

DATE

The Honorable Lisa P. Jackson  
Administrator  
U.S. Environmental Protection Agency  
1200 Pennsylvania Avenue, N.W.  
Washington, DC 20460

Subject: Review of EPA's Draft Assessment entitled *Toxicological Review of Libby Amphibole Asbestos* (August 2011)

Dear Administrator Jackson:

EPA's Office of Research and Development (ORD) requested the Science Advisory Board (SAB) to conduct a peer review of EPA's draft Integrated Risk Information System (IRIS) assessment, entitled *Toxicological Review of Libby Amphibole Asbestos* (August 2011). The draft document is the first IRIS assessment specific to Libby Amphibole asbestos (LAA), a term used to refer to the mixture of amphibole mineral fibers identified in the Rainy Creek complex near Libby, Montana. The SAB was asked to comment on the scientific soundness of the hazard and dose-response assessment of LAA-induced cancer and non-cancer health effects.

The SAB finds the EPA's draft assessment to be comprehensive and generally clear, logical and well-written. However, there are many areas that need more consideration, and we provide recommendations to further enhance the clarity and strengthen the scientific basis for the conclusions presented. The SAB responses to the EPA's charge questions are detailed in the enclosed report. The SAB's major comments and recommendations are provided below:

- Localized pleural thickening is an appropriate health endpoint for the derivation of the inhalation reference concentration (RfC). It is an irreversible structural, pathological alteration of the pleura and is generally associated with reduced lung function. The SAB has identified additional references and recommends that the agency include a more detailed review of the literature to further support this conclusion.
- The SAB supports the derivation of an RfC for LAA based on radiographic evidence of localized pleural thickening in an occupationally exposed Marysville, Ohio, cohort. However, the SAB recommends that EPA conduct additional analyses to substantiate the RfC (to the extent data permit) of pleural abnormalities using the recently published studies on two other cohorts.
- The SAB recommends that more justification be provided for the selection of the "best" model for non-cancer exposure-response analysis. The SAB also recommends examining other exposure metrics besides the simple cumulative exposure, such as time-weighting of exposures. In addition, more justification is needed for the selection of 10 percent extra risk as the benchmark response since it is not consistent with EPA's guideline for epidemiological data.

- 1 • A composite uncertainty factor of 100 was applied to the point of departure to obtain the RfC.  
2 EPA applied an uncertainty factor of 10 to account for human variability and to account for  
3 sensitive subpopulations, and a database uncertainty factor of 10 to account for database  
4 deficiencies in the available literature for the health effects of LAA. The SAB recommends that  
5 the EPA re-evaluate the use of default database uncertainty factor of 10 as part of the  
6 consideration of additional studies.  
7
- 8 • The SAB agrees that the weight of evidence for LAA supports the descriptor “Carcinogenic to  
9 Humans by the Inhalation Route” in accordance with EPA’s *Guidelines for Carcinogen Risk*  
10 *Assessment*. The SAB views the mode of carcinogenic action of LAA as complex, and therefore  
11 the default linear extrapolation at low doses is appropriate.
- 12 • The SAB supports the selection of the Libby worker cohort for the derivation of the inhalation  
13 unit risk (IUR) and agrees that the use of the subcohort post-1959 for quantification is  
14 reasonable due to the lack of exposure information for many of the workers in earlier years. The  
15 SAB finds it appropriate to use lung cancer and mesothelioma as endpoints for the derivation of  
16 the IUR. However, the SAB recommends a more detailed discussion and justification of how the  
17 use of mortality data rather than incidence data may have resulted in an undercount of cases of  
18 lung cancer and mesothelioma.
- 19 • The draft assessment clearly described the methods selected to conduct the exposure-response  
20 modeling for lung cancer and mesothelioma. However, the SAB recommends that the agency  
21 provide more support for its choice of statistical models for the exposure-response analysis. The  
22 SAB recommends that the EPA evaluate the time dependence of disease by providing tabulation  
23 of mesothelioma mortality rates and lung cancer standardized mortality ratios by time since first  
24 exposure, duration of exposure, and period of first exposure for both the full cohort and the  
25 subcohort.
- 26 • The SAB recommends consideration of several models in addition to the Poisson and Cox  
27 models used in the draft assessment. Use of the two-stage clonal expansion (TSCE) model, for  
28 example, could allow for a more direct evaluation of, and possibly justification for, age-  
29 dependency of the IUR. The agency has been overly constrained by reliance on model fit  
30 statistics as the primary criterion for model selection. The SAB recommends graphical display  
31 of the fit to the data for both the main models and for a broader range of models in the draft  
32 document to provide a more complete and transparent view of model fit. The SAB also  
33 recommends EPA consider literature on epidemiological studies of other amphiboles for model  
34 selection for dose-response assessment.
- 35 • The EPA has summarized many sources of uncertainty, sometimes quantitatively, as well as the  
36 direction and magnitude of the likely impact of each source of uncertainty. The SAB  
37 recommends that model uncertainty be evaluated by estimating risks using a more complete set  
38 of plausible models, including the Cox and Poisson models, for the exposure response  
39 relationship. This sensitivity analysis, while not a full uncertainty analysis, would make explicit  
40 the implications of these key model choices.

41 Finally, the SAB has identified critical research needs to strengthen future assessment in three areas:  
42 (a) continue monitoring mortality among Libby workers (including those residing in Libby and  
43 nearby towns such as Troy, Montana) and residents of Libby and nearby towns such as Troy,

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1 respectively ; (b) conduct mode-of-action and animal inhalation studies of LAA; and (c) develop an  
2 improved transmission electron microscopy method to obtain equivalent LAA fiber measurements  
3 in air samples to those of the phase- contrast optical microscopy method.  
4

5 The SAB appreciates the opportunity to provide the EPA with advice on this important subject. The  
6 SAB urges the agency to move expeditiously to finalize this IRIS document for LAA. We look  
7 forward to receiving the agency's response.  
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9 Sincerely,  
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17 Enclosure  
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**NOTICE**

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\*Dr. Ferson did not concur with the final draft report submitted to the chartered SAB for their quality review and approval.

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## Abbreviations and Acronyms

AIC	Akaike Information Criteria
ADAF	age-dependent adjustment factor
ATS	American Thoracic Society
ATSDR	Agency for Toxic Substances and Disease Registry
BMC	benchmark concentration
BMCL	lower 95% confidence limit of the benchmark concentration
BMD	benchmark dose
BMDL	lower 95% confidence limit of the benchmark dose
BMR	benchmark response
BW	body weight
CHEEC	cumulative human equivalent exposure for continuous exposure
CI	confidence interval
COPD	chronic obstructive pulmonary disease
DPT	diffuse pleural thickening
EDS	energy dispersive spectroscopy
EPA	Environmental Protection Agency
FEV1	forced expiratory volume in one second
ICD	International Classification of Diseases
ILO	International Labor Organization
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LAA	Libby Amphibole asbestos
LOAEL	Lowest-Observed-Adverse-Effect Level
LPT	Localized Pleural Thickening
MCMC	Markov Chain Monte Carlo
MOA	mode of action
NAS	National Academy of Sciences
NCI	National Cancer Institute
NIOSH	National Institute for Occupational Safety and Health
NOAEL	No-Observed-Adverse-Effect Level
NRC	National Research Council
NTP	National Toxicology Program
OR	odds ratio
ORD	Office of Research and Development
PCM	phase contrast microscopy
PCME	phase contrast microscopy equivalent
POD	point of departure
RfC	reference concentration
ROS	reactive oxygen species
RR	relative risk
RTW	residence time-weighted
SAED	Selected Area Electron Diffraction
SEER	Surveillance, Epidemiology, and End Results
SEM	scanning electron microscopy

SMR	standardized mortality ratio
SIR	standardized incidence ratio
TEM	transmission electron microscopy
Th1	T Helper Cell Type 1
Th2	T Helper Cell Type 2
UCL	Upper Confidence Limit
UF	uncertainty factor
UF <sub>D</sub>	Database uncertainty factor
UF <sub>H</sub>	Human inter-individual variability uncertainty factor
UF <sub>L</sub>	LOAEL-to-NOAEL uncertainty factor
UF <sub>S</sub>	subchronic-to-chronic uncertainty factor
WDS	wavelength dispersive spectroscopy
XRD	X-ray diffraction

## 1. EXECUTIVE SUMMARY

EPA's Office of Research and Development (ORD) requested the Science Advisory Board (SAB) to conduct a peer review of EPA's draft Integrated Risk Information System (IRIS) assessment, entitled *Toxicological Review of Libby Amphibole Asbestos (August 2011)*. The draft document is the first IRIS assessment specific to Libby Amphibole asbestos (LAA), a term used to refer to the mixture of amphibole mineral fibers identified in the Rainy Creek complex near Libby, Montana. The SAB was asked to comment on the scientific soundness of the hazard and dose-response assessment of LAA-induced cancer and non-cancer health effects.

The SAB finds the EPA's draft assessment to be comprehensive and generally clear, logical and well-written. However, there are many areas that need more consideration, and we provide recommendations to further enhance the clarity and strengthen the scientific basis of the analyses. The SAB's major findings and recommendations are summarized below.

