

## Libby Amphibole asbestos; CASRN Not Applicable

Human health assessment information on a chemical substance is included in IRIS only after a comprehensive review of toxicity data by U.S. EPA health scientists from several program offices, regional offices, and the Office of Research and Development. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the positions that were reached during the review process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website at <http://www.epa.gov/iris/backgrd.html>.

### STATUS OF DATA FOR LIBBY AMPHIBOLE ASBESTOS

**File First On-Line 12/08/2014**

Category (section)	Assessment Available?	Last Revised
<b>Oral RfD (I.A.)</b>	not evaluated; message	12/08/2014
<b>Inhalation RfC (I.B.)</b>	yes	12/08/2014
<b>Carcinogenicity Assessment (II.)</b>	yes	12/08/2014

## **I. HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS**

### **I.A. REFERENCE DOSE (RfD) FOR CHRONIC ORAL EXPOSURE**

Substance Name—Libby Amphibole asbestos

CASRN—Not applicable

Section I.A. Last Revised—12/08/2014

The reference dose (RfD) is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (possibly threshold) mode of action. It is expressed in units of mg/kg-day. Please refer to the guidance documents at <http://www.epa.gov/iris/backgrd.html> for an elaboration of

these concepts. Because RfDs can be derived for the noncarcinogenic health effects of substances that are also carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

An oral RfD for Libby Amphibole asbestos was not previously available on the IRIS database.

#### **\_\_\_I.A.1. CHRONIC ORAL RfD SUMMARY**

An oral RfD was not derived. Oral exposure was not assessed because inhalation is the primary route of concern and oral data for Libby Amphibole asbestos is lacking.

#### **\_\_\_I.A.2. PRINCIPAL AND SUPPORTING STUDIES**

Not applicable.

#### **\_\_\_I.A.3. UNCERTAINTY FACTORS**

Not applicable.

#### **\_\_\_I.A.4. ADDITIONAL STUDIES/COMMENTS**

Not applicable.

#### **\_\_\_I.A.5. CONFIDENCE IN THE CHRONIC ORAL RfD**

Not applicable.

#### **\_\_\_I.A.6. EPA DOCUMENTATION AND REVIEW OF THE CHRONIC ORAL RfD**

Not applicable.

#### **\_\_\_I.A.7. EPA CONTACTS**

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) (email address).

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#### **\_\_\_I.B. REFERENCE CONCENTRATION (RfC) FOR CHRONIC INHALATION EXPOSURE**

Substance Name—Libby Amphibole asbestos  
CASRN—Not applicable  
Section I.B. Last Revised—12/08/2014

The reference concentration (RfC) is 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. The RfC considers toxic effects for both the respiratory system (portal of entry) and for effects peripheral to the respiratory system (extrarrespiratory effects). The inhalation RfC (generally expressed in units of mg/m<sup>3</sup>) is analogous to the oral RfD and is similarly intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (possibly threshold) mode of action.

Inhalation RfCs are derived according to *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). Because RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

An inhalation RfC for Libby Amphibole asbestos was not previously available on the IRIS database.

### I.B.1. CHRONIC INHALATION RfC SUMMARY

Critical Effect	Point of Departure*	UF	Chronic RfC
<b>Localized pleural thickening</b>	2.6 × 10 <sup>2</sup> fiber/cc	300	9 × 10 <sup>-5</sup> fiber/cc
<b>Occupational epidemiology study</b>			
<a href="#"><u>Rohs et al. (2008)</u></a>			

\*Conversion Factors and Assumptions—fibers/cc = unit of phase contrast microscopy (PCM) measurements. 0.000001 fiber/cc = 1 fiber/m<sup>3</sup>. A benchmark response (BMR) of 10% extra risk of localized pleural thickening (LPT) was used in the estimation of the point of departure (POD).

UF = uncertainty factor.

## **I.B.2. PRINCIPAL AND SUPPORTING STUDIES**

**Principal Study.** The RfC was derived from a study of O.M. Scott, Marysville, OH plant workers [([Rohs et al., 2008](#)); see Table 4-4 of the Toxicological Review]. This study included 298 workers, of whom 280 completed the study interview (with work history and smoking history) and chest x-ray. The evaluation of each worker included an interview to determine work and health history, pulmonary examination, and chest x-ray. Libby Amphibole asbestos (LAA) exposure was estimated using the procedure described in the toxicological review. In the Rohs et al. study, exposure was assumed to occur from 1963 to 1980 in this study, assuming an 8-hour workday and 365 days of exposure per year ([Benson, 2014](#)). Each worker supplied a detailed work history (start and end date for each area within the facility). The exposure reconstruction resulted in a cumulative exposure estimate for each individual. The estimated cumulative exposure for this study ranged from 0.01 to 19.03 fibers/cc-year (mean = 2.48). The time from first exposure ranged from 23 to 47 years. Exposure outside of work was assumed to be zero.

Three board-certified radiologists, blinded to all identifiers, independently classified the radiographs using the 2000 ILO classification system ([ILO, 2002](#)). [Rohs et al. \(2008\)](#) determined that diffuse pleural thickening was present when at least two of the three readers recorded pleural thickening with blunting of the costophrenic angle, localized pleural thickening was present when at least two of the three readers recorded thickening, with or without calcification, excluding solitary costophrenic angle blunting, and that interstitial abnormalities indicative of asbestosis were present if at least two of the three readers identified small irregular opacities of profusion 1/0 or greater. Radiographs classified as unreadable (*n* not reported) were not used in the analysis.

**Overview of Studies.** Epidemiology studies demonstrate consistent results pertaining to the association between LAA exposure and various forms of respiratory effects, with effects seen in both occupationally exposed worker populations and in community populations with nonoccupational exposure. The risk of mortality related to asbestosis (parenchymal disease) and other forms of nonmalignant respiratory disease is elevated in the Libby, MT vermiculite mining and processing operations workers, with a pattern of increasing risk with increasing cumulative exposure (more than a 10-fold increased risk of asbestosis and a 1.5- to 3-fold increased risk of nonmalignant respiratory disease) in the analyses using internal referent groups in [McDonald et al. \(2004\)](#), [Sullivan \(2007\)](#), and [Larson et al. \(2010b\)](#). Radiographic evidence of small opacities (evidence of parenchymal damage) and pleural thickening has also been shown in studies of Libby workers ([Larson et al., 2012a](#); [Larson et al., 2010a](#); [Whitehouse, 2004](#); [Amandus et al., 1987a](#); [McDonald et al., 1986b](#)), and in the studies of workers in the Marysville, OH plant ([Rohs et al., 2008](#); [Lockey et al., 1984](#)). In the Marysville cohort, the prevalence of small opacities (interstitial changes in the lung) increased from 0.2% in the original study to 2.9% in the follow-up study, and the prevalence of pleural thickening increased from 2 to 28.6%. No effects

on lung function were found in the original study ([Lockey et al., 1984](#)), and lung function was not reported for the [Rohs et al. \(2008\)](#) analysis of the cohort follow-up. Data from the Agency for Toxic Substances and Disease Registry (ATSDR) community health screening study in Libby, MT (details available in Table 4-11 in Toxicological Review) indicate that the prevalence of pleural abnormalities, identified by radiographic examination, increases substantially with increasing number of exposure pathways ([Peipins et al., 2003](#)). The presence of pleural plaques is associated with a small decrement in lung function (approximately 5%) when evaluated based on mean values ([Weill et al., 2011](#)), and the presence of LPT is associated with an increased risk of restrictive lung function ([Larson et al., 2012b](#)). Stronger associations are seen with the presence of DPT in both of these studies. Additional evidence of respiratory effects of LAA exposure comes from the study of residents in an area surrounding a processing plant in Minneapolis, MN ([Alexander et al., 2012](#)).

