U.S. EPA's External Review Draft Toxicological Review of Libby Amphibole Asbestos

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Science Advisory Board
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Overview

- Noncancer Assessment
- Cancer Assessment
- New Publications

Why Assess Libby Amphibole Asbestos Specifically?

- Clear awareness of noncancer effects in those exposed to Libby amphibole and no IRIS value explicitly for noncancer effects of asbestos.

- Opportunity with epidemiology data to study exposures to the material as mined at Libby and processed rather than estimate its risk from its component minerals.

Toxicological Review

- Review of the available scientific literature most relevant to evaluating the potential health hazard posed from exposures to Libby amphibole asbestos (LAA).

- Aware of the broader literature on asbestos generally, but not trying to publish a review of the entire asbestos literature.

Elements of Toxicological Review

- Hazard description.
- Reference Concentration (RfC): "An estimate *(with uncertainty spanning perhaps an order of magnitude)* of a continuous inhalation exposure to the human population *(including sensitive subgroups)* that is likely to be without an appreciable risk of deleterious effects during a lifetime."
- Inhalation Unit Risk (IUR): "An inhalation unit risk (IUR) is typically defined as a plausible upper bound on the estimate of cancer risk per $\mu g/m^3$ air breathed for 70 years." [fibers/cc in this case]

Literature Search in Support of the Libby Amphibole Assessment

- Used search terms for relevant mineral forms:
  - Libby amphibole (“Libby”, “Libby asbestos,” etc.)
  - Tremolite
  - Winchite
  - Richterite
- Focused additional search on some related issues (e.g. fiber toxicokinetics, susceptible populations, MOA for asbestos in general).
- Drew from a range of literature sources
  - Peer-reviewed journals
  - Government reports
  - Materials submitted to the EPA docket

Section 4: Noncancer Hazard Identification

- Weight of evidence is adequate for:
  - Localized pleural thickening / pleural plaques
  - Diffuse pleural thickening
  - Asbestosis

- Data were insufficient for hazard determination:
  - Other systemic effects

Study Selection Criteria for RfC Quantification

(Table 5-2, Section 5.2.1.1)

- Exposure estimates are available for the study group
- Good study design characteristics
  - Sufficient follow-up
  - Study size / participation rates and no indication of bias
  - Design/analytic approach to address relevant sources of potential confounding
- Relevant exposures
  - Chronic studies versus subchronic or acute
  - Exposure intensity (inform environmental scenarios)
- Good measurements of exposure
  - Measured data (site/task specific)
  - Sample collection / analysis
  - Availability of individual-level exposure data
  - Quality of exposure reconstruction
- Good ascertainment of effects (health outcomes)
  - Severity of effect (precursor, minimal effect, more severe effect)
  - Measurement techniques adequate and sensitive
  - Measurement of effects independent of knowledge of exposure level/group

Two occupational cohorts for RfC Derivation
(Section 5.1)

- Miners in Libby, Montana
  [Amandus et al. (1987 a,b); McDonald et al. (1986b)]

- O. M. Scott workers in Marysville, Ohio
  (vermiculite from Libby, MT)
  [Lockey et al. (1984); Rohs et al. (2008)]

Advantages of O.M. Scott Cohort: (Section 5.2.1.3.2)

- Adequate follow-up
- Minimal exposure outside of the workplace
- Better quality radiographs (ILO 2000, for some)
- Lower exposures – closer to POD
- Ability to consider more covariates

EPA decided to conduct its own exposure-response modeling with individual data

- Published data only presented by exposure quartiles.
- New analysis would allow for explicit evaluation of important covariates.
- …allow use of the higher quality data (sub-cohort); increasing confidence in the resulting exposure-response relationship.
- …allow sensitivity analyses

Several Radiological Endpoints Considered
(Section 5.2.1.4)

- Available data for exposure-response modeling was limited to effects as viewed using standard radiographs:
  - Small opacities – asbestosis
  - Costophrenic angle (blunting/obliteration)
  - Pleural thickening
    - Localized pleural thickening (LPT)
    - Diffuse pleural thickening (DPT)

Criteria for Selecting Critical Effect

(applied in Section 5.2.2)

- Adverse itself, a precursor to an adverse effect or a biologic marker for a relevant health effect.
- Confounding can be adequately accounted for.
- Measured with adequate sensitivity for the results to be biologically relevant.
- Adequate data to define an exposure-response relationship (BMDL or LOAEL/NOAEL).