### **Mineralogy**

The SAB notes that the section on mineralogy provides an important foundation for understanding the properties of Libby Amphibole asbestos (LAA) as related to the evaluation of its potential toxicity and carcinogenicity. The SAB recognizes that there is a mismatch between the mineralogical detail embodied in the definition of mineral species and the detail available relative to specific exposures at Libby, Montana. Mineral species define a very specific structure (e.g., an amphibole) and a specific composition or a range of compositions (e.g., winchite or tremolite amphibole). Given that these and other factors (length and width) affect a mineral's physical and chemical behavior, they may in principle be factors to consider for potential hazard. However, this level of detail has not typically been available for toxicity studies to allow its application to the evaluation of LAA *per se*. The observed unique aspects of amphibole asbestos support the evaluation of LAA by comparison with other amphiboles based on particle morphology and amphibole designation. Nevertheless, the SAB encourages a more rigorous and accurate description of LAA in the document, while noting the potential ambiguities in the use of mineral-species names in other studies.

### **Fiber Toxicokinetics**

The SAB finds the section on fiber toxicokinetics to be neither clear nor concise, especially since it does not distinguish between chrysotile and amphibole fibers. Moreover, it is inaccurate in many places. Since the focus of the draft document is on LAA fibers, it would be better to limit most of the literature reviews and discussion to those dealing with the family of amphibole asbestos fibers. Chrysotile asbestos fibers are very different from amphibole fibers in terms of their airborne concentration measurement errors and uncertainties; much lower biopersistence due to faster clearance; different translocation pathways; and lower health risks. Literature on risks associated with exposures to chrysotile should be excluded from this draft document. There also are some notable misstatements and omissions of knowledge on fiber deposition and dosimetry in the document. The authors of this section should draw on more authoritative and comprehensive reviews in the literature to correctly specify and clarify these issues.

1 **Noncancer Health Effect**

2  
3 *Selection of Critical Studies and Effects*

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5 The SAB supports the EPA's selection of the Marysville, Ohio, cohort for development of the RfC. The  
6 SAB finds it reasonable to select the subcohort for the main analysis (118 workers who began work in  
7 1972 or later when exposure data were available and who had X-rays from the 2002-2005 exam), with  
8 the full cohort of 434 workers used for additional substantiating analysis. However, the SAB believes  
9 additional analyses/cohorts are needed to strengthen and support the RfC. The SAB suggests that the  
10 EPA include any X-ray abnormalities as the outcome [localized pleural thickening (LPT), diffuse pleural  
11 thickening (DPT), or asbestosis]. The SAB also suggests that the EPA conduct analogous analyses (to  
12 the extent the data permit) of pleural abnormalities among the Libby workers cohort and the  
13 Minneapolis Exfoliation Community cohort.

14  
15 The SAB agrees that the radiographic evidence of LPT in humans is the appropriate adverse critical  
16 effect for the derivation of the RfC. LPT has the appropriate specificity and is not confounded by  
17 cigarette smoking. It is a permanent structural, pathological alteration of the pleura and is generally  
18 associated with reduced lung function. The reported findings are compatible with the animal data  
19 showing tissue injury and inflammation. The SAB has identified additional relevant publications and  
20 recommends that the agency include a more detailed review of the literature to further support this  
21 conclusion.

22  
23 *Use of Animal and Mechanistic Studies*

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25 In general, the SAB finds the laboratory animal studies listed in Tables 4-15 and 4-16 and summarized  
26 in Appendix D of the EPA draft report to be appropriate and complete. Laboratory animal studies using  
27 a variety of non-inhalation routes of exposure have been used to ascertain the potential fibrogenic and  
28 carcinogenic potential of LAA. While inhalation is regarded as the most physiologically relevant means  
29 of fiber exposure in animals, there is no published study using this route of exposure for delivery of  
30 LAA to experimental animals. Therefore, the deposition of particles and fibers cannot be adequately  
31 addressed. However, inhalation studies have been conducted with tremolite, an asbestiform amphibole  
32 that is a component of LAA. The relative potency of inhaled LAA should be compared with that of  
33 tremolite in rodents to add new information for refining the RfC for LAA.

34  
35 Limited mechanistic studies using *in vitro* assay systems have utilized non-specific endpoints (e.g., pro-  
36 inflammatory cytokines, enzyme release and oxidative stress markers), and will probably not shed much  
37 light on the mechanisms of LAA-induced disease.

38  
39 **Carcinogenicity**

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41 *Weight of Evidence Characterization*

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43 The SAB agrees that the weight of evidence for LAA supports the descriptor "Carcinogenic to Humans  
44 by the Inhalation Route," in accordance with EPA's *Guidelines for Carcinogen Risk Assessment*. The  
45 occupational studies showed dose-related increased risks of lung cancer and mesothelioma among  
46 workers exposed by inhalation, although the number of mesothelioma cases is small. The case series in  
47 the community, while supportive, does not provide the same level of evidence for an association, or for

1 the strength of the association. Effects from short term intra-tracheal instillation studies in mice and rats  
2 include altered gene expression, collagen induction, and inflammatory response, and are consistent with  
3 the early-stage pathological change induced by other amphibole fibers. The EPA also has provided  
4 supporting evidence of the carcinogenic potential of LAA from studies with tremolite fibers, in light of  
5 LAA being about 6 percent tremolite by composition.

#### 6 7 *Mode of Action*

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9 The SAB agrees that the weight of evidence for the mode of action (MOA) of LAA based on laboratory  
10 studies is weak, although there are abundant MOA data for other amphiboles such as crocidolite and  
11 tremolite that are likely similar to the MOA for LAA. The SAB views the mode of action of LAA as  
12 complex and supports the EPA's conclusion that there is insufficient information to identify the mode of  
13 carcinogenic action of LAA, and that the use of the default linear extrapolation at low doses is  
14 appropriate.

#### 15 16 *Selection of Critical Study and Endpoint*

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18 The SAB agrees that the selection of the Libby cohort for the derivation of the inhalation unit risk (IUR)  
19 is scientifically supported and clearly described. This cohort has been studied thoroughly, with detailed  
20 work histories and a job exposure matrix. This cohort had elevated asbestos exposure, a wide range of  
21 measurements of asbestos exposure, and available cancer mortality data. Limitations of this cohort  
22 include limited smoking information, and the endpoints of mortality based on death certificates could  
23 undercount cancer endpoints, especially mesothelioma. The study population may not be representative  
24 of the larger population since most of its members are white males exposed as adults, and because it  
25 contains more cigarette smokers than the larger population.

26  
27 The SAB finds the use of the subcohort post-1959 is reasonable due to the lack of exposure information  
28 in many of the workers in earlier years; out of 991 workers hired before 1960, 706 had all department  
29 and job assignments listed as unknown.

30  
31 The SAB agrees that lung cancer and mesothelioma should be used as endpoints for derivation of the  
32 IUR. Since determining the cancer outcome from mortality rather than incidence data may have resulted  
33 in an undercount of both cancer outcomes, the SAB recommends more detailed discussion on how the  
34 use of mortality data could impact the derived IUR. It also would have been useful to know other major  
35 categories of mortality in this cohort.

#### 36 37 *Use of Laboratory Animal and Mechanistic Studies*

38  
39 The SAB agrees that the database of laboratory animal and mechanistic studies pertaining to LAA is  
40 appropriately presented in the report and its Appendices for support of its analysis of the human effects  
41 observed. However, the SAB finds the body of the document deficient in not utilizing what is known  
42 about the dimensions of the administered fibers from Appendix D. It is now widely accepted that  
43 differences in biological potency among the various amphibole fiber types are due primarily to  
44 differences in dimensions, especially in fiber length distributions. The SAB also recommends that  
45 Section 4.6.2.2 be modified to reflect that there are insufficient data to determine the mode of action for  
46 LAA.

1 An understanding of the basic carcinogenic mechanisms of LAA will be extremely useful in deriving a  
2 realistic risk assessment. In light of the lack of data on the mode of action of LAA, the SAB  
3 recommends that action be taken to fill the gaps in knowledge by performing research in appropriate  
4 lung cell types *in vitro* (e.g., mesothelial cells, macrophages, fibroblasts) and in rodents *in vivo* that will  
5 elucidate basic pathological pathways. Furthermore, animal inhalation studies should be performed with  
6 LAA concentrations relevant to human environmental and occupational exposures in order to identify  
7 key physical and chemical aspects of LAA that mediate disease, including the role of fiber length in  
8 initiating and exacerbating biological lesion formation and progression.

## 10 **Inhalation Reference Concentration (RfC)**

### 12 *Estimates of Human Exposure Concentration*

14 The approach described (in Appendix F of the EPA document) for exposure reconstruction is detailed  
15 and specific. Due to large uncertainties associated with the unmeasured pre-1972 exposures, the SAB  
16 agrees that the draft document appropriately eliminates this set of estimates and adheres only to  
17 exposure estimates based on measured concentrations for the derivation of the RfC.

19 In Appendix F, natural-log-transformed exposure data were used to calculate the geometric mean for the  
20 job groups for use in developing the cumulative exposure metric (fiber/cc-years). The EPA should re-  
21 evaluate the raw exposure data and review pertinent sampling documentation to bolster its use of the  
22 geometric mean to represent the job group exposures, rather than an estimate of the arithmetic mean, and  
23 consider whether a sensitivity analysis using the minimum variance unbiased estimator (MVUE) of the  
24 mean is warranted in the development of the cumulative exposure metric. The SAB recommends that the  
25 EPA consider sensitivity analyses of additional exposure metrics, such as no exposure since 1980 in any  
26 cohort members, and alternative weighting schemes (e.g., residence time weighting).