Although data exist that define exposures from some activities in the Libby, MT community studies (see Section 2.3 of the Toxicological Review), the available exposure data were insufficient to estimate exposure at the individual level. Only studies that include exposure measurement data allowing estimation of individual exposures and that identify appropriate health effects are considered for RfC derivation ([Alexander et al., 2012](#); [Larson et al., 2012a](#); [Rohs et al., 2008](#); [Amandus et al., 1987a](#); [McDonald et al., 1986b](#); [Lockey et al., 1984](#)). Among these six candidate principal studies (see Figure 5-1), one study was of the community surrounding a vermiculite processing facility in Minneapolis, MN ([Alexander et al., 2012](#)), three were occupational studies of exposed workers in Libby, MT ([Larson et al., 2012a](#); [Amandus et al., 1987a](#); [McDonald et al., 1986b](#)), and two were studies in workers from the Marysville, OH facility ([Rohs et al., 2008](#); [Lockey et al., 1984](#)). The studies by [Larson et al. \(2012a\)](#) and [Rohs et al. \(2008\)](#) represent the most recent evaluations of the occupational studies of exposed workers in Libby, MT and Marysville, OH workers, respectively, and were considered as candidate principal studies for the derivation of the RfC, along with the study of the Minneapolis community by [Alexander et al. \(2012\)](#).

As detailed in Section 5.2.1 of the Toxicological Review, each of the available studies has strengths and weaknesses. The cohort of Marysville, OH workers ([Lockey et al., 1984](#)) and the follow up by [Rohs et al. \(2008\)](#) was selected over the Libby worker cohort as the principal cohort for deriving the RfC. The reasons for this selection are that the Marysville cohort studies (1) lack confounding by residential and community exposure, (2) contain information on availability of important covariates (e.g., body mass index), (3) have an exposure-response relationship defined for lower cumulative exposure levels (particularly the workers hired in 1972 or later and evaluated in 2002–2005), (4) have adequate length of follow-up, (5) use more recent criteria for evaluating radiographs ([ILO, 2002](#)), (6) have high-quality exposure estimates based on numerous industrial hygiene samples and work records (see Section 5.2.1 of the

Toxicological Review for details), and (7) contain availability of data on time since first exposure (TSFE) matched to the exposure data. The study of Libby workers ([Larson et al., 2012a](#)) had many of these same attributes (e.g., adequate follow-up and high-quality exposure estimates), but exposure levels were generally higher in this group compared to the Marysville workers, and the Libby workers may have experienced greater levels of undocumented “take home” and other ([Larson et al., 2012a](#)) nonoccupational exposure for which TSFE data were more uncertain. The main limitation in the study of Minneapolis community residents ([Alexander et al., 2012](#)) was the relatively lower quality of the exposure information; exposure estimates were based on a small number of total dust measurements from stack emissions combined with air dispersion modeling, and the authors estimate that the individual exposure estimates are likely to have an order of magnitude of uncertainty. Thus, the study of Marysville workers with a focus on the subset of workers hired in 1972 or later and evaluated in 2002–2005 ([Rohs et al., 2008](#)) was selected as the principal study for RfC derivation.

**Selection of Critical Effect.** LPT was selected as the critical effect for derivation of the RfC, with a BMR of 10% extra risk. LPT was selected because, among the noncancer radiographic endpoints evaluated in the principal study, it is the endpoint that generally appears soonest after exposure and at the lowest levels of exposure (i.e., is deemed the most sensitive endpoint). LPT is a pathological change associated with decreased pulmonary function and thus is considered an appropriate adverse effect for deriving the RfC (see discussion in the Toxicological Review in Section 5.2.2.3 and systematic review and meta-analysis in Appendix I). EPA has found statistically significant decrements of 4.09 % predicted forced vital capacity (FVC, 95% CI: 2.31, 5.86) and 1.99 % predicted forced expiratory volume (FEV<sub>1</sub>, 95% CI: 0.22; 3.77) in people exposed to asbestos with pleural plaques (LPT was introduced as a term in the 2000 ILO guidance. LPT includes plaques on the chest wall and at other sites (e.g. diaphragm). Plaques on the chest wall can be viewed either face-on or in profile. A minimum width of about 3 mm is required for an in-profile plaque to be recorded as present according to the 2000 ILO guidance. In 2000 ILO, the terms LPT and pleural plaques are the same. In earlier ILO guidelines, pleural plaques are defined differently than pleural plaques or LPT in 2000 ILO). [Larson et al. \(2012a\)](#) showed a statistically significant increased risk of people with LPT having “restrictive spirometry” and concluded that this abnormality may result in lung function impairment. However, the available data do not lead EPA to conclude LPT should be considered a frank effect and thus EPA selects a BMR of 10% extra risk for this endpoint.

In the principal study ([Rohs et al. \(2008\)](#)), pleural thickening was observed in 80 workers (28.7%), and small opacities ( $\geq 1/0$ ) were observed in 8 (2.9%). The 80 workers with pleural thickening include 68 with LPT (85%) and 12 with DPT (15%). Six of the eight participants with small opacities also had pleural thickening (four as LPT, two as DPT). The prevalence of pleural thickening increased across exposure quartiles from 7.1% in the first quartile to 24.6,

29.4, and 54.3% in the second, third, and fourth quartiles, respectively [see Table 4-9 of the Toxicological Review; ([Rohs et al., 2008](#))].

At the individual level, LPT and the associated decrement in mean FVC or FEV<sub>1</sub> may or may not have a noticeable effect for a given patient. The American Thoracic Society ([ATS, 2004](#)) stated that “[a]lthough pleural plaques have long been considered inconsequential markers of asbestos exposure, studies of large cohorts have shown a significant reduction in pulmonary function attributable to the plaques, averaging about 5% of FVC, even when interstitial fibrosis (asbestosis) is absent radiographically.” The analyses of x-ray and high-resolution computed tomography (HRCT) studies individually (see Figures I-4 and I-5 of the Appendix I of the Toxicological Review) suggest that subclinical fibrosis does not fully explain the observed associations between pleural plaques and pulmonary function decrements. At the population level, [ATS \(2000\)](#) stated that “any detectable level of permanent pulmonary function loss attributable to air pollution exposure should be considered as adverse.” Even small changes in the mean of a distribution of pulmonary function parameters can result in a much larger proportion of the exposed population shifted down into the lower “tail” of the pulmonary function distribution.

**Methods of Analysis.** Analysis supporting the RfC is derived based on data from a subset of the Marysville workers—those who were evaluated in 2002–2005 and hired in 1972 or later. These workers were selected due to the greater certainty in their exposure assessment. Benchmark concentration (BMC) modeling was used to derive the POD. Statistical models were evaluated based on biological and epidemiological considerations (see Section 5.2.2.6.1 of the Toxicological Review) and EPA’s Benchmark Dose Technical Guidance ([U.S. EPA, 2012](#)). Considerations included (1) the nature of the data set (i.e., cross-sectional, dichotomous health outcome data), (2) ability to estimate the effect of exposure and of covariates, (3) appropriate inclusion of a plateau term representing theoretical maximal prevalence of the outcome, and (4) appropriate estimation of the background rate of the outcome. A number of models were evaluated, and the Dichotomous Hill model with the plateau parameter fixed at a literature-derived value of 85% was selected for the derivation of a POD and sensitivity analyses. This model had very similar fit to others evaluated and was thought to provide the greatest flexibility and ability to determine sensitivity of model results to various assumptions. EPA considered several exposure metrics informed by general biology and the epidemiologic literature, including mean exposure intensity, cumulative exposure (which incorporates duration of exposure), and residence time-weighted (RTW) exposure (which incorporates TSFE by weighting more heavily exposures occurring in the more distant past). EPA selected mean exposure intensity for the RfC based on satisfactory statistical fit of the modeling.