EPA selected localized pleural thickening (LPT)

EPA Has Requested Review of the Exposure Reconstruction (Section 5.2.3.1, Appendix F)

O.M. Scott workers

- Original Job Exposure Matrix (Lockey 1985)
  - No exposure measurements prior to 1972;
  - Engineering controls implemented from 1968 on
  - 235 air samples
- Additional information available for exposure reconstruction
  - 589 new air samples
  - Focus groups
  - Seasonal work schedules

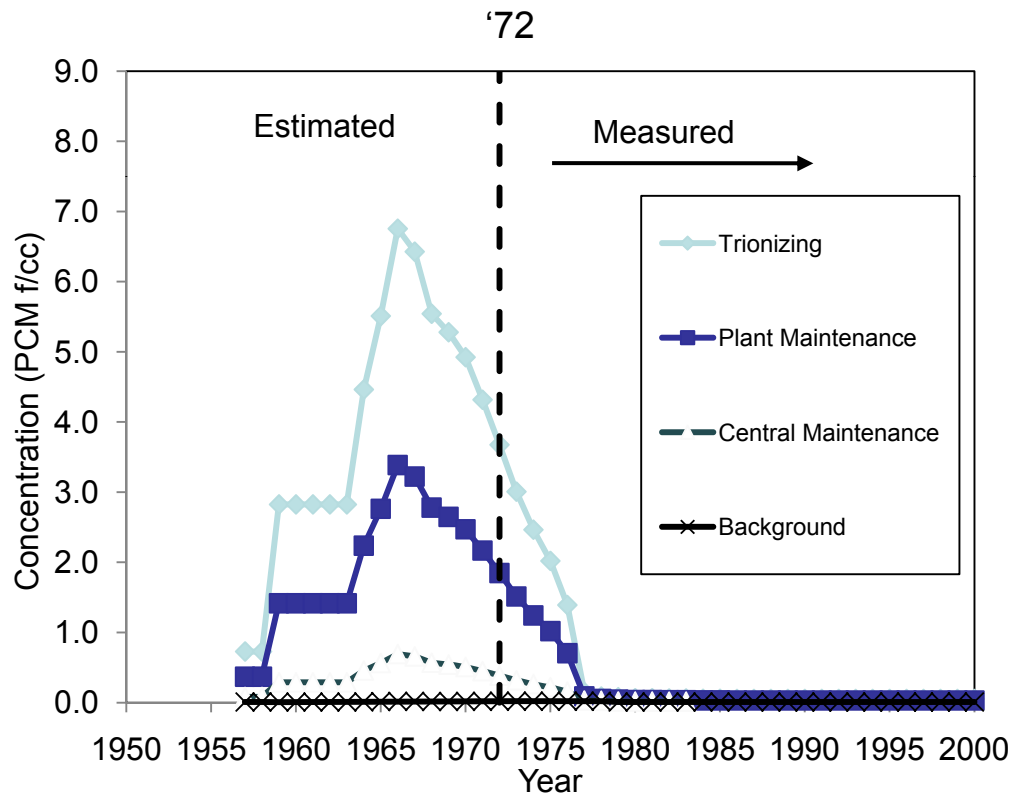


Figure 5-1. Estimated and measured exposure concentrations in Marysville, OH facility

Criteria for selection of the Sub-cohort from O.M. Scott (Marysville, Ohio) (Section 5.2.3.2)