### 28 *Exposure-Response Modeling*

30 The SAB recommends that the document provide a clearer description of how the Michaelis-Menten or  
31 another alternative model was chosen as the “best” model. According to EPA’s *Benchmark Dose*  
32 *Technical Guidance*, the point of departure (POD) from the model with the smallest Akaike Information  
33 Criteria (AIC) should be selected if, among models that adequately fit the data, the lower 95%  
34 confidence limits of the benchmark doses (BMDLs) are all sufficiently close given the needs of the  
35 assessment. Otherwise, the lowest BMDL should be used as the POD. The lower 95% confidence limits  
36 of the benchmark concentrations (BMCLs) from the candidate models differ by more than a factor of  
37 three. If the EPA can defend this range as being “sufficiently close,” then its choice of the POD is  
38 consistent with the technical guidance; if not, then according to the decision tree, the lowest BMCL  
39 should be used as the POD.

41 The SAB recommends a more thoughtful approach and discussion of model selection, including  
42 considering that biological/epidemiological plausibility, combined with careful examination of the data,  
43 should play important roles along with the AIC in determining the choice of models. Likewise, the fitted  
44 Michaelis-Menten model has an upper plateau of 60% LPT incidence, which is lower than the  
45 prevalence of 85% reported in a study of highly exposed asbestos insulation workers. The Marysville  
46 cohort does not support precise estimation of the plateau. Thus, the EPA should consider fixing the  
47 plateau level.

1  
2 The SAB recommends that model features also should be considered when choosing a model. The SAB  
3 suggests examining other exposure metrics besides the simple cumulative exposure, such as time  
4 weighting of exposures. The SAB suggests a thoughtful approach may lead to the selection of the  
5 dichotomous Hill model with the plateau fixed at a literature-based value. In addition, the document uses  
6 a 10% Extra Risk (ER) as the benchmark response level (BMR) which is in line with EPA's *Benchmark*  
7 *Dose Technical Guidance* for the analysis of quantal datasets from animal studies. However, according  
8 to this technical guidance, a BMR of 1% ER is typically used for human quantal response data since  
9 larger ERs, such as 10%, would often involve upward extrapolation. The authors of the draft document  
10 should explain what features of the dataset or outcome variable led them to choose a BMR that is  
11 considerably greater than the norm for epidemiological data.

### 12 13 *Alternative Modeling Approach*

14  
15 The SAB agrees that the rationale for performing additional analyses of the full Marysville cohort is  
16 scientifically justified; the analysis of the entire cohort increases the number of cases of LPT available  
17 for analysis and substantiates the RfC estimated using the subcohort. However, the rationale for the  
18 agency's analysis methods is not well justified. The EPA should clarify the scientific basis for the use of  
19 time since first exposure (TSFE) in the models. The SAB also finds the method for incorporating TSFE  
20 into the full cohort analysis is not well justified and recommends that the analysis be revised. In the draft  
21 document, the EPA uses TSFE as a predictor for the plateau in the Cumulative Normal Michaelis-  
22 Menten model. The plateau provides the maximum proportion of the population that would experience  
23 LPT given sufficient exposure and time to develop the disease. No biological justification is given for  
24 why this maximum proportion would vary with TSFE. The SAB recommends that the EPA consider a  
25 dichotomous Hill model that allows the slope to be estimated as an alternative to the Michaelis-Menten  
26 model. The SAB also recommends following the approaches for the subcohort analysis, such as fixing  
27 the plateau using literature values.

### 28 29 *Evaluation of Potential Confounders and Covariates*

30  
31 The SAB recommends a revised strategy for evaluation of confounders and covariates. The quantity of  
32 interest in the analyses of the Marysville cohort is the POD (BMCL). The evaluation of the various  
33 covariates should be made with respect to this quantity. The SAB suggests that the covariates fall into  
34 two classes: *exposure-related covariates* (various exposure metrics and TSFE) and *non-exposure-related*  
35 *covariates* [age, body mass index (BMI), gender, and smoking status]. The SAB also provides  
36 recommended revised strategies for considering these two classes of covariates that follow directly from  
37 consideration of the quantity of interest.

38  
39 In addition, the SAB recommends the justification for considering BMI as a covariate be briefly  
40 explained. TSFE is an important determinant of LPT because individuals' lung tissues exposed at an  
41 earlier age might be more susceptible to the damaging effects of asbestos fibers, and because asbestos'  
42 effect over time is increasingly damaging. TSFE is correlated with exposure since subjects with the  
43 longest TSFE were exposed in the early years of the cohort when exposure levels were higher. The SAB  
44 does not agree with the use of the Cumulative Normal Michaelis-Menten model to adjust for TSFE  
45 because it makes the assumption that it only affects the plateau, an assumption that lacks biological  
46 support. Instead, the SAB recommends that EPA consider alternative approaches to account for TSFE.  
47 The SAB suggests the discussion on the evidence linking pleural changes and smoking be moved into

1 the body of the report. The SAB does not consider gender to be a serious concern as it is reasonable to  
2 assume that females and males have similar risks of LPT.

### 3 4 *Conversion from Cumulative Occupational Exposure to Lifetime Exposure*

5  
6 The modeled POD is based on cumulative exposure estimates for the worker cohort examined. The SAB  
7 recommends using the full 70-year lifetime when converting cumulative to continuous exposure rather  
8 than 60 (70 minus the lag of 10 used for exposure in the POD derivation) i.e., do not correct for the lag  
9 of 10 for a 10-year lagged exposure.

### 10 11 *Selection of Uncertainty Factors*

12  
13 A composite uncertainty factor of 100 (an intraspecies uncertainty factor of 10 to account for human  
14 variability and sensitive subpopulations; and a database uncertainty factor of 10 to account for database  
15 deficiencies) was applied to the POD for derivation of the RfC. Although it may be difficult to identify  
16 specific data on LAA to support departure from the default value of 10 for human variability, concern  
17 for the impact on susceptible subpopulations, especially women and children, remains an issue. The  
18 SAB also recommends that the EPA consider additional data to justify the application of a database  
19 uncertainty factor (UF<sub>D</sub>) of 10. First, additional data have recently been published for the community  
20 surrounding a Minnesota expansion plant. Second, LAA is generally considered as having very similar  
21 composition, physical properties, and biological effects as those seen for other amphiboles. This  
22 consideration of additional data (Minnesota cohort and data on other amphiboles) might support a lower  
23 value, such as 3, for UF<sub>D</sub>. In addition, a subchronic-to-chronic uncertainty factor higher than 1 may be  
24 used, given that the mean and maximum exposure duration in the study are well below the lifetime  
25 exposure of interest. There also is concern that the BMR of 10% for a severe endpoint is not reflected by  
26 the choice of a LOAEL- to- NOAEL uncertainty factor (UF<sub>L</sub>) of 1. It appears appropriate to consider  
27 either a lower BMR or the application of a larger uncertainty factor (UF<sub>L</sub>) for this endpoint. Thus, this  
28 question deserves additional consideration and more thorough analysis than it receives in the assessment  
29 report.

### 30 31 *Characterization of Uncertainties*

32  
33 Overall, the SAB found the discussion on uncertainties in the methodology and approach on the  
34 derivation of the RfC to be thorough, detailed and logical. However, the RfC uncertainty assessment can  
35 be strengthened. A key consideration of any assessment is whether the estimated RfC is adequately  
36 protective of public health. The SAB recommends that additional work be done to substantiate the RfC  
37 estimate through additional sensitivity analyses and discussion of results and insights from other datasets  
38 and studies. In sensitivity analyses, EPA can consider alternative exposure metrics (prioritizing  
39 residence time weighted metrics and excluding exposures after 1980), methods to fine-tune the RfC  
40 estimate from the subcohort (particularly fixing rather than estimating the plateau), and added sensitivity  
41 analyses for the full cohort. An additional source of uncertainty—the uncertainty in the RfC due to  
42 relying on a single study— also should be considered.

43  
44 With respect to exposure assessment, variations in analytical methods and environmental conditions are  
45 substantial contributors to uncertainty because of differences between the 1970s and today. PCM was  
46 the only acceptable method for measuring airborne fiber concentrations until the 1980s, when fiber  
47 concentrations were much higher than they are now. At the 1970's study site, the vast majority of fibers

1 were almost certainly LAA, so PCM's inability to identify asbestos did not create much uncertainty.  
2 Today, even ambient air sampling will yield fiber concentrations that exceed the RfC. Thus, it is  
3 important that transmission electron microscopy (TEM) be used to identify and count amphibole  
4 asbestos fibers longer than 5, 10, and 20  $\mu\text{m}$  in air samples for RfC purposes.

## 5 6 **Inhalation Unit Risk (IUR)**

### 7 8 *Exposure-Response Modeling*

9  
10 The SAB supports the agency's reliance on the Libby worker subcohort for derivation of the IUR  
11 because of its focus on good quality exposure data that are, specific for LAA. However, it is important  
12 to acknowledge that this small subcohort may have its own limitations as a basis for modeling exposure-  
13 response relationships. When selecting the models with which to characterize exposure-response  
14 relationships, a larger population over a lifetime should be considered.