An important feature of the exposure response analysis is the ability to include effects of TSFE in the modeling. TSFE has been shown in the literature to be important in evaluating risk of

LPT, and studies have shown that prevalence of LPT can increase with increasing TSFE, even after exposure has ceased. EPA evaluated TSFE as a predictor in the primary analytic group of workers hired after 1972 and evaluated in 2002–2005, but found that TSFE was not significantly associated with LPT in this group—likely due to the very low variability in TSFE for this particular population. Thus, EPA used a hybrid modeling approach to use information on the effect of TSFE from a larger subset of the Marysville workers evaluated in 2002–2005 with greater variability in TSFE. The model was fit to the data for the group of all workers evaluated in 2002–2005 (regardless of hire date), including both LAA exposure and TSFE as predictors. The regression coefficient corresponding to TSFE was then set as a fixed parameter in the model for the primary analytic group of workers hired in 1972 or later. In this hybrid modeling, mean exposure was used due to its superior model fit compared to cumulative exposure. RTW exposure was not used because TSFE was included as a separate covariate (to avoid collinearity of predictors). Using this modeling approach (details in Section 5.2.2.6.2 of the Toxicological Review), the resulting  $BMC_{10}$  under these modeling assumptions is 0.0923 fiber/cc; the corresponding lower 95% confidence limit of the  $BMC_{10}$  ( $BMCL_{10}$ ) is 0.026 fiber/cc.

### **\_\_\_I.B.3. UNCERTAINTY FACTORS**

UF = 300

- An interspecies uncertainty factor,  $UF_A$ , of 1 is applied for extrapolation from animals to humans because the POD used for the derivation of the RfC was based on human data.
- An intraspecies uncertainty factor,  $UF_H$ , of 10 was applied to account for human variability and potentially susceptible individuals. Only adults sufficiently healthy for full-time employment were included in the principal study and the study population was primarily male. Other population groups, such as the elderly, children, and those with pre-existing health conditions, were not evaluated in the principal study and may have a more sensitive response to LAA exposure.
- An uncertainty factor for extrapolating from a lowest-observed-adverse-effect level (LOAEL) to a no-observed-adverse-effect level (NOAEL),  $UF_L$ , of 1 was applied because this factor was addressed as one of the considerations in selecting a BMR for BMC modeling.
- A database uncertainty factor,  $UF_D$ , of 3 was applied to account for database deficiencies in the available literature for the health effects of LAA.

Although a large database exists for asbestos in general, only four study populations exist for LAA specifically: the Minneapolis, MN community study, the Marysville, OH worker cohort, the Libby worker cohort, and the ATSDR community screening (which includes some Libby worker cohort participants). Studies conducted in three of these populations Minneapolis community study ([Alexander et al., 2012](#)); Libby worker cohort; ([Larson et al.,](#)



2012a); and Marysville workers; (Rohs et al., 2008)] have all demonstrated substantial numbers of LPT cases occurring at the lowest exposure levels examined in each study (Christensen et al., 2013), lending confidence to the use of LPT as a critical effect and (Rohs et al., 2008) as the principal study for RfC derivation.

However, studies in the Libby population have also demonstrated an association between exposure to LAA and autoimmune effects [i.e., self-reported autoimmune disease and autoimmune markers in Libby residents (Marchand et al., 2012; Noonan et al., 2006; Pfau et al., 2005)]. Because these studies did not provide exposure-response information, it is unknown whether a lower POD or RfC would be derived for these effects. For other (non-Libby) forms of amphibole asbestos there is evidence for autoimmune effects from a study of individuals in a community exposed to tremolite. In the Metsovo population, there were changes in immune parameters in tremolite-exposed individuals without pleural plaques, and additional immune markers (including autoantibodies) were increased in individuals with pleural plaques (Zerva et al., 1989). Also, it has been hypothesized that shorter asbestos fibers reach the pleura via passage through lymphatic channels (Peacock et al., 2000), although experimental evidence is lacking for this or alternative potential mechanisms of fiber migration. This uncertainty in the sequence of health effects (pleural or autoimmune) is the basis for selecting a UF<sub>D</sub> of 3.

- In addition, this assessment applied a data-informed UF. A data-informed subchronic-to-chronic uncertainty factor, UF<sub>S</sub>, of 10 was applied because, for this particular health endpoint, even ~30 years of observation (Rohs et al., 2008) is insufficient to describe lifetime risks. Although chronic exposure has been generally defined as more than approximately 10% of lifetime, the EPA's RfC guidance (U.S. EPA, 1994) states that for human data “[t]he best data to use for calculating an RfC would be a population study of humans that includes sensitive individuals exposed for lifetime or chronic duration, and that evaluates the critical endpoint or an appropriate early marker for the disease.... However, the amount of exposure in a human study that constitutes subchronic is not defined, and could depend on the nature of the effect and the likelihood of increased severity or greater percent response with duration.” Similarly, the 2014 *Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation* (U.S. EPA, 2014) advises that “[e]xtrapolation is most scientifically robust when data are first evaluated before using defaults.” Consistent with those documents, EPA first evaluated the data on follow-up time (in this case TSFE) both with respect to the data on LAA and what is known from the literature about other amphiboles and asbestos generally before considering extrapolation.

For LAA, the study by Rohs et al. (2008) is a follow-up on the Lockey et al. (1984) investigation, and while the earlier study showed the prevalence of all pleural abnormalities together as 2.0% in 1980 (see Table 4-8 of the Toxicological review), the study by Rohs et al. (2008) showed that in 2002–2005, the prevalence of LPT increased to 26.2% (in workers

without other asbestos exposure; see Table 5-3 and Figure 5-2 of the Toxicological review), a 13.1-fold increase in 22-23 years with very low additional exposure during the additional years of follow-up.

There are no epidemiologic data on the relationship between TSFE and the prevalence of pleural plaques for other amphiboles. There are data on other epidemiologic cohorts exposed to general asbestos. While the type of fiber exposure is not defined in any of the other studies of pleural plaques and TSFE, it could be reasonably inferred from listed occupations to be either mostly chrysotile or mixed chrysotile and amphibole exposures.

One study of shipyard workers likely exposed to mostly chrysotile that also used x-ray to diagnose pleural plaques ([Järholm, 1992](#)) presented data by 5-year intervals of TSFE from 0 to 54 years. Although people with higher TSFE were likely exposed to higher concentrations (due to relative lack of historical industrial hygiene), the prevalence of having pleural plaques was consistently greater with longer TSFE and the prevalence increased with increasing time. The prevalence increased from 1.7% at 12 years of TSFE to 24% at 27 years of TSFE and then to 86% at 52 years of TSFE—a rise of 50-fold in 40 years. A 3.6-fold increase was observed for the last 25 years. The prevalence at 27 years of TSFE is similar to prevalence as in the Marysville, OH cohort which had a 26.2% prevalence at about 33 years of TSFE.

One study of multiple occupations with undetermined asbestos exposure, likely mostly chrysotile or mixed chrysotile and amphibole exposures, that used HRCT to diagnose pleural plaques ([Paris et al., 2009](#)) presented data by quartiles of TSFE. Note that, since HRCT is known ([ATS, 2004](#)) to identify 1.5–2 times more plaques than x-ray detects, the relationship with TSFE may be different than with x-ray data. In this HRCT study, the prevalence increased 3.2 fold in 42 years, from 11.7% at 18 years of TSFE to 37.6% at 60 years of TSFE. However, unlike [Järholm \(1992\)](#), the intervals of TSFE in this study were of widely divergent length. For example, the growth between two narrowly defined intervals of similar length was 1.7-fold in only 5.5 years from TSFE of 39.5 years to TSFE of 45 years. Note that in both of these studies, the growth rate was consistent, but uneven over periods of observations.

It is clear from supporting studies on exposure to other types of asbestos (some of which use HRCT rather than x-ray data and therefore are identifying a different outcome) that the qualitative pattern holds true that prevalence of pleural plaques continue to increase with TSFE as high as 50–60 years, but the range of rates varies across these studies from a 3.2-fold increase after 42 years to a 50-fold increase after 40 years TSFE. Data specific to LAA (where x-rays were used to diagnose LPT) shows a 13.1-fold increase in the 22–23 years observed between the original analysis of the LAA-exposed cohort by [Lockey et al. \(1984\)](#) and the follow-up study by [Rohs et al. \(2008\)](#).

The risk of LPT, continues to increase throughout life (even with less-than-lifetime exposures). Because the RfC is intended to apply to noncancer effects due to lifetime exposure, the limitation in the observed TSFE in the principal study and in the supporting epidemiologic data strongly suggests extrapolation from known exposures to lifetime exposures.

