)^3 - (T-10-d)^3] \quad \text{for } T > 10+d \qquad (2.3)$$

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

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

where:

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

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

"T" is the time since first exposure; and

all other factors have been previously defined.

This is an absolute risk model, which means that the incidence of mesothelioma predicted by the model does not depend on the background incidence of the disease. Background mesothelioma cases are rare in the general population in any case. This model also assumes that mesothelioma risk from exposure in any increment of time increases forever, even after exposure ceases. The validity and implications of this latter assumption are addressed in Section 6.2.2 of Part 2 of this report.

To apply the model described in Equation 2.3 for estimating mesothelioma risks to a specific population, the following data are required:

- annualized (age-specific) smoking- and sex-specific total mortality rates for the specific population of interest;
- time-dependent (rather than time-averaged) exposure estimates that can be integrated to produce annualized (time-dependent) cumulative exposure; and
- an appropriate value to use for the risk coefficient, K_M.

AS FOR THE LUNG CANCER MODEL DESCRIBED ABOVE, ALL EXPOSURE ESTIMATES TO BE USED AS INPUTS TO THE MESOTHELIOMA MODEL MUST BE EXPRESSED SPECIFICALLY IN TERMS OF C_{OPT} AS DEFINED IN EQUATION 2.2 AND SUCH ESTIMATES MUST BE DERIVED FROM MEASUREMENTS OBTAINED AS DESCRIBED IN SECTION 2.3 OR RISK ESTIMATES MAY NOT BE VALID.

The value to be employed for K_M in Equation 2.3 shall be selected from the values presented in Table 2-1, based on the type of asbestos being considered (i.e. chrysotile or one of the amphiboles).

Procedures for evaluating Equation 2.3 are presented in Appendix A, which describes a lifetable analysis.

2.2 ESTIMATING RISKS USING THE RISK TABLE

Because sufficient data will rarely be available to apply the models presented in Section 2.1, a risk table (Table 2-2) is presented in this section to provide a simpler

procedure for assessing asbestos risks. The only data required to assess risks using the risk table are estimates of long-term average exposure (*derived from appropriate measurements, as described in Section 2.3*) for each particular exposure scenario and population of interest.

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

In Table 2-2, separate risk estimates are provided for males and females and for smokers and non-smokers. Separate estimates are also presented for exposures containing varying fractions (in percent) of fibrous structures greater than 10 µm in length.

Separate estimates are presented for smokers and nonsmokers because the lifetime asbestos-induced risk of both lung cancer and mesothelioma differ between smokers and non-smokers. The asbestos-induced risk of lung cancer is higher among smokers because the lung cancer model (Equation 2.1) assumes that the increased mortality rate from lung cancer risk due to asbestos exposure is proportional to background lung cancer mortality, which is higher among smokers.

The asbestos-induced risk of mesothelioma is smaller among smokers because the mesothelioma model (Equation 2.3) assumes that risk from constant exposure increases with the cube of age, with the result that the predicted mortality rate is highest among the elderly. Thus, since smokers have a shorter life span than non-smokers, their risk of dying from mesothelioma is also predicted to be smaller.

Separate estimates are provided for different fractions of fibrous structures longer than 10 µm because the model assumes that structures longer than 10 µm are more potent than structures between 5 and 10 µm in length (in a manner consistent with Equation 2.2). The derivation of this model is described in detail in Chapters 5 and 6 of the companion Technical Background Document.

Risks from lifetime exposures to asbestos levels other than 0.0005 may be estimated from the appropriate entry in Table 2-2 by multiplying the value in the selected cell from the Table by the airborne asbestos concentration of interest and dividing by 0.0005 (i.e., by assuming that the additional risk is proportional to the asbestos exposure level). Airborne asbestos concentrations to be used in this manner *must* be estimates of lifetime average exposure and *must* be expressed as structures longer than 5 µm and thinner than 0.5 µm derived as described in Section 2.3. Estimates of the fraction of these structures that are also longer than 10 µm must also be determined to select the appropriate cell of the table from which to derive the risk estimate. Note that the

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

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

two size fractions that are combined to determine C_{opt} (Equation 2.2) are separately enumerated (not combined) when they are to be used in conjunction with Table 2-2.

The procedure described above for estimating risks using Table 2-2 should provide good approximations as long as the projected risk is no greater than 1,000 per 100,000. Risks greater than 1,000 per 100,000 (i.e. 1 in 100) that are derived from the Table are likely to be over-estimated.

Table 2-2 was derived using the approach described in Appendix A by incorporating the age-, sex-, and smoking-specific death rates reported for the general U.S. population and assuming that exposure is constant and continuous at the level indicated in the table. The underlying models are provided in Section 2.1 for cases in which exposure is either not constant or not continuous and for which sufficient data exist to characterize the time-dependence of such exposure. If available, there may also be cases in which it is advantageous to employ mortality data from a control population that better matches the exposed population of interest than the U.S. population as a whole.