15  
16 The SAB agrees that the agency clearly described the methods used to conduct the exposure-response  
17 modeling for lung cancer and mesothelioma. However, the SAB recommends that the agency consider  
18 other models and provide more justification for its choice of statistical models to characterize the  
19 exposure-response function. First, the SAB recommends that the agency more clearly explain why,  
20 when considering model selection, it appeared to discount the epidemiological evidence for  
21 mesothelioma that suggests the lifetime risk of developing the disease is increased for those whose  
22 exposure is first received earlier in life. The SAB recommends that the agency evaluate the time  
23 dependence of disease by providing tabulation of mesothelioma mortality rates and lung cancer SMRs  
24 by time since first exposure, duration of exposure, and period of first exposure for both the full and sub-  
25 cohort.

26  
27 A second and related point is that there are several other models—e.g., Weibull and two stage clonal  
28 expansion (TSCE)—that could have been used instead of or in addition to the Poisson and Cox models,  
29 and that these models might have provided very different estimates of risk that are not discussed. Use of  
30 the TSCE model, for example, could allow for a more direct evaluation of, and possibly justification for,  
31 age-dependency of the IUR.

32  
33 Third, the SAB finds that the agency had been overly constrained by reliance on model fit statistics as  
34 the primary criterion for model selection. The SAB recommends graphical display of the fit to the data  
35 for both the main models and a broader range of models in the draft document to provide a more  
36 complete and transparent view of model fit.

37  
38 Having made these points, the SAB recognizes that the agency did conduct extensive sensitivity  
39 analyses of their chosen models in various ways to characterize exposure in the Libby cohort. Consistent  
40 with their model and the EPA's *Guidelines for Carcinogen Risk Assessment*, these sensitivity analyses  
41 largely relied on the assumption that the effect of exposure can be modeled as a function of cumulative  
42 dose. These analyses, coupled with comparisons of IUR estimates using other published approaches to  
43 analysis of the same cohort, provide some reassurance. However, the analyses rely on essentially the  
44 same underlying models. They do not address the fundamental question of model uncertainty – that is,  
45 whether any one model can or should be assumed to represent the exposure-response relationship for  
46 LAA. This issue is of particular concern for the estimation of risks from partial lifetime exposure where  
47 risk is essentially assumed to be independent of when in the course of a lifetime exposure occurs.

1 Recommendations for addressing model uncertainty are discussed under response to charge question 5  
2 in Section 3.2.6.5.

3  
4 *Approach for Quantification of Inhalation Unit Risk*

5  
6 In order to derive an IUR that represents the combined risk of mortality from lung cancer and  
7 mesothelioma, a cancer-specific unit risk for each tumor type was calculated according to the *Guidelines*  
8 *for Carcinogen Risk Assessment* (USEPA, 2005) by linear extrapolation from the corresponding POD.  
9 The IUR was then determined as a combined upper bound risk estimate for mortality considering both  
10 cancers. The SAB considers the approach to be consistent with the agency's own guidance, and found  
11 the description of the procedure used to be clear. However, the SAB recommend the EPA should  
12 acknowledge that the assumption of independence is a theoretical limitation of the analysis and should  
13 provide a fuller justification for this assumption. EPA may cite the cancer risk assessment guidelines and  
14 the NRC (1994) analysis as suggesting the impact of this issue is likely to be relatively small. As a  
15 sensitivity analysis, the EPA should consider quantitatively accounting for dependence in the risks of  
16 mesothelioma and lung cancer mortality, either using a method which models the dependence explicitly  
17 or a bounding study that evaluates the numerical consequences of the assumption of independence.  
18

19 *Potential Confounding by Smoking*

20  
21 The SAB agrees that the agency's use of the Richardson (2010) method for exploring possible  
22 confounding for smoking was appropriate. However, the SAB finds the statement that there is no  
23 evidence of confounding by smoking is too strong, and relies more heavily than it needs to on the p-  
24 values that are marginally non-significant. More compelling is the observation of a negative association  
25 with COPD. It is possible that negative confounding is occurring, in which case the risk of lung cancer  
26 associated with asbestos exposure would be understated.  
27

28 *Adjustment for Mesothelioma Mortality Under-ascertainment*

29  
30 The number of mesothelioma deaths was adjusted for under-ascertainment stemming from inadequate  
31 coding in death certificates. The procedure is not described in any detail, but can be found in Kopylev et  
32 al. (2011). A total of 18 mesotheliomas were observed in the Libby cohort from 1980 to 2006. The  
33 estimated number of 24 mesotheliomas was obtained after using a Monte Carlo analysis. The ratio of 24  
34 to 18 yields the median of 1.33. The study by Kopylev et al. (2011) also provides a figure of 1.39 in  
35 Table 3, which is the mean later reported in the EPA document. The EPA method appears to be  
36 scientifically supported, but is not clearly described. The SAB recommends that this section be  
37 expanded to provide a more detailed statement of how the numbers were calculated.  
38

39 *Characterization of Uncertainties*

40  
41 The EPA has summarized the many sources of uncertainty and, sometimes quantitatively, the direction  
42 and likely impact of these sources of uncertainty. However, the sensitivity analyses do not take into  
43 account the magnitude and likelihood of multiple sources of uncertainty in the same analysis so the  
44 overall distribution of uncertainty in the estimated IURs remains unknown. The SAB notes that an  
45 important source of uncertainty, that of model uncertainty, might not be accounted for in the use of the  
46 95% upper confidence limit (UCL) on the IUR and the combined IUR. The SAB recommends that a  
47 more straightforward and transparent treatment of model uncertainty would be to estimate risks using a

1 more complete set of plausible models for the exposure-response relationship, including the Poisson  
2 models. This sensitivity analysis would make explicit the implications of these key model choices.

3  
4 *Long-Term Research Needs*

5  
6 The SAB identifies long-term research needs for epidemiological studies, mode of action, and  
7 measurement methods for LAA.

- 8 • The National Institute for Occupational Safety and Health (NIOSH) and Agency for Toxic  
9 Substances and Disease Registry (ATSDR) should continue to monitor mortality among Libby  
10 workers and residents of Libby and Troy, respectively, to determine the number of new lung  
11 cancers, mesotheliomas, and non-malignant pulmonary diseases in these two populations. In  
12 addition to a dose-response evaluation of Libby workers, an overall SMR should be calculated  
13 for lung cancer in this population by comparison to both the Montana and U.S. populations. An  
14 analysis specific for community, non-occupationally exposed, individuals should be extended  
15 through 2011. Early-life exposure to LAA could possibly be obtained from surrogate interview  
16 information from the community population. Smoking, occupational, and residential histories  
17 should be obtained for the lung cancer, mesothelioma, and non-malignant respiratory disease. A  
18 non-malignant respiratory health update since 2001 would be useful.
- 19 • The SAB recommends future research on mode of action on LAA to focus on biomarkers that  
20 are more clearly and specifically related to non-cancer endpoints (i.e., asbestosis) or cancer  
21 endpoints (e.g. mesothelioma). Inhalation studies in animal models that can provide both  
22 quantitative as well as mechanistic insight should be included.
- 23 • EPA should develop a TEM method that provides equivalent data to PCM. This TEM method  
24 must recognize fundamental differences between TEM and PCM analysis, and define differences  
25 between these two methods in analyzable areas, methodology in measuring complex fibrous  
26 structures and obscured fibers. This method should also define changes in PCM resolution over  
27 time, analysis parameters, and inter-laboratory variations and their causes.

## 2. INTRODUCTION

EPA's Office of Research and Development requested the Science Advisory Board (SAB) to review the *Draft IRIS Toxicological Review of Libby Amphibole Asbestos* (hereafter referred to as the draft document). The draft document is based on a comprehensive review of the available scientific literature on the health effects of Libby Amphibole asbestos (LAA), a term used to refer to the mixture of amphibole mineral fibers of varying elemental composition (e.g., winchite, richelite and tremolite) that have been identified in the Rainy Creek complex near Libby, Montana. The draft document provides the scientific and quantitative basis for toxicity values that will be entered into EPA's online Integrated Risk Information System (IRIS) database. Specifically, this draft IRIS assessment provides an overview of sources of exposure to LAA, and characterizes the hazard posed by exposure to LAA for carcinogenicity and noncancer health effects based on the available scientific evidence. The assessment includes the derivation of a chronic inhalation reference concentration (RfC) and an inhalation unit risk (IUR) that can be combined with exposure information in a risk assessment to estimate noncancer hazard and carcinogenic risk, respectively, in humans. The assessment does not address oral exposure to LAA.

In response to the agency's request, the SAB convened an expert panel (the Libby Amphibole Asbestos Review Panel) to conduct the review. The SAB panel discussed its responses to the EPA's charge questions (see Appendix A) during a February 6-8, 2012 face-to-face meeting and on public teleconferences on May 1, May 8, and July 25, 2012. There were two general charge questions on the organization, presentation, and clarity of the draft document, as well as specific charge questions that focus on: mineralogy and toxicokinetics, hazard assessment of non-cancer and cancer health effects, exposure-response assessment for derivation of an RfC for non-cancer endpoints, cancer weight of evidence classification, mode of action of LAA carcinogenicity, and exposure-response assessment for derivation of an IUR for LAA.

The Executive Summary highlights the SAB's major findings and recommendations. The SAB's full responses to the charge questions are detailed in Section 3 and brief recommendations on long-term research needs are provided in Section 4.