As the first attempt at extrapolation, EPA considered basing the point of departure on the modeled BMCL for lifetime exposure and follow-up (TSFE = 70 years) and the target benchmark response rate of 10% extra risk. However, there is considerable uncertainty in that extrapolation as indicated by a ratio of 1,000 when comparing lifetime BMC to lifetime BMCL ( $BMC_{70y} = 0.0027$ ;  $BMCL_{70y} = 2.7 \times 10^{-6}$ ). Next, EPA examined the ratio of the central estimates from the model. EPA calculated the ratio of the model-predicted BMC at TSFE of 28 to the modeled BMC at TSFE of 70 years; that ratio is approximately 34.

As noted on page 5-40, EPA also used the model to examine the estimated increase in the central estimate of the response rate for increases in TSFE from the 28 years used to derive the point of departure to a TSFE of 70 years. That ratio depends on the concentration whose risk is being evaluated, so EPA calculated that ratio at the point of departure concentration (0.026 fiber/cc) that is the primary modeling result. For that concentration, the central estimate of the risk at TSFE = 70 years is ~10-fold greater than the central estimate of the risk at TSFE = 28 years (from 6% to 61%) as shown in Figure 5-4 of the Toxicological review.

There is some uncertainty as to whether the prevalence would increase in the same manner for additional years of TSFE outside the range of observed data as it does within the range of the observed data on LAA. There are limited non-Libby asbestos data and extrapolations that point to an uncertainty value of about 3. However, having considered the epidemiologic data and the potential extrapolation information, EPA concluded that a data-informed  $UF_S$  of 10 is appropriate in this situation where most of the epidemiologic data, including the LAA data, predicts a 10-fold increase or more in the prevalence of pleural plaques (or LPT). Some extrapolations project a factor that might be as high as 34-fold, but only if the rate of increase remained the same at larger values of TSFE. For these reasons, a data-informed  $UF_S=10$  was applied.

$$\text{Composite UF} = UF_A \times UF_H \times UF_L \times UF_D \times UF_S = 1 \times 10 \times 1 \times 3 \times 10 = 300$$

The derivation of the RfC from the study of the Marysville, OH worker cohort [i.e., ([Rohs et al., 2008](#))] was calculated from a  $BMCL_{10}$  for LPT of 0.026 fiber/cc (the POD), divided by a composite UF of 300. As derived below, the chronic RfC is  $8.67 \times 10^{-5}$  fiber/cc, rounded to  **$9 \times 10^{-5}$  fiber/cc** for LAA:

$$\begin{aligned}\text{Chronic RfC for LPT} &= \text{BMCL}_{10} \div \text{UF} \\ &= 0.026 \text{ fiber/cc} \div 300 \\ &= 8.67 \times 10^{-5} \text{ fiber/cc, rounded to } \mathbf{9 \times 10^{-5} \text{ fiber/cc}}\end{aligned}$$

Note that for the RfC calculations, the fiber concentrations are presented as continuous lifetime exposure in fibers/cc where exposure measurements are based on analysis of air filters by phase contrast microscopy (PCM). Current analytical instruments used for PCM analysis have resulted in a standardization of minimum fiber width considered visible by PCM between 0.2 and 0.25  $\mu\text{m}$ . Historical PCM analysis (1960s and early 1970s) generally had less resolution, and fibers with minimum widths of 0.4 or 0.44  $\mu\text{m}$  were considered visible by PCM ([Amandus et al., 1987b](#); [Rendall and Skikne, 1980](#)). Methods are available to translate exposure concentrations measured in other units into PCM units for comparison.

While this assessment is informed by studies of other types of asbestos, it is not a complete toxicity review of other amphiboles or of chrysotile asbestos.

**Alternative RfCs.** Although EPA derived the RfC above on a model based on mean exposure, Section 5.2.4 of the Toxicological Review illustrates an alternative derivation of an RfC from the same cohort with an alternative exposure metric of cumulative exposure. EPA also conducted modeling of the full Marysville cohort using all individuals who participated in the health examination in 1980 ([Lockey et al., 1984](#)) and 2002–2005 ([Rohs et al., 2008](#)), and who were not exposed to asbestos from a source outside of the Marysville facility (see Table 5-3 and Appendix E of the Toxicological Review for details). The alternative analyses were conducted to substantiate the derivation of the RfC derived from the subset of workers evaluated in 2002–2005 and hired in 1972 or later. Due to differences in the 1980 x-ray evaluations compared with the 2002–2005 x-ray evaluations, the modeling of this full cohort ( $n = 434$  individuals) was performed using an alternative critical effect of “any pleural thickening” (APT). A BMR of 10% extra risk was used in the modeling analyses (modeling of the combined cohort is described in detail in Appendix E of the Toxicological Review). These analyses yielded five other RfC values (presented in Table E-11 of the Toxicological Review). All of the alternative values were within threefold of the RfC of  $9 \times 10^{-5}$  fiber/cc described above. This series of derivations further substantiates the RfC derived from the subset of Marysville workers evaluated in 2002–2005 and hired in 1972 or later.

#### **I.B.4. ADDITIONAL STUDIES/COMMENTS**

The major noncancer health effects observed following inhalation exposure to LAA are effects on the lungs and pleural lining surrounding the lungs. These effects have been observed primarily in studies of exposed workers and community members, and are supported by laboratory animal studies. Recent studies have also examined other noncancer health effects

following exposure to Libby Amphibole, including autoimmune effects and cardiovascular disease; this research base is currently not as well developed as that of respiratory noncancer effects. Adequate data are not available to differentiate the health effects of the predominant mineralogical forms composing LAA. Although the adverse effects of tremolite are reported in the literature, the contribution of winchite and richterite to the aggregate effects of LAA has not been determined.

Laboratory animal and mechanistic studies of LAA are consistent with the noncancer health effects observed in both Libby workers and community members. Pleural fibrosis was increased in hamsters after intrapleural injections of LAA ([Smith, 1978](#)). More recent studies have demonstrated increased collagen deposition consistent with fibrosis following intratracheal instillation of LAA fibers in mice and rats ([Padilla-Carlin et al., 2011](#); [Shannahan et al., 2011a](#); [Shannahan et al., 2011b](#); [Smartt et al., 2010](#); [Putnam et al., 2008](#)). Pulmonary fibrosis, inflammation, and granulomas were observed after tremolite inhalation exposure in Wistar rats ([Bernstein et al., 2005](#); [Bernstein et al., 2003](#)) and intratracheal instillation in albino Swiss mice ([Sahu et al., 1975](#)). [Davis et al. \(1985\)](#) also reported pulmonary effects after inhalation exposure in Wistar rats, including increases in peribronchiolar fibrosis, alveolar wall thickening, and interstitial fibrosis.

Limited research is available on noncancer health effects occurring outside the respiratory system and pleura. [Larson et al. \(2010b\)](#) examined cardiovascular-disease-related mortality in the cohort of exposed workers from Libby (see Section 4.1 in the Toxicological Review). Mechanistic studies have examined the potential role of iron and the associated inflammation for both respiratory and cardiovascular disease ([Shannahan et al., 2012a](#); [Shannahan et al., 2012c](#); [Shannahan et al., 2012b](#); [Shannahan et al., 2012d](#); [Shannahan et al., 2011b](#)). Other studies examined the association between asbestos exposure and autoimmune disease ([Noonan et al., 2006](#)) or autoantibodies and other immune markers [([Pfau et al., 2005](#)); see Table 4-15 in the Toxicological Review]. However, limitations in the number, scope, and design of these studies make it difficult to reach conclusions as to the role of asbestos exposure in either cardiovascular disease or autoimmune disease.