Criteria	Full Cohort	Sub-cohort (Limit to those hired after 1971)
Type and Quality of Outcome Assessment [i.e. Radiographs]	Merge 1980 and 2000-2005 exam data	2002-2005 exam data
Quality of exposure data (measured, reconstructed, quality of information for reconstruction)	Missing measured data for pre-1972 exposures. Pre-1972 exposures were reconstructed (Appendix F).	Post-1971 **exposure estimates based on measured data**
Sample size (statistical power)	N=434, 61 LPT cases	N=118, 12 LPT cases
Data available to address covariates (age, DOB, sex, BMI, smoking , hire date etc.)	Not available for the 1980 cohort (e.g. smoking and BMI)	Lower proportion of missing data (i.e. BMI)
Available endpoints for consideration as the critical effect	LPT, DPT and asbestosis	LPT (only 1 case DPT)
Time to x-ray, from first exposure	Range: (6 mo. to 47 years)	Range: (23.2 to 32.6 years)

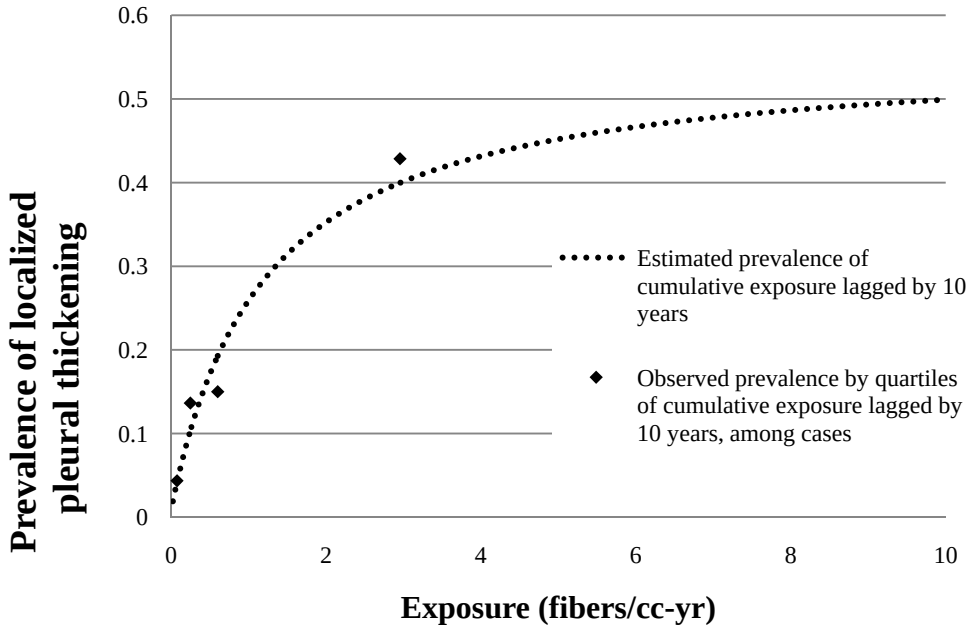
RfC Exposure-Response Modeling

(Section 5.2.3.3, Appendix E)

Best-fitting model was a Michaelis-Menten model

P(LPT) = background + (Plateau - background) × CE ÷ [exp(-a) + CE]

Benchmark dose software suite of models evaluated.



Graph of observed and estimated prevalence of localized pleural thickening calculated using the Michaelis-Menten model with 10-year lagged exposure.

Reference Concentration (Section 5.2.4)

- Point of Departure: 0.1177 (fibers/cc) × year
  The lower 95th confident interval on exposure causing a 10% LPT response
- Converted to lifetime exposure concentration:
  0.1177÷ (70-10) yrs
  $=1.96 \times 10^{-3}$ fibers/cc
- Uncertainty Factors Applied: Total of 100
  1.96×10^{-3} fibers/cc ÷ 100

RfC = 2×10^{-5} fibers/cc; lifetime exposure

Note: The alternative full cohort model provided a POD of 0.0136 (fibers/cc) × year, where T=40 years. If UF total of 100 were applied that would yield an RfC of 4×10^{-6} fibers/cc for lifetime exposure.