### 3. RESPONSES TO EPA'S CHARGE QUESTIONS

#### 3.1. General Charge Questions

##### 3.1.1. Overall Clarity

*Question 1. Is the Toxicological Review logical, clear, and concise? Has EPA clearly, and in sufficient detail, presented and synthesized the scientific evidence for health hazards from Libby Amphibole asbestos?*

In general, the SAB finds the toxicological review to be well-written, logical and appropriately referenced relative to the health hazards and exposure response of Libby Amphibole asbestos (LAA). However, the SAB has identified sections where extraneous and repetitive materials could be deleted. Examples include the following:

- For Section 3, since the focus of the draft document is on Libby amphibole fibers, it would be better to limit the literature reviews and discussions to those dealing with the family of amphibole asbestos fibers. Chrysotile asbestos fibers are very different from amphibole fibers in terms of their airborne concentration measurement errors and uncertainties, much lower biopersistence, faster clearance, different translocation pathways, and lower health risks.
- There are a large number of analyses in Section 4, nine community studies (4.1.4) and two case reports (4.1.5), that appear to offer nothing new, with no detailed exposure information and an exposed population, respectively.
- Discussions that offer little or no new insights into the toxicology of asbestos should be briefly summarized.
- Some sections are repetitive (e.g., Section 5.4.4 and 5.4.5).

Regarding clarity and sufficient detail in the presentation and synthesis of the scientific evidence for health hazards from LAA, the SAB finds the scientific evidence for health effects of LAA to be reasonably well presented. However, the SAB has identified areas where the draft document could be clarified and some aspects of EPA's analysis that require more explanation and justification, as provided in the responses to specific questions in subsequent sections. In addition, the SAB has comments on the following areas:

##### *Relevance of Other Literature Related to Amphiboles*

- The toxicological review does not make clear the relevance of the extensive literature on the health effects of other amphibole fibers. There are numerous publications on the mode of action of other amphiboles, inhalation studies in rodents, and epidemiological studies of populations exposed to amphiboles environmentally. Literature on epidemiological studies of other amphiboles is particularly useful for model selection for dose-response assessment of LAA.

##### *Early Lifestage Susceptibility*

- There is inconsistency in the tone of the conclusions in Section 4.7.1.1 (Lifestage Susceptibility) and in Section 6.3.3 (Applications to Early Lifetime and Partial Lifetime Environmental Exposure Scenarios for IUR) to either support or refute early lifestage susceptibility. We recognize that no firm conclusion can be drawn about differential risk of adverse health effects after early life stage exposure to LAA compared to exposure during adulthood, due to the limited

1 and inconclusive studies on other forms of asbestos. However, the limited evidence pointing to  
2 excess risk for exposures during childhood that is available needs to be considered when  
3 considering a margin of safety.

#### 4 **Recommendations**

- 5
- 6 • The draft document would benefit from greater usage of graphs and figures to highlight  
7 conclusions. A figure describing the two major occupational groups studied, including their time-  
8 lines of exposure, would be very helpful.
- 9
- 10 • Add discussion of known amphibole fiber toxicity determinants [dose, durability, dimension  
11 (especially length), surface chemistry].
- 12
- 13 • Add some additional causes of death (e.g., COPD) to full- and sub-cohorts (Table 5-6, 5-8).
- 14
- 15 • The section on susceptible populations could be better organized and more succinctly  
16 summarized. The section should especially focus on childhood asbestos exposure, the asbestos  
17 susceptibility issue most relevant to this EPA document, and probably the topic where there is at  
18 least some (albeit limited) data.
- 19
- 20 • Encourage the continued monitoring of relevant Libby residents for early onset asbestos  
21 associated diseases.
- 22
- 23 • Re-evaluate other models that might be a better fit for determination of early lifestage  
24 susceptibility.
- 25
- 26 • The draft document could be enhanced with quantitative comparison of the environmental  
27 exposures that have taken place in other geographic regions of the world (i.e., the Anatolia  
28 region of Turkey and Greece) (Sichletidis et al., 2006; Constantopoulos, 2008; Gogou et al.,  
29 2009; Carbone et al., 2011; Metintas et al., 2008, 2010, 2012) with the Libby, Montana,  
30 community with regard to airborne tremolite. This comparison should include numbers of fibers  
31 and fiber size distribution in relation to of health effects.
- 32
- 33 • The final proposed IUR should be compared with those calculated for other types of amphibole  
34 asbestos. A table comparing these results with the results from the earlier 1988 EPA analysis  
35 (USEPA, 1988) on asbestos would be helpful.

#### 36 **3.1.2. Additional Literature**

37 *Question 2. Please identify any additional peer-reviewed studies from the primary literature that should*  
38 *be considered in the assessment of noncancer and cancer health effects of Libby Amphibole asbestos.*  
39

40 The SAB has identified additional studies to be considered in the assessment:

41

42 Adgate, JL; Cho, SJ; Alexander, BH; Ramachandran, G; Raleigh, KK; Johnson, J; Messing, RB;  
43 Williams, AL; Kelly, J; Pratt, GC. (2011). Modeling community asbestos exposure near a vermiculite

1 processing facility: Impact of human activities on cumulative exposure. *J Expo Sci Environ Epidemiol*  
2 21: 529-535.

3  
4 Alexander, BH; Raleigh, KK; Johnson, J; Mandel, JH; Adgate, JL; Ramachandran, G; Messing, RB;  
5 Eshenaur, T; Williams, A. (2012). Radiographic evidence of nonoccupational asbestos exposure from  
6 processing Libby vermiculite in Minneapolis, Minnesota. *Environ Health Perspect* 120: 44-49

7  
8 Antao, VC; Larson, TC; Horton, DK. (2012). Libby vermiculite exposure and risk of developing asbestos-  
9 related lung and pleural diseases. *Curr. Opin. Pulmonary Med.* 18:161-167, PMID: 22139761.

10  
11 Berman, DW (2011). Apples to apples: The origin and magnitude of differences in asbestos cancer risk  
12 estimates derived using varying protocols. *Risk Analysis* 31: 1308-1326.

13  
14 Cyphert, JM; Padilla-Carlin, DJ; Schladweiler, MC; Shannahan, JH; Nyska, A; Kodavanti, UP; Gavett,  
15 SH. (2012). Long-term response of rats to single intratracheal exposure of libby amphibole or amosite. *J*  
16 *Toxicol Environ Health A* 75: 183-200. <http://dx.doi.org/10.1080/15287394.2012.641203>.

17  
18 Marchand, LS; St-Hilaire, S; Putnams, EA., et al. (2012). Mesothelial cell and anti-nuclear autoantibodies  
19 associated with pleural abnormalities in an asbestos exposed population of Libby MT. *Toxicology Letters*  
20 208: 168-173.

21  
22 Shannahan, JH; Nyska, A; Cesta, M; Schladweiler, MC; Vallant, BD; Ward, WO; Ghio, AJ; Gavett, SH;  
23 Kodavanti, UP. (2012). Subchronic pulmonary pathology, iron overload, and transcriptional activity  
24 after libby amphibole exposure in rat models of cardiovascular disease. *Environ Health Perspect* 120:  
25 85-91.

26  
27 Shannahan, JH; Ghio, AJ; Schladweiler, MC; Richards, JH; Andrews, D; Gavett, SH; Kodavanti, UP.  
28 (2012). Transcriptional activation of inflammasome components by Libby amphibole and the role of  
29 iron. *Inhalation Toxicology* 24:60-69, PMID: 22168577

30  
31 Webber, JS; Blake, DJ; Ward, TS; Pfau, JC. (2008). Separation and Characterization of Respirable Amphibole  
32 Fibers from Libby, Montana. *Inhal. Toxicol.* 20: 8, 733 - 740.

33  
34 Zeka A; Gore R; Kriebel D (2011). The two-stage clonal expansion model in occupational cancer  
35 epidemiology: results from three cohort studies. *Occupational and Environmental Medicine* 68:618-24.

### 36 **3.2. Specific Charge Questions**

#### 37 **3.2.1. Mineralogy**

38 *Question 1a. Please comment on whether the presentation of the available data on the mineralogy of*  
39 *Libby Amphibole asbestos is clear, concise and accurate.*

40  
41 Section 2, Geology and Mineralogy of Libby Amphibole Asbestos, provides a discussion of the  
42 mineralogical and geological aspects of Libby Amphibole. In general, the SAB finds that this section  
43 provides an important foundation for understanding the nature of Libby Amphibole asbestos (LAA) as  
44 related to evaluation of potential exposures. There are places where the clarity and accuracy of the  
45 section can be improved, and these are detailed below.

1  
2 There is a mismatch between the mineralogical detail embodied in the definition of mineral species and  
3 the detail available relative to specific exposures in Libby. Specifically, mineral species define a very  
4 specific structure (e.g., amphibole) and a specific composition or range of compositions (e.g., winchite  
5 or tremolite). Given that these factors affect a mineral's physical and chemical behavior, they may in  
6 principle be factors to consider for potential hazard. The SAB recognizes that this level of detail is not  
7 typically available for toxicity studies to allow its application to the evaluation of LAA *per se*. In  
8 general, however, the observed unique aspects of amphibole asbestos support the evaluation of LAA  
9 through comparison with other amphiboles based on particle morphology and amphibole designation.  
10 Nevertheless, the SAB encourages a rigorous and accurate description of LAA in Section 2, perhaps  
11 while noting the potential ambiguities in the use of mineral-species names in other studies.