*For more detail on Susceptible Populations, exit to [the toxicological review, Section 4.7 \(PDF\)](#).*

#### **\_\_\_I.B.5. CONFIDENCE IN THE CHRONIC INHALATION RfC**

Study—Medium

Database—Medium

RfC—Medium

Confidence in the database is medium. The database consists of long-term mortality and morbidity studies in humans exposed via inhalation to LAA. The mortality studies do not provide appropriate data for RfC derivation for pleural abnormalities, although the two other morbidity studies ([Alexander et al., 2012](#); [Larson et al., 2012a](#)) support the conclusion that low levels of exposure to LAA are associated with increased prevalence of LPT. It is known that inhaled asbestos fibers migrate out of the lung and into other tissues (see Section 3.1 of the Toxicological Review), which leads to uncertainty regarding the assumption that other health effects would not be expected. While a potential for autoimmune effects and cardiovascular disease is noted in exposed individuals, data are insufficient to provide a quantitative exposure-response relationship for these endpoints. It is unknown whether an RfC based on these other health effects would result in a higher or lower estimate for the RfC. Nor is there evidence whether any of these other effects would occur earlier than LPT following exposure to LAA. No data exist on general systemic effects in laboratory animals or humans. Confidence in the principal study is medium. The [Rohs et al. \(2008\)](#) study was conducted in a population of occupationally exposed workers with long-term, relatively low-intensity, exposures. The exposure assessment in the principal study is based on measured data. The main source of uncertainty in the exposure estimates is incomplete exposure measurements for some of the occupations/tasks before industrial hygiene improvements that started about 1973 or 1974 and continued throughout the 1970s (see Appendix F, Figure F-1 of the Toxicological Review). The principal study assessed the health outcome cross sectionally and this may underrepresent the true health burden, as individuals with more severe disease could have left employment or may have died and not been included in the follow-up study, resulting in an underestimation of overall toxicity. However, for health outcomes not considered to be frank effects, such as LPT, this underestimation should be minimal. Further, [Rohs et al. \(2008\)](#) compared the study participants with the complete study population and found no evidence of major differences in the two group's exposure distributions. Thus, the potential for selection bias is considered to be low. In terms of the sensitivity of the principal study to detect the critical effect (LPT) by radiograph, it is known that HRCT can identify asbestos-related lesions in the respiratory tract that cannot be identified by standard radiographs [e.g., ([Lebedova et al., 2003](#); [Janković et al., 2002](#); [Šimundić et al., 2002](#))]. Thus, the technology employed for determining the prevalence of radiographic changes in the Marysville cohort will likely underestimate the prevalence of pleural lesions that could be detected using HRCT. Therefore, overall confidence in the RfC is medium, reflecting medium confidence in the principal study and medium confidence in the database.

***For more detail on Characterization of Hazard and Dose Response, exit to [the toxicological review, Section 6 \(PDF\)](#).***

## **\_\_I.B.6. EPA DOCUMENTATION AND REVIEW OF THE CHRONIC INHALATION RfC**

Source Document—*Toxicological Review of Libby Amphibole Asbestos* ([U.S. EPA, 2014](#)).

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and the Executive Office of the President, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Libby Amphibole Asbestos* ([U.S. EPA, 2014](#)). [To review this appendix, exit to the toxicological review, Appendix A, EPA Response to Major External Peer Review and Public Comments \(PDF\)](#).

Agency Completion Date—12/08/2014

## **\_\_I.B.7. EPA CONTACTS**

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) (email address).

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## **\_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE**

Substance Name—Libby Amphibole asbestos

CASRN—N/A

Section II. Last Revised—12/08/2014

This section provides information on three aspects of the carcinogenic assessment for the substance in question: the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral and inhalation exposure. Users are referred to Section I of this file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS are described in the *Guidelines for Carcinogen Risk Assessment* ([U.S. EPA, 2005a](#)) and the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* ([U.S. EPA, 2005b](#)). The quantitative risk estimates are derived from the application of a low-dose extrapolation procedure, and are presented in two ways to better facilitate their use. First, route-specific risk values are presented. The “oral slope factor” is a plausible upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a “unit risk” is a plausible upper bound on the estimate of risk per unit of concentration, either per µg/L drinking water (see

Section II.B.1.) or per  $\mu\text{g}/\text{m}^3$  air breathed (see Section II.C.1.). Second, the estimated concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000 is also provided.

This is the first IRIS assessment for LAA. Therefore, no previous characterization of cancer potential or quantitative evaluation exists for LAA. An assessment of asbestos (CASRN 1332-21-4) not specific to LAA was posted on the IRIS database in 1988.

## II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

### II.A.1. WEIGHT-OF-EVIDENCE CHARACTERIZATION

Under the EPA *Guidelines for Carcinogen Risk Assessment* ([U.S. EPA, 2005a](#)), LAA is “carcinogenic to humans” following inhalation exposure based on epidemiologic evidence that shows a convincing association between exposure to LAA fibers and increased lung cancer and mesothelioma mortality ([Larson et al., 2010b](#); [Moolgavkar et al., 2010](#); [Sullivan, 2007](#); [McDonald et al., 2004](#); [Amandus and Wheeler, 1987](#); [McDonald et al., 1986a](#)). These results are further supported by animal studies that demonstrate the carcinogenic potential of LAA fibers and tremolite fibers in rodent bioassays (see Section 4.1, 4.2, Appendix D of the Toxicological Review). As LAA is a durable mineral fiber of respirable size, this weight-of-evidence descriptor is consistent with the extensive published literature that documents the carcinogenicity of amphibole fibers [as reviewed in ([Aust et al., 2011](#); [Broaddus et al., 2011](#); [Bunderson-Schelvan et al., 2011](#); [Huang et al., 2011](#); [Mossman et al., 2011](#))].

EPA guidance provides a framework for analyzing the potential mode(s) of action (MOA) by which physical, chemical, and biological information is evaluated to identify key events in an agent’s carcinogenicity ([U.S. EPA, 2005a](#)). Agents can work through more than one MOA, and a MOA can differ for various endpoints (e.g., lung cancer vs. mesothelioma). Reasonably, the analysis of a MOA would start with some knowledge of an agent’s biological activity that leads to cellular transformation resulting in cancer. Although early steps in the process often can be identified, carcinogenicity is a complex process resulting from multiple changes in cell function. Due to the limited data available specific to LAA, the MOA of LAA for lung cancer and mesothelioma following inhalation exposure cannot be established.

EPA’s *Guidelines for Carcinogenic Risk Assessment* ([U.S. EPA, 2005a](#)) indicates that for tumors occurring at a site other than the initial point of contact, the weight of evidence for carcinogenic potential may apply to all routes of exposure that have not been adequately tested at sufficient doses. An exception occurs when there is convincing information (e.g., toxicokinetic data) that absorption does not occur by other routes. Information on the carcinogenic effects of LAA via the oral and dermal routes in humans or animals is absent. The increased risk of lung cancer and mesothelioma following inhalation exposure to LAA has been established by studies in humans,



but these studies do not provide a basis for determining the risk from other routes of exposure. Mesothelioma occurs in the pleural and peritoneal cavities, and therefore, is not considered a portal-of-entry effect. However, the role of indirect or direct interaction of asbestos fibers in disease at these extrapulmonary sites is still unknown. No information exists on the translocation of LAA to extrapulmonary tissues following either oral or dermal exposure, and limited studies have examined the role of these routes of exposure in cancer. Therefore, LAA is considered “carcinogenic to humans” by the inhalation route of exposure.

*For more detail on Characterization of Hazard and Dose Response, exit to [the toxicological review, Section 6 \(PDF\)](#).*

*For more detail on Susceptible Populations, exit to [the toxicological review, Section 4.7 \(PDF\)](#).*

#### **II.A.2. HUMAN CARCINOGENICITY DATA**

Libby, MT workers have been the subject of multiple mortality studies demonstrating increased cancer mortality in relation to estimated fiber exposure (see Section 4.1.4 in Toxicological Review). Occupational studies conducted in the 1980s ([Amandus and Wheeler, 1987](#); [McDonald et al., 1986a](#)) as well as the extended follow-up studies published in more recent years ([Larson et al., 2010b](#); [Sullivan, 2007](#); [McDonald et al., 2004](#)) and additional analyses of the extended follow-up ([Moolgavkar et al., 2010](#)) provide evidence of an increased risk of lung cancer mortality and of mesothelioma mortality among the workers exposed to LAA in the Libby vermiculite mining and processing operations. This pattern is seen in the lung cancer analyses using an internal referent group in the larger follow-up studies ([Larson et al., 2010b](#); [Sullivan, 2007](#); [McDonald et al., 2004](#)), with cumulative exposure analyzed using quartiles or as a continuous measure, and in the studies reporting analyses using an external referent group [i.e., standardized mortality ratios; ([Sullivan, 2007](#); [Amandus and Wheeler, 1987](#); [McDonald et al., 1986a](#))]. [McDonald et al. \(2004\)](#) also reported an increasing risk of mesothelioma across categories of exposure; the more limited number of cases available in earlier studies precluded this type of exposure-response analysis. This association is also supported by the case series of 11 mesothelioma patients among residents in or around Libby, MT, among family members of workers in the mining operations ([Whitehouse et al., 2008](#)), and by the observation of three cases of mesothelioma (two of which resulted in death) in the Marysville, OH worker cohort identified as of June 2011 ([Dunning et al., 2012](#)).