Sensitivity Analyses (Section 5.3.1)

- Limited Quantitative impact:
  - Sensitivity to background rate of LPT (15%)
  - Sensitivity to lag (50%)
- Smoking status
  - Statistical power is limited, but analysis suggests a POD for smokers might be lower
- Extrapolation to full-lifetime exposures
  - Two alternatives presented
  - PODs vary by a factor of 4
- Choice of critical effect (Table 5-5)
  - As expected, POD for LPT was lower than PODs for DPT and small opacities
  - Limitation of critical effect to bilateral LPT would result in similar POD: 0.1337 vs. 0.1177 (fibers/cc) yrs

Charge asks your advice on key decision points:

Data on which the RfC is based:

- Exposure reconstruction
- Choice of sub-cohort
- Endpoint selection

Quantitative assessment:

- Exposure-response modeling
  - Evaluation of covariates
  - Selection of best-fit model
- Extrapolation to full-lifetime exposures
- Application of uncertainty factors

Section 4: Evaluation of Carcinogenicity

"Carcinogenic to Humans"

- Associated with increased mortality
  - Lung cancer
  - Mesothelioma

Criteria for Study/Dataset Selection

1) All studies of cancer incidence or mortality in people exposed to Libby Amphibole asbestos
2) Excluded studies without quantitative exposure data (community studies)
3) Excluded studies without well-defined populations (case studies)

Libby workers cohort (Sullivan, 2007)

- Cohort study of inhalation exposures of chronic duration
- Well-documented design, methods, and population characteristics
- Could (with researcher, Dr. Sullivan) extend mortality follow-up and conduct individual-level data analysis

Original analysis

Individual-level data allow for more detailed cancer analysis than from using only summary results in the literature.

- Better understanding of important **aspects of the job exposure matrix** (5.4.3.5)
- Allows explicit control of important **covariates** (5.4.3.6)
- Allows investigation of various **parameterizations of exposure** (5.4.2.4)
- Allows accounting for **time-varying aspects of exposure** (5.4.3.6.2)
- Allows sensitivity analysis of **influence of early high exposure intensities** (5.4.3.6.4)
- Allows sensitivity analysis of **potential confounding by smoking** (5.4.3.6.5)

Prior published analyses have sometimes used the full cohort and sometimes sub-cohorts.

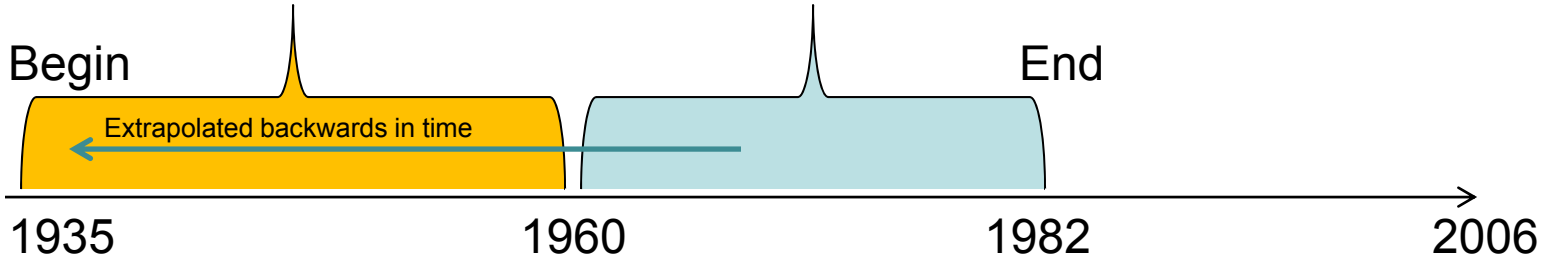
Reference	Cohort definition	Employment Requirement	Mortality Follow-up	Study size (N)
McDonald et al. (1986a and 2004)	Males hired prior to 1963 Exposures 1935−1982	1 year or more	1999	**406**
Amandus and Wheeler (1987)	Males hired prior to 1970 Exposures 1935−1982	1 year or more	1982	**575**
Sullivan (2007)	White males still alive post-1959 Exposures 1935−1982	1 day or more	2001	**1,672**
* Berman and Crump (2008)	White males still alive post-1959 Exposures 1935−1982	1 day or more	2001	**1,672**
Larson et al. (2010a)	Full cohort Exposures 1935−1993	1 day or more	2006	**1,862**
* Moolgavkar et al. (2010)	White males still alive post-1959 Exposures 1935−1982	1 day or more	2001	**1,662**
		1 year or more	2001	**801**