12  
13 Comments on the subsections follow:

- 14
- 15 • Discussions of mineralogy and morphology in Sections 2.2.1.1. and 2.2.1.2. are good, with  
16 appropriate discrimination between methods/definitions that are applied to field samples versus  
17 terms/definitions that are applied to environmental samples (lines 4 and 5 of page 2-10).  
18
  - 19 • Section 2.1 is generally sufficient for providing a background on historical aspects of the mining  
20 operations in Libby, Montana.  
21
  - 22 • Section 2.2 needs significant modification. This section should lay a foundation for  
23 understanding the nature of Libby Amphibole (e.g., mineralogical characteristics such as  
24 composition and morphology), information on how the material may vary spatially and  
25 temporally (with respect to mining operations), and other factors that may impact exposures. The  
26 section does contain much relevant information. There are parts of the section that are incorrect  
27 and misleading; recommendations to address these issues include:
    - 28 ○ *Consistent use of terminology associated with particle morphology.* The section mixes a  
29 number of terms that address particle morphology, and these are critically important in  
30 assessing potential exposures and subsequent impacts. As an example, “fibers (e.g.,  
31 acicular...)” implies fibrous and acicular are the same, when in conventional usage they are  
32 different (e.g., see Veblen and Wyllie, 1993). A tight use of terms that are defined up front  
33 should be followed, recognizing that a lax use of terms may nevertheless exist in the  
34 literature cited. A partial attempt is provided in Section 2.2.1.2, but it could be expanded and  
35 carefully vetted with respect to accepted terminology. The four most important terms to lay  
36 out clearly are fibrous, acicular, prismatic, and asbestiform. If the report's intent is to note  
37 differences in these terms, they should be discussed; if the conclusion is that there are poorly  
38 defined distinctions, that topic also should be discussed. One specific example of inaccurate  
39 usage is the term “prismatic,” which by definition is “prism”-shaped (meaning parallel sides;  
40 it is incorrectly used in multiple places).
    - 41 ○ *Double-check all mineral formulae.* There are numerous incorrect compositions in the report;  
42 although some of these may be typos (which, of course, should be fixed), some may be  
43 incorrectly reported. An example of one incorrect formula is that attributed to vermiculite  
44 (which is listed incorrectly as:  $[(Mg,Fe,A)_3(Al,Si)_2O_{10}(OH)_2 \cdot 4H_2O]$ ).

1           ○ *Double check that all mineral-species definitions used are accepted mineralogical standards.*  
2           Mineral species are fundamental terms that describe a material with a specific structure and a  
3           specific composition or ranges of compositions; both factors are primary determinants of a  
4           material's properties. Indeed, at the heart of this report is the definition of likely exposures to  
5           (and risks from) inhaled particles and other fibers based on the use of mineral-species names.  
6           The problems in this category are probably most widespread in Section 2.2.1.1, which details  
7           amphibole mineralogy (which is central to the report). For example, anthophyllite is not a  
8           Libby amphibole.  
9

- 10           ● The SAB appreciates the discussions that highlighted the complexity and variability of LAA in  
11           the context of compositional solid solutions, emphasizing that even the use of mineral-species  
12           names for LAA may mislead readers to believe that LAA is represented by a few discrete  
13           materials as opposed to a mixture of materials with varying compositions. Overall, the  
14           mineralogy section could benefit from some technical editing. It presents some irrelevant  
15           material (e.g., section 2.2.1, which is a general description of silicate mineral hierarchy), omits  
16           some critical information (e.g., section 2.2.1.1 does not provide the mineralogical definitions of  
17           key minerals like winchite or richterite), and presents some erroneous and irrelevant  
18           characterizations (e.g., some of the vermiculite-mineralogy descriptions in section 2.2.2).  
19
- 20           ● The report provides a good summary of available information on the LAA. One specific  
21           observation that could be added is one reported by Sanchez et al. (2008), namely that they  
22           observed no correlation between morphology (fibrous vs. prismatic) and major-/minor-element  
23           chemistry. Webber et al. (2008) similarly concluded that there was no correlation between  
24           mineral species and fiber width for respirable fibers. In other words, this is consistent with the  
25           implication that the large set of compositional data from Meeker et al. (2003) shown in the report  
26           reflects the range of compositions associated with inhaled-fiber exposures.  
27
- 28           ● Discussion on page 2-10 glosses over a serious shortcoming of phase contrast microscopy  
29           (PCM): its inability to detect fibers narrower than  $\sim 0.25 \mu\text{m}$ . These thin fibers are among the  
30           most biologically potent according to the Stanton-Pott hypothesis. The fact that only a third of  
31           the Transmission Electron Microscopy (TEM)-visible Libby fibers were PCM-visible is buried  
32           in McDonald et al. (1986). Furthermore, Text Box 2-2 does not adequately contrast the  
33           capability of EM versus PCM. EM's capability to yield elemental composition via Energy  
34           Dispersive Spectroscopy (EDS) and Wavelength Dispersive X-ray Spectroscopy (WDS)  
35           provides information to identify different asbestos types. PCM, in contrast, cannot even  
36           determine if the fiber is mineral. Furthermore, the Selected Area Electron Diffraction (SAED)  
37           capability of TEM allows determination of crystalline structure, e.g., amphibole versus  
38           serpentine. Finally, Box 2-2 incorrectly states that scanning electron microscopy (SEM)  
39           "produces three-dimensional (3-D) images". Rather, SEM produces 2-D images that reveal  
40           surface structure of particles.  
41
- 42           ● The electron microscopy section on page 2-11 could be clarified. SEM and TEM provide higher  
43           magnification to allow better particle morphological analysis. Electron diffraction allows  
44           mineralogical assessment. Energy dispersive X-ray analysis allows elemental composition  
45           determination, which can corroborate the mineralogical determination. X-ray diffraction (XRD)  
46           mentioned in this section is useful for bulk sample mineralogy measurements.

### 3.2.2. Toxicokinetics

*Question 1b. In the absence of toxicokinetic information specific to Libby Amphibole asbestos, the draft assessment contains a general summary description of fiber toxicokinetics. Please comment on whether this overview of general fiber toxicokinetics is clear, concise and accurate.*

The discussion of general fiber toxicokinetics is not clear, nor concise, especially since it fails to distinguish between chrysotile and amphibole fibers. Furthermore, it is inaccurate in too many places, as noted below.

- In view of the fact that the focus of the document is on Libby Amphibole fibers, it would be better to limit most of the literature reviews and discussions to those dealing with the various kinds of amphibole asbestos fibers. Chrysotile asbestos fibers, which are not a significant complication in exposures to Libby vermiculate, are very different from amphibole fibers in terms of their: (a) airborne concentration measurement errors and uncertainties; (b) much lower biopersistence; (c) clearance and translocation pathways and rates; and (d) risks. One rationale for the exclusion of chrysotile fibers from this document of the literature on risks associated with exposures to chrysotile is that most of the risks have been associated with amphibole fibers within the chrysotile ores than to the much more numerous chrysotile fibers that dominate the measured airborne fiber concentrations.
- There are some notable misstatements and omissions of knowledge on fiber deposition and dosimetry in the document.
  - The authors should draw on more authoritative and comprehensive reviews in the literature (e.g., Lippmann, 2009; Mossman et al., 2011). One misstatement in the draft is that impaction is affected by fiber length. Another is that interception is affected by aspect ratio. The document should cite the work by Sussman et al. (1991a,b) that demonstrates that interception of amphibole (crocidolite) fibers is only demonstrably in excess when fiber lengths are >10  $\mu\text{m}$ . Also, the report should cite the work of Brody and colleagues (Brody et al., 1981; Brody and Roe, 1983; Warheit and Hartsky, 1990) on chrysotile fiber deposition in the alveolar region in rodents. In terms of deposition sites, there should be no significant difference between chrysotile and amphibole fibers.
  - Another misstatement is that mucociliary clearance is complete within minutes or hours rather than the true time frame of hours to a few days (Albert et al., 1969). The authors also need to acknowledge that particles depositing in the alveolar region can reach the tracheobronchial tree in two ways: (a) on surface fluids drawn onto the mucociliary escalator by surface tension, and (b) by passing through lymphatic channels that empty onto the mucociliary escalator at bronchial bifurcations. The report also should acknowledge that macrophage-related clearance of fibers is only applicable to short fibers that can be fully phagocytosed. Nearly all of the references to chrysotile in the discussion of translocation should be deleted. The Libby asbestos fibers are essentially all amphibole fibers, and there is very little commonality among serpentine and amphibole fibers in terms of translocation or long-term retention.
  - There are also toxicokinetic misstatements in Section 4.2 describing cancer bioassays in animals. The section should cite the inhalation study of Davis et al. (1985) with fibrous

1 tremolite, which is very similar to Libby amphibole. Also, this section should discuss the  
2 tremolite inhalation study of Bernstein et al. (2003, 2005) that is cited in Table 4-16, as well  
3 as the more recent study by Bernstein et al. (2011) that demonstrated pleural translocation in  
4 rats using non-invasive means following airborne amosite asbestos exposure. The study  
5 examined animals for up to one year following a short 1-week exposure to amphibole and  
6 characterized the size of fibers that were present in parietal pleura. Non-cancer inflammatory  
7 pleural changes were demonstrated associated with fiber translocation. This paper shows  
8 rapid translocation of fibers to the pleura (at least of rodents) and it should be referenced for  
9 completeness on toxicokinetic issues. Furthermore, the results of the various studies cited in  
10 Section 4.2 are almost all very difficult to interpret with respect to the toxic effects that were,  
11 or were not, reported, since no information was provided on the key dosimetric factor of fiber  
12 dimensions in Tables 4.15 and 4.16. There were comprehensive summaries of available  
13 information on fiber dimensions of materials administered in the bioassays in Appendix D,  
14 including numbers of long fibers, but Section 4.2.5 is deficient, as a summary of animal  
15 studies for LAA and tremolite, in not discussing how the content of long fibers in the  
16 administered materials had an influence on the effects observed.