In summary, there is convincing evidence of a causal association between exposure to LAA and mesothelioma and lung cancer in workers from the Libby, MT vermiculite mining and milling operations as well as workers from the Marysville, OH plant ([Larson et al., 2010b](#); [Sullivan, 2007](#); [McDonald et al., 2004](#); [Amandus et al., 1988](#); [Amandus and Wheeler, 1987](#); [McDonald et](#)

[al., 1986a](#)). Increased lung cancer and mesothelioma deaths are also reported for worker cohorts exposed to other forms of amphibole fibers (amosite and crocidolite) ([de Klerk et al., 1989](#); [Seidman et al., 1986](#); [Henderson and Enterline, 1979](#)).

### **II.A.3. ANIMAL CARCINOGENICITY DATA**

Limited in vivo studies have been performed exposing laboratory animals to LAA (see details in Tables 4-19 and 4-20, Appendix D of the Toxicological Review). One intrapleural injection study using tremolite from the Libby, MT area is included in this section under LAA because earlier terminology for LAA was often tremolite ([Smith, 1978](#)). Hamsters in the Smith study were exposed to LAA and developed fibrosis and mesothelioma following exposure. In other studies, intratracheal instillation studies of LAA in rats showed increased collagen gene expression at 2-years postexposure ([Cyphert et al., 2012](#)). Subchronic-duration studies in mice ([Smartt et al., 2010](#); [Putnam et al., 2008](#)) demonstrated gene and protein expression changes related to fibrosis production following exposure to LAA. Finally, short-term-duration studies in rats demonstrated an increase in inflammatory and cardiovascular disease markers following exposure to LAA ([Padilla-Carlin et al., 2011](#); [Shannahan et al., 2011a](#); [Shannahan et al., 2011b](#)).

Because tremolite is a component of LAA, results from tremolite studies are also described in the Toxicological Review. In general, fibrous tremolite has been shown to cause pulmonary inflammation, fibrosis, and/or mesothelioma or lung cancer in rats ([Bernstein et al., 2005](#); [Bernstein et al., 2003](#); [Davis et al., 1991](#); [Davis et al., 1985](#); [Wagner et al., 1982](#)) and hamsters ([Smith et al., 1979](#)). The single short-term-duration study on mice showed limited response to tremolite ([Sahu et al., 1975](#)). The one chronic-duration oral study ([McConnell et al., 1983](#)) did not show increased toxicity or carcinogenicity; this study, however, used only nonfibrous tremolite, which a later study showed to be less toxic and carcinogenic than fibrous tremolite ([Davis et al., 1991](#)).

Although experimental data in animals and data on toxicity mechanisms are limited for LAA, tumors that were observed in animal tissues were similar to those seen in humans (e.g., mesotheliomas, lung cancer), indicating that the existing data are consistent with the cancer effects observed in humans exposed to LAA. [Smith \(1978\)](#) reported an increased incidence of mesotheliomas in hamsters after intrapleural injections of LAA. Additionally, studies in laboratory animals (rats and hamsters) exposed to tremolite via inhalation ([Bernstein et al., 2005](#); [Bernstein et al., 2003](#); [Davis et al., 1985](#)), intrapleural injection ([Roller et al., 1997, 1996](#); [Davis et al., 1991](#); [Wagner et al., 1982](#); [Smith et al., 1979](#)), or implantation ([Stanton et al., 1981](#)) have shown increases in mesotheliomas and lung cancers. The tremolite used in these studies was from various sources and varied in fiber content and potency (see Section 4.2, Appendix D of the Toxicological Review). Although [McConnell et al. \(1983\)](#) observed no increase in

carcinogenicity following oral exposure to nonfibrous tremolite, the ability of this study to inform the carcinogenic potential of fibrous tremolite through inhalation is unclear, and the study results contribute little weight to the evaluation of the carcinogenicity of fibrous LAA.

#### **II.A.4. SUPPORTING DATA FOR CARCINOGENICITY**

Chronic inflammation is hypothesized to lead to a carcinogenic response through the production of reactive oxygen species (ROS) and increased cellular proliferation ([Hanahan and Weinberg, 2011](#)). Although limited, the data described in Section 4.2 of the Toxicological Review suggest an increase in inflammatory response following exposure to LAA and tremolite asbestos similar to that observed for other durable mineral fibers [reviewed in ([Mossman et al., 2007](#))]. Whether this inflammatory response then leads to cancer is unknown. Studies examining other types of asbestos (e.g., crocidolite, chrysotile, and amosite) have demonstrated an increase in chronic inflammation as well as respiratory cancer related to exposure [reviewed in ([Kamp and Weitzman, 1999](#))]. Chronic inflammation has also been linked to genotoxicity and mutagenicity following exposure to some particles and fibers ([Driscoll et al., 1997](#); [Driscoll et al., 1996](#); [Driscoll et al., 1995](#)). The evidence described suggests chronic inflammation is observed following LAA and tremolite asbestos exposure; however, the role of inflammation and whether it leads to lung cancer or mesothelioma following exposure to LAA is unknown.

Reactive oxygen species (ROS) production has been measured in response to both LAA and tremolite asbestos exposure. [Blake et al. \(2007\)](#) demonstrated an increase in the production of superoxide anions following exposure to LAA. [Blake et al. \(2007\)](#) also demonstrated that total superoxide dismutase (SOD) was inhibited, along with a decrease in intracellular glutathione (GSH), both of which are associated with increased levels of ROS. These results are supported by a recent study in human mesothelial cells [[Hillegass et al., 2010](#)]; described in Section 4.4 and Appendix D]. Increased ROS production was also observed in human airway epithelial cells (HAECs) following exposure to LAA [[Duncan et al., 2010](#)]; described in Section 4.4 and Appendix D]. This increase in ROS and decrease in glutathione are common effects following exposure to asbestos fibers and particulate matter. [Pfau et al. \(2012\)](#) examined the role of the amino acid transport system  $x_c^-$ , which is one of the pathways murine macrophages use to detect and respond to stressful conditions. This study demonstrated that ROS production increases  $x_c^-$  activity. Although ROS production is relevant to humans, based on similar human responses as compared to animals, information on the specifics of ROS production following exposure to LAA is limited to the available data described here. Therefore, the role of ROS production in lung cancer and mesothelioma following exposure to LAA is unknown.

Research on multiple types of elongate mineral fibers supports the role of multiple modes of action following exposure to LAA. Of the MOAs described above, the evidence that chronic inflammation, genotoxicity and cytotoxicity, and cellular proliferation may all play a role in the

carcinogenic response to LAA is only suggestive (see Table 4-23 of the Toxicological Review). In vitro studies provide evidence that amphibole asbestos is capable of eliciting genotoxic and mutagenic effects in mammalian respiratory cells; however, direct evidence of mutagenicity in respiratory cells following inhalation exposure is lacking. Results of the in vivo studies described here are consistent with the hypothesis that some forms of amphibole asbestos act through a MOA dependent on cellular toxicity. This conclusion is largely based on the observations that cytotoxicity and reparative proliferation occur following subchronic exposure and that bronchiolar tumors are produced at exposure levels that produce cytotoxicity and reparative proliferation. However, dose-response data in laboratory animal studies for damage/repair and tumor development are limited because of the lack of inhalation studies using multiple doses of fibers that exist. Although evidence is generally supportive of a MOA involving chronic inflammation or cellular toxicity and repair, there is insufficient evidence to establish key events to describe a MOA. It is possible that multiple MOAs discussed above, or an alternative MOA, may be responsible for tumor induction.