* Re-analysis of Sullivan (2007)

NIOSH Job Exposure Matrix: important information is missing regarding pre-1960 exposures.

Exposure data extrapolated back in time from late 1960s

Job-specific exposure information with range 1-188 fibers/cc



71% of workers had missing department and job title (706/991) during this time.

Only 1% of workers had missing department and job title (9/880)

EPA identified the sub-cohort hired after 1959 as most appropriate study population.

- Reduces measurement error
- Reduces bias

Variety of Exposure Metrics Evaluated

(Section 5.4.2.5)

- **Responsive to SAB's review of OSWER asbestos modeling.**

- **Allows exploration of the influence of early versus late exposures**
  - CE metric gives equal weight to **all** exposures
  - Residence-time weighted CE gives relatively greater weight to **early** exposures
  - Decay (half-lives) gives relatively greater weight to **late** exposures

- **When also considering lags and decay rates, a suite of 40 different parameterizations of exposure metrics considered:**

  Lag time to account for cancer latency (0,5,10, 15, or 20 years)

  Decay of exposure metric (half-life of 5,10, 15, or 20 years)

- **For mesothelioma, the metric proposed by Peto and used by Nicholson in IRIS assessment of asbestos (EPA, 1986a) was also evaluated.**

Cancer Exposure-Response Modeling

(Section 5.4.3.6)

- **For each kind of cancer modeled, EPA used a model form similar to those in the literature for this cohort.**
  - Mesothelioma:
    - Absolute risk model [EPA, 1986a; Moolgavkar et al., 2010]
    - Specifically, a Poisson regression absolute risk model used for rare events (McDonald et al., 2004)
  - Lung cancer:
    - Relative risk model [EPA, 1986a; Sullivan, 2007]
    - Specifically, Cox regression relative risk models used for analysis of time-varying exposures [Larson et al., 2010a; Moolgavkar et al., 2010]
- **Model / exposure metric selection criteria based on relative model fit; then selected health-protective when similar fit.**

Cancer Exposure-Response Results

(Section 5.4.4)

- **Model / exposure-metric results**

  - Mesothelioma:
    - The best-fitting approach had lagged CE with decay (Table 5-11)
    - The metrics that gave more weight to early exposures, such as the Peto model used by Nicholson used in the 1986 IRIS assessment of asbestos (EPA, 1986a) and RTW models, did not fit this data well.
  - Lung cancer:
    - Adequate model fit with multiple exposure metrics (Table 5-12)
    - The best-fitting approach had lagged CE with or without decay

Derivation of the Cancer IUR (Section 5.4.5)

1) Point of Departure (POD): (Appendix G)
   - Exposure-response models for each cancer were used to calculate lifetime cancer risk
   - Response: 1% extra risk of mortality for continuous lifetime exposure (central estimate and 95% lower bound)

2) Cancer-specific unit risks were obtained by dividing the extra risk (1%) by the POD (lower bound on risk-specific exposure).
   - Mode of action not established.
   - Linear extrapolation default.