2.3 REQUIREMENTS FOR ASBESTOS MEASUREMENTS

As indicated previously, estimates of airborne asbestos concentrations that are required to support risk assessment can be derived either by extrapolation from airborne measurements or by modeling release and dispersion of asbestos from sources (soils or other bulk materials). In either case, exposure estimates must be representative of actual (time-dependent or time-integrated) exposure and must provide measurements of the specific size fractions of asbestos that are components of the optimum exposure index defined by Equation 2.2. Additional considerations that need to be addressed to assure the validity of risk estimates derived using this protocol are indicated below.

2.3.1 Requirements for Measuring Airborne Asbestos to Support Risk Assessment

Considerations that need to be addressed to assure the validity of risk estimates derived from measurements of airborne asbestos include:

- the array of samples collected for estimating airborne asbestos concentrations must be representative of the exposure environment;
- the time variation of airborne asbestos concentrations must be properly addressed;

- airborne samples must to be collected on membrane filters that are suitable for preparation for analysis by transmission electron microscopy (TEM). Appropriate procedures for sample collection are described in Chatfield and Berman (1990) or the ISO Method (ISO 10312)[1];

- sample filters must be prepared for analysis using a direct transfer procedure (e.g. ISO 10312). Should indirect preparation be required (due, for example, to problems with overloading of sample filters), a sufficient number of paired samples will need to be collected and analyzed to establish a site-specific correlation between directly and indirectly prepared samples;

- samples must be analyzed by TEM;

- samples must be analyzed using the counting and characterization rules defined in the ISO Method (ISO 10312) with one modification: only structures longer than 5 μm need to be enumerated. Separate scans for counts of total structures longer than 5 μm and longer than 10 μm are recommended to increase the precision with which the longest structures are enumerated. Importantly, ISO Method rules require separate enumeration and characterization of component fibers and bundles that are observed within more complex clusters and matrices. Such components, if they meet the dimensional criteria defined in Equation 2.2 must be included in the structure count;

- if risks are to be estimated using the risk models (Section 2.1), asbestos concentrations derived from the above-described measurements must be expressed as the weighted sum of structures between 5 and 10 μm in length and structures longer than 10 μm in length, per the exposure index defined in Equation 2.2. Only structures thinner than 0.5 μm are to be included in these counts. Both fibers and bundles that are isolated structures and fibers and bundles that are components of more complex structures are to be included in structure counts (as long as each structure counted satisfies the defined size criteria for the size category in which it is included);

- if risks are to be estimated using the risk models (Section 2.1), the risk coefficient(s) selected from Table 2-1 must be appropriate for the fiber

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

type (i.e. chrysotile or amphibole) and the disease end point (i.e. lung cancer or mesothelioma) relevant to the situation of interest; and

- if risks are to be estimated using Table 2-2 (Section 2.2), rather than deriving the weighted sum described in Equation 2.2, the concentration of asbestos structures longer than 10 μm and thinner than 0.5 μm must be derived to determine the appropriate column of the Table from which to estimate risk and the concentration of total asbestos structures longer than 5 μm and thinner than 0.5 μm must be derived, divided by 0.0005, and multiplied by the risk estimate listed in the appropriate cell of the Table to generate the risk estimate of interest.

2.3.2 Requirements for Estimating Airborne Exposures from Soil or Bulk Measurements Combined with Release and Transport Modeling

Considerations that need to be addressed to assure the validity of risk estimates derived from soil or bulk measurements combined with release and transport modeling include:

- the array of samples collected for estimating source concentrations must be representative of the surface area or volume of source material from which asbestos is expected to be released and contribute to exposure;

- samples must to be prepared and analyzed using the Superfund method for soils and bulk materials (Berman and Kolk 1997), which is the only method capable of providing bulk measurements that can be related to risk;

- membrane filters samples prepared using the tumbler and vertical elutriator per the Superfund method must themselves be prepared for TEM analysis using a direct transfer procedure;

- TEM analysis must be conducted using the counting and characterization rules defined in the ISO Method (ISO 10312) in precisely the same manner that is described above for air measurements. Also, the same size categories need to be evaluated in the same manner described in Section 2.3.1, whether results are to be used to support assessment using risk models or using the risk table; and

- release and dispersion models that are selected for assessing risks must be appropriate to the exposure scenario and environmental conditions of interest. Such models must also be adapted properly so that they accept input estimates expressed in terms of fiber number concentrations.

Procedures suggested for adapting such models are illustrated in a recent publication (Berman 1998).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

then

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The resulting mortality rates are listed in Table B1.

Table B1

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

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