### 17 **3.2.3. Noncancer Health Effects of Libby Amphibole Asbestos**

#### 18 **3.2.3.1. Selection of Critical Studies and Effects**

19 *Question 1. An occupational cohort of workers in a Marysville, OH facility exposed to Libby Amphibole*  
20 *asbestos (Lockey et al., 1984; Rohs et al., 2008) was selected as the basis for the derivation of the*  
21 *reference concentration (RfC). Please comment on whether the selection of this study population is*  
22 *scientifically supported and clearly described. If a different study population is recommended as the*  
23 *basis for the RfC, please identify this study and provide scientific support for this choice.*  
24

25 The rationale for the use of the Marysville, Ohio, cohort for development of the RfC was well described  
26 and scientifically supported. However, there are clear drawbacks to this cohort due to the lack of  
27 exposure sampling prior to 1972 when most of the cohort began work, the use of self-reported work  
28 histories, the end of Libby vermiculite use in 1980 and the mixture of vermiculite sources used  
29 throughout the life of the plant. These drawbacks are offset by the solely occupational exposure of this  
30 cohort, the use of better quality radiographs taken for research purposes, the use of 2000 ILO standards  
31 for reading radiographs, and a cohort with exposures closer to environmental levels. The selection of  
32 the subcohort for the main analysis has a clear and strong rationale. (There were 118 workers who began  
33 work in 1972 or later when exposure data were available, and who had X-rays from the 2002-2005  
34 exam).The full cohort of 434 workers was used for analyses to substantiate the subcohort findings.  
35

36 Although the SAB agrees that the Marysville subcohort represents the best population upon which to  
37 base the RfC, there was discussion about the need for additional analyses/cohorts, but to strengthen and  
38 support the RfC. One suggestion is to use the Marysville cohort but include any X-ray abnormalities as  
39 the outcome [LPT, diffuse pleural thickening (DPT), or asbestosis]. In addition, cause of death might be  
40 assessed for those who died between the two exams. Another suggestion for providing support and  
41 perspective to the Marysville findings is to conduct analogous analyses (to the extent the data permit) of  
42 pleural abnormalities among the Libby workers cohort (Larson et al., 2012) and among the Minneapolis  
43 exfoliation community cohort (Adgate et al., 2011; Alexander et al., 2012). The Libby workers have  
44 higher, well characterized occupational exposures compared to the Marysville cohort. The Minneapolis  
45 cohort of non-workers generally had estimated exposures at the lower end of the Marysville cohort but

1 included women and children, thus providing a cohort more representative of the general population.  
2 However, because the Minneapolis cohort had estimated, not measured exposures, it would not be  
3 suitable for the primary RfC analysis. Similarly, because the Libby workers have both environmental  
4 and occupational exposures, this cohort should not be used for primary RfC analysis.

5  
6 *Question 2. Radiographic evidence of localized pleural thickening in humans was concluded by EPA to*  
7 *be an adverse effect and was selected as the critical effect for the derivation of the RfC. Pleural*  
8 *thickening is associated with restrictive lung function, breathlessness during exercise and, for some*  
9 *individuals, chronic chest pain. Please comment on whether the selection of this critical effect and its*  
10 *characterization is scientifically supported and clearly described. If a different health endpoint is*  
11 *recommended as the critical effect for deriving the RfC, please identify this effect and provide scientific*  
12 *support for this choice.*

13  
14 Radiographic evidence of localized pleural thickening (LPT) in humans is the appropriate adverse and  
15 critical effect for the derivation of the RfC. This is clearly described and well supported by the lines of  
16 evidence presented in section 4.1.1.4.2. However, the SAB believes additional evidence is available to  
17 further support this view and should be reported.

18  
19 While other health endpoints might have been considered candidates for the critical effect for deriving  
20 the RfC, such as diffuse pleural thickening and small opacity profusion, the use of LPT is appropriate  
21 and well supported. LPT is a permanent, structural, pathological alteration of the pleura. LPT is found at  
22 a significantly elevated prevalence in exposed individuals, has the appropriate specificity and is not  
23 confounded by cigarette smoking. LPT is also associated with reduced lung function. Furthermore the  
24 findings reported in this section are compatible with the animal data showing tissue injury and  
25 inflammation.

26  
27 It is important to provide for a more detailed review of the literature to support the use of LPT as the  
28 appropriate endpoint, including studies addressing the relationship between LPT and both pathologic  
29 and physiologic abnormalities. Published studies that address the relationship between LPT and lung  
30 function suggested by the SAB include (Lilis et al., 1991b; Paris et al., 2009; Clin et al., 2011), along  
31 with those referenced in the American Thoracic Society (ATS) Statement entitled, *Diagnosis and Initial*  
32 *Management of Nonmalignant Diseases Related to Asbestos: Official Statement of the American*  
33 *Thoracic Society* (ATS, 2004) (Ohlson et al., 1984; 1985; Jarvolm and Sanden, 1986; Hjortsberg et al.,  
34 1988; Oliver et al., 1988; Bourbeau et al., 1990; Schwartz et al., 1990; Miller et al., 1992; Van Cleemput  
35 et al., 2001; Miller, 2002; Whitehouse, 2004; Sichletidis et al., 2006; Wilken et al., 2011). Consistent  
36 with that Statement, the SAB believes that large cohort studies have shown significant reduction in lung  
37 function, including diminished diffusing capacity and vital capacity associated with LPT.

38  
39 The SAB also suggests that the EPA consider looking at LPT, DPT and small opacity profusion score  
40 together as an outcome. There is evidence that LPT is not always the first adverse effect that is detected  
41 on chest radiographs, and some individuals with LAA exposure can develop either DPT or increased  
42 profusion of small opacities without developing evidence of LPT. Combining outcomes is appropriate,  
43 since the goal is to define an exposure level below which LAA is unlikely to have adverse health effects.

44  
45 **Recommendations:**

- 1 • Include a more detailed review of the literature to support the selection of LPT through detailing  
2 the studies that show the relationship between LPT and both pathologic and physiologic  
3 abnormalities, and also risk of other non-cancer asbestos-related diseases.
- 4 • In addition to LPT, include an analysis that uses all radiographic outcomes (LPT, DPT and small  
5 opacities), recognizing this change may have little impact on the current analysis.

### 6 **3.2.3.2. Use of Animal and Mechanistic Studies**

7 *Question 3. The database of laboratory animal and mechanistic studies of Libby Amphibole asbestos is*  
8 *summarized in the draft assessment (see Section 4.2 and 4.3, details in Appendix D) to inform the*  
9 *mechanisms of the biological response to Libby Amphibole asbestos and support the epidemiology*  
10 *studies used for derivation of the RfC. Please comment on whether the laboratory animal and*  
11 *mechanistic information presented is used appropriately in the draft assessment.*  
12

13 The EPA draft document discusses the different types of minerals present in LAA and it is uncertain  
14 how the various components relate to adverse health effects. LAA contains ~6% tremolite and there  
15 is clear evidence from human and animal studies that tremolite causes adverse health effects in  
16 humans and experimental animals. However, since LAA also contains winchite (84%) and richterite  
17 (~11%), it would be prudent to determine whether these mineral forms contribute to the adverse  
18 health effects of LAA or whether there are interactive effects of winchite or richterite that modify the  
19 toxicity of tremolite. The SAB recommends that this issue be highlighted, since it is well-known that  
20 tremolite is highly fibrogenic, and causes malignant mesothelioma (MM). However, the contribution  
21 of winchite or richterite to adverse health effects is apparently unknown.

22  
23 In general, the listing of the laboratory animal studies in Tables 4-15 and 4-16 and the underlying data  
24 summary in Appendix D are appropriate and complete. However, Tables 4-15 and 4-16, and the  
25 summary data in Appendix D do not include the distributions of fiber lengths, and Section 4.2.5 is  
26 therefore deficient, as a summary of animal studies for LAA and tremolite, in terms of not discussing  
27 how the content of long fibers in the administered materials had an influence on the effects observed.  
28 The report text in Section 4.2.5 is also deficient in not discussing how the contents of long fibers in the  
29 administered materials had an influence on the effects observed. Therefore, the issue of the influence of  
30 fiber dimensions, and especially of fiber length, needs to be strengthened. The LAA fiber dimensions,  
31 listed in Table D-5 (page D6) should be moved to the main text in Section 4.4 Mechanistic Data and  
32 Other Studies in Support Of the Mode of Action. A recent paper by Berman (2011), which was not cited  
33 in the draft report, suggests that cancer risk coefficients for various amphiboles are more consistent  
34 when fiber length was taken into consideration. Berman (2011) also suggests that the health risks  
35 presented by amphibole are greater than those of chrysotile.