Derivation of the Cancer IUR (Section 5.4.5)

3) Mesothelioma unit risk adjusted to compensate for underascertainment of deaths (Kopylev et al., 2011)
   - Adjustment factor of 1.39 times (39% increase)

4) The cancer-specific unit risk estimates for mortality from mesothelioma and lung cancer separately were then statistically combined to derive the proposed IUR=0.17 per fibers/cc (see Section 5.4.5.3 for combined cancer)

- **Comparison with other result shows a very similar estimate of mesothelioma cancer unit risks.**
- **EPA's central estimate of lung cancer unit risk is higher than that of others using this cohort.**

Study	Mesothelioma		Lung Cancer	
	Cases/*N*	Estimated lifetime risk (per fibers/cc)	Cases/*N*	Estimated Lifetime risk (per fibers/cc)
EPA (this assessment)	**7/880**	**Upper Bound = 0.12 Central = 0.08**	**32/880**	**Upper Bound = 0.068 Central = 0.040**
Sullivan, 2007	15/1,672	(No estimates of absolute risk)	99/1,672	Upper Bound = 0.037 Central = 0.023
Berman and Crump, 2008	19/1,672	(No estimates provided)	93/1,672	Upper Bound = 0.079 Central = 0.027
Moolgavkar et al., 2010	15/1,662	Upper Bound ≈ 0.13 Central ≈ 0.08	95/1,662	Upper Bound = 0.011 Central = 0.009
Larson et al., 2010	19/1,862	(No estimates of absolute risk)	98/1,862	Upper Bound = 0.010 Central = 0.007

Smoking and Lung Cancer (Section 5.4.6)

- **Looked at potential confounding of lung cancer results (Section 5.4.6.1.6).**
  - Restriction to sub-cohort partially limits confounding by smoking
  - Modeling of birth date partially addresses changes in smoking patterns
  - Proportional hazard test did not show changes over time when smoking rates were changing after Surgeon General's report (1964)
- **Method of Richardson (2010) to evaluate confounding by smoking in the absence of data on smoking did not suggest any confounding. (Section 5.4.3.6.5)**
- **Lung cancer results may reflect effect modification (Section 5.4.6.1.7)**
  - Possible that the estimated effect for lung cancer is actually the risk for an interaction between Libby Amphibole asbestos and smoking
  - Would overestimate risk in populations with lower smoking rates

Charge asks your advice on key decision points:

Data on which the IUR is based:

- Choice of sub-cohort
- Missing data (employment)

Quantitative assessment:

- Exposure-Response Modeling
  - Exposure metric
  - Model selection
- Adjustment for mesothelioma under ascertainment
- Derivation of combined unit risk for lung cancer and mesothelioma mortality
- Smoking as a potential confounder

Additional Literature

- **Supports EPA's finding that pleural thickening is observed in the low exposure range.**

Association Between Cumulative Fiber Exposure and Respiratory Outcomes Among Libby Vermiculite Workers {*Larson et al., JOEM, 2012)*

Radiographic Evidence of Non-occupational Asbestos Exposure from Processing Libby Vermiculite in Minneapolis Minnesota *{Alexander, et al., EHP, 2011}*

Modeling community asbestos exposure near a vermiculite processing facility: Impact of human activities on cumulative exposure *{Adgate et al., Journal of Exposure Science and Environmental Epidemiology (2011) 21, 529–535}*

Additional Literature

- **Supports EPA's finding that pleural plaques may contribute to observations of restrictive lung function deficits.**

Do asbestos-related pleural plaques on HRCT scans cause restrictive impairment in the absence of pulmonary fibrosis? **{**Clin et al ., 2011, Thorax 2011 Nov;66(11):985-91**}**

Radiographic Abnormalities and Spirometry Results in a Cohort Exposed to Libby Amphibole. Larson et al., 2009-abstract Am J Respir Crit Care Med 179;2009:A5894. {Full publication upcoming}

Additional Literature

- **Supports EPA's focus sub-cohort that minimizes exposure measurement error.**

A meta-analysis of asbestos and lung cancer: Is better quality exposure assessment associated with steeper slopes of the exposure-response relationships? {Lenters et al. 2011, Env. Health Perspectives, Nov;119(11):1547-55.}

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Thank You

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