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## **\_\_II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE**

An oral slope factor for Libby Amphibole asbestos was not derived in this assessment. Oral exposure was not assessed because inhalation is the primary route of concern and oral data for Libby Amphibole asbestos is lacking.

### **\_\_II.B.1. SUMMARY OF RISK ESTIMATES**

Not applicable.

## **\_\_II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE**

### **\_\_II.C.1. SUMMARY OF RISK ESTIMATES**

\_\_II.C.1.1. Inhalation Unit Risk—0.17 per fiber/cc.

[If rounded off to one significant digit, Inhalation Unit Risk is 0.2 per fiber/cc]

The inhalation unit risk (IUR) is defined as an upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 µg/L in water, or 1 µg/m<sup>3</sup> in air. However, current health standards for asbestos are based on health effects observed in occupational cohorts and are given in fibers/cc of air as counted by PCM ([OSHA, 1994](#); [U.S. EPA, 1988](#)). Thus, when examining the available health effects data on cancer for LAA, the best available studies at this time report exposure concentration in terms of fibers/cc counted by

PCM. The cancer effects identified in populations with exposure to LAA (see Section 4.1.4 of the Toxicological Review) are cancer mortality from mesothelioma and lung cancer. Therefore, the IUR represents the upper-bound excess lifetime risk of mortality from either mesothelioma or lung cancer in the general U.S. population from chronic inhalation exposure to LAA at a concentration of 1 fiber/cc of air.

IURs are based on human data when appropriate epidemiologic studies are available. The general approach to developing an IUR from human epidemiologic data is to first quantitatively evaluate the exposure-response relationship (slope) for that agent in the studied population. For this assessment, the first step was to identify the most appropriate data set available to quantitatively estimate the effects of LAA exposure on cancer mortality. Once the relevant data describing a well-defined group of individuals along with their exposures and health outcomes were selected (see Section 5.4.2 of the Toxicological Review), an appropriate statistical model form (i.e., Poisson or Cox) was selected that adequately fit the specific nature of the data, and then each person's individual-level exposures were modeled using a variety of possible exposure metrics informed by the epidemiologic literature. Exposure-response modeling was conducted for each cancer mortality endpoint individually (see Section 5.4.3 of the Toxicological Review). In some cases, the statistical model forms and the specific metrics of exposure used for each cancer endpoint may have been different. These models were then evaluated to assess how the different exposure metric representing estimated occupational exposures fit the observed epidemiologic data. The empirical model fits were compared against those models suggested by the epidemiologic literature before selecting one model for mesothelioma mortality and one for lung cancer mortality.

The selected cancer exposure-response relationships (slopes) for mesothelioma (KM) and lung cancer (KL), which were estimated from the epidemiologic data on the Libby workers cohort, were then applied to the general U.S. population in a life-table analysis using age-specific mortality statistics to determine the exposure level that would be expected to result in a specified level of response over a lifetime of continuous exposure. EPA typically selects a response level of 1% extra risk because this response level is generally near the low end of the observable range for such data. Extra risk is defined as equaling  $(R_x - R_o) \div (1 - R_o)$ , where  $R_x$  here is the lifetime cancer mortality risk in the exposed population and  $R_o$  is the lifetime cancer mortality risk in an unexposed population (i.e., the background risk). In the case of lung cancer, the expected lifetime risk of lung cancer mortality in the unexposed general U.S. population is approximately 5%; thus, this assessment seeks to estimate the level of exposure to LAA that would be expected to result in a 1% extra lifetime risk of lung cancer mortality equivalent to a lifetime risk of lung cancer mortality of 5.95%:  $[(0.0595 - 0.05) \div (1 - 0.05) = 0.01]$ . This corresponds to a relative risk ( $R_x/R_o$ ) of about 1.2, which is near the low end of the observable range for most epidemiologic studies of cancer. For mesothelioma mortality, an absolute risk was considered, rather than extra risk, for two reasons: (1) mesothelioma is very rare in the general population

and (2) mesothelioma is almost exclusively caused by exposure to asbestos and other mineral fibers, including LAA. Because the background rate of mesothelioma is negligible, absolute risk models of exposure-response were considered more appropriate than relative risk models, thereby justifying the definition of the target response rate in absolute terms rather than in relative terms.

A life-table analysis (see Appendix G of the Toxicological Review for details) was used to compute the 95% lower bound on the level of LAA at which a lifetime exposure corresponds to a 1% extra risk of lung cancer mortality (1% absolute risk for mesothelioma) in the general U.S. population using age-specific mortality statistics and the exposure-response relationships for each cancer endpoint as estimated in the Libby worker cohort. This lower bound on the level of exposure serves as the POD for extrapolation to lower exposures and for deriving the unit risk. Details of this analysis are presented in Section 5.4.5 of the Toxicological Review. Cancer-specific unit risk estimates were obtained by dividing the extra risk (1%) by the POD. The cancer-specific unit risk estimates for mortality from either mesothelioma or lung cancer were then statistically combined to derive the final IUR (see table below).

### Air Concentrations at Specified Risk Levels

Risk level	Lifetime exposure concentration
$1.0 \times 10^{-4}$ (1 in 10,000)	$5.9 \times 10^{-4}$ fiber/cc
$1.0 \times 10^{-5}$ (1 in 100,000)	$5.9 \times 10^{-5}$ fiber/cc
$1.0 \times 10^{-6}$ (1 in 1,000,000)	$5.9 \times 10^{-6}$ fiber/cc

#### II.C.1.2. Extrapolation Method

Following the recommendations of the Guidelines for Carcinogen Risk Assessment ([U.S. EPA, 2005a](#)), a linear low dose extrapolation below the POD was used because the MOA for LAA for lung cancer and for mesothelioma is largely unknown.

#### II.C.2. DOSE-RESPONSE DATA

Tumor type—Cancer mortality from lung cancer and mesothelioma

Test species—Humans

Route—Inhalation

Reference—[Sullivan \(2007\)](#)

**Estimates of the combined central estimate of the unit risk for mesothelioma and lung cancer and the combined upper-bound lifetime unit risks for mesothelioma and lung cancer risks (the Inhalation Unit Risk) for different combinations of mesothelioma and lung cancer models.<sup>ab</sup> Primary IUR value in bold.**

Lung cancer	Mesothelioma	Combined central estimate per fiber/cc	Combined upper bound per fiber/cc
<b>Selected IUR based directly on the Libby data</b>			
CE10	CE10 5-yr half-life	0.115	<b>0.169</b>
<b>Best models from the epidemiologic literature (Peto models with clearance)</b>			
CE10	Peto with clearance Decay rate of 6.8%/yr Power of time = 3.9	0.089	0.135
CE10	Peto with clearance Decay rate of 15%/yr Power of time = 5.4	0.061	0.092
<b>Alternative model from the epidemiologic literature (Peto model)</b>			
CE10	Peto No decay Power of time = 3	0.061	0.092

<sup>a</sup>It should be noted that for all the IUR values presented in this table, the fiber concentration are presented here as continuous lifetime exposure in fibers/cc where exposure measurements are based on analysis of air filters by phase contrast microscopy (PCM). Current analytical instruments used for PCM analysis have resulted in a standardization of minimum fiber width considered visible by PCM between 0.2 and 0.25 μm. Historical PCM analysis (1960s and early 1970s) generally had less resolution, and fibers with minimum widths of 0.4 or 0.44 μm were considered visible by PCM ([Amandus et al., 1987b](#); [Rendall and Skikne, 1980](#)). Methods are available to translate exposure concentrations measured in other units into PCM units for comparison.

<sup>b</sup>While this assessment is informed by studies of other types of asbestos, it is not a complete toxicity review of other amphiboles or of chrysotile asbestos.

CE10 = cumulative exposure with 10-year lag; yr = year.

### **II.C.3. ADDITIONAL COMMENTS**

EPA used two approaches to address the potential confounding of lung cancer results by smoking, including restriction to the subcohort and an analytic evaluation of the potential for confounding by smoking, including the method described by [Richardson \(2010\)](#). [Richardson \(2010\)](#) describes a method to determine whether an identified exposure relationship with lung

cancer is confounded by unmeasured smoking in an occupational cohort study. EPA implemented this methodology to model the potential effects of LAA on the risk of chronic obstructive pulmonary disease (COPD) mortality on the subcohort of workers hired after 1959 (see Section 5.4.3.8). Summarizing these findings, EPA used the method described by [Richardson \(2010\)](#) to evaluate whether exposures to LAA predicted mortality from COPD as an indication of potential confounding by smoking and found a nonsignificant negative relationship, which was inconsistent with confounding by smoking.

For mesothelioma, the undercounting of cases (underascertainment) is a particular concern given the limitations of the International Classification of Diseases (ICD) classification systems used before 1999. In practical terms, this means that some true occurrences of mortality due to mesothelioma are missed on death certificates and in almost all administrative databases such as the National Death Index. Even after introduction of a special ICD code for mesothelioma with the introduction of ICD-10 in 1999, detection rates are still imperfect ([Camidge et al., 2006](#); [Pinheiro et al., 2004](#)), and the reported numbers of cases typically reflect an undercount of the true number. [Kopylev et al. \(2011\)](#) reviewed the literature on this underascertainment and developed methods to account for the likely numbers of undocumented mesothelioma deaths. To compensate for mesothelioma underascertainment attributable to ICD coding, the mesothelioma mortality unit risk was further adjusted following the analysis of [Kopylev et al. \(2011\)](#).

Once the cancer-specific lifetime unit risks are selected, the two are then combined. It is important to note that this estimate of overall potency describes the risk of mortality from cancer at either of the considered sites and is not just the risk of both cancers simultaneously. Because each of the unit risks is itself an upper-bound estimate, summing such upper-bound estimates across mesothelioma and lung cancer mortality is likely to overpredict the overall risk. Therefore, following the recommendations of the *Guidelines for Carcinogen Risk Assessment* ([U.S. EPA, 2005a](#)), a statistically appropriate upper bound on combined risk was derived to gain an understanding of the overall risk of mortality resulting from mesothelioma and from lung cancer. For mesothelioma, the exposure-response models developed by EPA using personal exposure data on the subcohort (see Table 5-50 of the Toxicological Review) provided better fit to the subcohort data than the Peto model and the Peto model with clearance that have been proposed in the asbestos literature. For lung cancer, this assessment selected the upper bound among the lung cancer lifetime unit risks from the plausible exposure metrics (regardless of the small residual differences in quality of fit). Because there were few metrics with unit risks higher than the best fitting metric's unit risk for lung cancer mortality endpoint, this method effectively selects the highest lifetime unit risk among those considered for the lung cancer mortality endpoint.



Several published studies have previously evaluated risk of mesothelioma and lung cancer [i.e., ([Larson et al., 2010b](#); [Moolgavkar et al., 2010](#); [Berman and Crump, 2008](#); [Sullivan, 2007](#))] in the Libby, MT workers cohort. For mesothelioma, only [Moolgavkar et al. \(2010\)](#) provided an exposure-response relationship for absolute risk of mesothelioma mortality that would be comparable with this assessment. Based on the full cohort, with mortality data through 2001 and a modification of the Peto/Nicholson exposure metric, life-table analysis would provide an upper-bound unit risk of approximately 0.13 per fiber/cc continuous lifetime exposure. Therefore, using the exposure response modeling of [Moolgavkar et al. \(2010\)](#) would provide an IUR for excess mesothelioma mortality in close agreement with the IUR derived in this assessment (see Section 5.4.5.3.1 of the Toxicological Review for more details).

For lung cancer, all of the studies provide exposure-response relationships in terms of relative risk of lung cancer mortality, and thus, may provide risk estimates comparable to this assessment. However, inclusion criteria, length of mortality follow-up, and analytic methods differ among the analyses—thus, the results are not necessarily interchangeable. For comparison purposes, the lung cancer unit risks from these studies are computed from life-table analyses (see Table 5-54 of the Toxicological Review). The lung cancer unit risks calculated based on the published literature, ranged from 0.010 to 0.079 per fiber/cc (based on the upper confidence limit). This is in close agreement with the assessment where an upper-bound estimate of 0.068 per fiber/cc continuous lifetime exposure is derived (see Section 5.4.5.3.1 of the Toxicological Review for more details).

#### **II.C.4. DISCUSSION OF CONFIDENCE**

Occupational studies demonstrate human health effects (e.g., lung cancer, mesothelioma) following exposure to LAA. Although the limited mechanistic data demonstrate biological effects similar to those of other mineral fibers following exposure to LAA, the existing literature is insufficient to establish an MOA for LAA for lung cancer or mesothelioma. These biological effects following exposure to LAA and/or tremolite are demonstrated in a limited number of laboratory animal and in vitro studies. Multiple key events for one particular MOA have not been identified; therefore, the MOA for LAA carcinogenicity cannot be established. However, multiple mechanisms of action (e.g., mutagenicity, chronic inflammation, cytotoxicity, and regenerative proliferation) can be hypothesized based on the available asbestos literature.

##### *Susceptible Populations*

A mutagenic MOA is considered relevant to all populations and life stages. According to EPA's Cancer Guidelines ([U.S. EPA, 2005a](#)) and Supplemental Guidance ([U.S. EPA, 2005c](#)), there may be increased susceptibility to early-life exposures for carcinogens with a mutagenic MOA. The weight of evidence is insufficient to support a mutagenic MOA for LAA carcinogenicity and in

the absence of chemical-specific data to evaluate differences in susceptibility, according to EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* ([U.S. EPA, 2005c](#)), the application of the age-dependent adjustment factors is not recommended.

Populations that may be more susceptible include those with varied fiber toxicokinetics related to potential anatomical, physiological, and biochemical differences which may impact fiber dosimetry (see Section 4.7 of the Toxicological Review). No data are available as to whether other factors can lead to different populations or life stages being more susceptible to the hypothesized MOA for LAA-induced tumors (e.g., chronic inflammation, cytotoxicity or mutagenicity). For instance, it is not known how the hypothesized key events in chronic inflammatory response (e.g., increased oxidative stress) to fibers interact with known risk factors for human pulmonary or pleural carcinomas.

#### *Linear Low-Dose Extrapolation*

A linear low-dose extrapolation approach was used to estimate human carcinogenic risk associated with LAA exposure due to the unavailability of data to support any specific mode of carcinogenic action of LAA. There is some uncertainty in the extrapolation of risks based on occupational exposure to general population exposure levels but this uncertainty is considered to be low as the lower range of occupational exposure overlaps with expected environmental exposure levels.

## **\_\_II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)**

### **\_\_II.D.1. EPA DOCUMENTATION**

Source Document—*Toxicological Review of Libby Amphibole Asbestos* ([U.S. EPA, 2014](#)).

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and the Executive Office of the President, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Libby Amphibole Asbestos* ([U.S. EPA, 2014](#)). [To review this appendix, exit to the toxicological review, Appendix A, EPA Response to Major External Peer Review and Public Comments \(PDF\)](#).

### **\_\_II.D.2. EPA REVIEW**

Agency Completion Date—12/08/2014

### **\_\_II.D.3. EPA CONTACTS**

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) (email address).

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**\_III. [reserved]**

**\_IV. [reserved]**

**\_V. [reserved]**

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## **\_VI. BIBLIOGRAPHY**

Substance Name—Libby Amphibole asbestos

CASRN—1314-62-1

Section VI. Last Revised—00/00/2014

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Not applicable.

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### **\_\_VI.B. INHALATION RfC REFERENCES**

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## **VII. REVISION HISTORY**

Substance Name—Libby Amphibole asbestos  
CASRN—Not applicable

File First On-Line 12/08/2014

<b>Date</b>	<b>Section</b>	<b>Description</b>
12/08/2014	I.B, II, VI.	RfC and cancer assessment added

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## **\_VIII. SYNONYMS**

Substance Name—Libby Amphibole asbestos

CASRN—Not Applicable

Last Revised—12/08/2014

- Libby Amphibole asbestos
- Libby Amphibole
- Libby asbestos