36 Laboratory animal studies utilizing various stocks and strains of mice and rats as well as hamsters,  
37 by a variety of non-inhalation routes of exposure, have been used to ascertain the potential  
38 fibrogenic and carcinogenic potential of the LAA. While inhalation is regarded as the most  
39 physiologically relevant means of fiber exposure in animals, there is no published study with the  
40 LAA mixture with this route of fiber administration in experimental animals. However, there has  
41 been intratracheal instillation of LAA in short-term studies with mice and rats that resulted in airway  
42 inflammatory change consistent with earlier changes seen in tremolite-exposed animals. The lack of  
43 any inhalation data in rats or mice is an important issue, since the deposition of particles and fibers  
44 cannot be adequately addressed using intratracheal instillation of a bolus of fibers delivered in

1 aqueous suspension. For example, the development of pleural lesions may be quite different when  
2 comparing fibrogenic or carcinogenic fibers or other particles by inhalation versus instillation. While  
3 inhalation studies have been conducted with tremolite (e.g., Bernstein et al., 2005), the relative  
4 potency of inhaled LAA should be compared to that of tremolite. This could add new information  
5 for refining the RfC for LAA.

6  
7 *In vitro* assay systems utilizing both primary cells and established human and mammalian cell lines  
8 have been used to provide mechanistic insights on the potential mode of action of LAA. These  
9 limited *in vitro* studies have demonstrated the importance of fiber-cell interactions, the ability of  
10 LAA to induce reactive radical species, inflammatory gene expression, and micronuclei, a marker of  
11 genomic instability. Unfortunately, with the exception of the latter, most of these endpoints are non-  
12 specific and can be demonstrated with any particles including glass fibers in short-term assays.  
13 Similarly, Section 4.4.1 (page 4-63) mentions increases in Th1 and Th2 cytokines that are not  
14 specific to the effects of LAA or other types of asbestos, but rather generalized mediators of non-  
15 allergic or allergic inflammatory responses. Likewise, pro-inflammatory cytokines (e.g., interleukin-  
16 8), enzymes (e.g., cyclooxygenase-2) and oxidative stress markers (e.g., heme oxygenase) are  
17 biomarkers of a wide variety of cellular stress and inflammation responses that will probably not  
18 shed much light on the mechanisms of LAA-induced disease. It would be valuable for future  
19 research on LAA mode of action to focus on biomarkers that are more clearly and specifically  
20 related to non-cancer endpoints (i.e., asbestosis) or cancer endpoints (e.g., mesothelioma). Critical  
21 genotoxicity studies including mutagenesis and chromosomal aberration studies have not been  
22 reported/ examined with LAA.

### 23 **3.2.4. Carcinogenicity of Libby Amphibole Asbestos**

#### 24 **3.2.4.1. Weight of Evidence Characterization**

25 *Question 1. Under EPA's Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005;*  
26 *www.epa.gov/iris/backgrd.html), the draft IRIS assessment characterizes Libby Amphibole asbestos as*  
27 *"carcinogenic to humans" by the inhalation route of exposure. Please comment on whether the cancer*  
28 *weight of evidence characterization is scientifically supported and clearly described.*

29  
30 Human epidemiological data supersede animal and other laboratory studies in the identification of a  
31 human carcinogen/toxicant. For LAA, the SAB agrees with the EPA that, while there are no concrete  
32 laboratory studies that unequivocally demonstrate carcinogenicity of the fiber mix, there are strong  
33 epidemiological data that support the notion that LAA fiber is closely linked to cancer incidence in  
34 humans under occupational settings. The occupational studies appeared most persuasive at showing  
35 dose-related increased risks of lung cancer and mesothelioma among workers exposed by inhalation.  
36 However, the number of mesothelioma cases is small. The case series in the community, while  
37 supportive, do not provide the same level of evidence for an association or for the strength of the  
38 association. Nonetheless, the epidemiologic evidence from the occupational studies does support the  
39 choice of descriptor "carcinogenic to humans by the inhalation route" for LAA under the conditions  
40 of exposure in those studies.

41  
42 On the other hand, the only solid evidence that the LAA is carcinogenic to animals is in hamsters  
43 injected intraperitoneally with a single 25-mg dose of the fiber mix, which is not a physiologically  
44 relevant route of exposure in humans. Although inflammation of the lung has been demonstrated  
45 using both mice and rats exposed to LAA by intra-tracheal instillation, these short-term studies

1 failed to demonstrate any cancer induction. The SAB, however, concurs with the EPA report that  
2 these findings—which include altered gene expression, collagen induction, and inflammation—are  
3 consistent with the early-stage disease process induced by other amphibole fibers. As such, the EPA  
4 has derived additional supporting evidence for the carcinogenic potential of LAA from studies with  
5 tremolite fibers. Although the SAB recognizes that these studies provide circumstantial, supporting  
6 evidence of the carcinogenic potential of LAA in light of its ~6% tremolite by composition, the  
7 limited data base on LAA *per se* cannot provide a well defined mode of action for either lung cancer  
8 or mesothelioma induction, as will be discussed in the following section.

#### 9 **3.2.4.2. Mode of Carcinogenic Action**

10 *Question 2. Due to the limitations of the data available, the draft assessment concludes that there is*  
11 *insufficient information to identify the mode of carcinogenic action of Libby Amphibole asbestos. Please*  
12 *comment on whether this determination is appropriate and clearly described. Note that in the absence of*  
13 *information to establish a mode of action, a linear low dose extrapolation is recommended by the*  
14 *Guidelines for Carcinogen Risk Assessment (U.S., EPA, 2005; Section 3.3). If it is judged that a mode of*  
15 *action can be established for Libby Amphibole asbestos, please identify the mode of action and its*  
16 *scientific support (i.e., studies that support the key events, and specific data available to inform the*  
17 *shape of the exposure-response curve at low doses).*

18  
19 The mechanisms by which amphibole fibers produce malignancy and fibrosis are complex and likely  
20 to be multifactorial in nature. The induction of reactive radical species through persistent interaction  
21 of fibers with target cells, the involvement of chronic inflammatory response, the activation of  
22 certain oncogenes and inactivation of yet to be identified suppressor gene(s), have been proposed as  
23 possible mechanisms. In addition, various *in vitro* and *in vivo* studies have shown that fiber  
24 dimensions, surface properties, shape and crystallinity, chemical composition, physical durability,  
25 and exposure route, duration, and dose are important determinants of the biological potency of  
26 fibers.

27  
28 With the LAA, neither the fairly limited amount of research conducted using *in vivo* as well as *in*  
29 *vitro* assays that are described in the review, nor the more extensive body of published work on other  
30 asbestiform minerals, which is also summarized, lead to clear conclusions as to a single mechanism  
31 of carcinogenic action. The SAB agreed with the EPA conclusion that the laboratory-based weight  
32 of evidence for the mode of action of LAA is weak. Given the limited data base available in the  
33 literature, the conclusion that there is insufficient information to identify the mode of carcinogenic  
34 action of LAA is fully justified. In view of these complexities and uncertainties, the default linear  
35 extrapolation at low doses is appropriate. This choice receives at least limited support from data on  
36 carcinogenesis by other amphiboles.

#### 37 **3.2.4.3. Selection of Critical Study and Endpoint**

38 *Question 3. An occupational cohort of workers from Libby, MT. exposed to Libby Amphibole asbestos*  
39 *(i.e., the Libby worker cohort) was selected as the basis for the derivation of the inhalation unit risk*  
40 *(IUR). Please comment on whether the selection of this study population is scientifically supported and*  
41 *clearly described. If a different study population is recommended as the basis for the IUR, please*  
42 *identify this study and provide scientific support for this choice.*

43  
44 The selection of the Libby cohort is scientifically supported and clearly described. It appears to be the  
45 best cohort available for cancer outcomes. This cohort has been thoroughly studied previously, had

1 detailed work histories with a job exposure matrix available, had elevated asbestos exposure, had a wide  
2 range of measurements of asbestos exposure (covering a range of two orders of magnitude), was large,  
3 and had cancer mortality data available. Limitations of this cohort include the possible environmental  
4 exposures to asbestos and limited smoking information available, especially given that smoking is an  
5 important risk factor for lung cancer (but not for mesothelioma) and also may have a synergistic effect  
6 with asbestos exposure. Also, outcomes are based on death certificates, which could undercount  
7 incidences of relevant endpoints.

8  
9 Libby Amphibole asbestos is the only possible source of the asbestos measured in the air samples (i.e.,  
10 there are no other sources of asbestos at the mine and associated facilities). It should be noted, however,  
11 that this study population may not be representative of the larger population, since most of its members  
12 are white males, exposed as adults, and it contains a higher proportion of cigarette smokers than the  
13 larger population. If a residential study is ever completed that includes a larger proportion of women,  
14 other races, and those exposed as children, the derivation of the IUR should be revisited. Additionally, it  
15 is noted that the endpoints are based on cancer mortality noted on death certificates. While this could  
16 lead to an undercounting of actual cases of lung cancer, it seems less likely that lung cancer in a heavily  
17 asbestos-exposed population would either be missed on a death certificate or would significantly  
18 undercount incidence more so than in the comparison population. Mesothelioma cases might not have  
19 been fully accounted for using death certificates, as mesothelioma did not have a distinct ICD code prior  
20 to ICD-10, implemented in 1999. However, death certificates were manually reviewed, as noted, and  
21 possible under-ascertainment of mesothelioma cases was addressed in the modeling.

22  
23 Use of the subcohort post-1959 seems reasonable due to the lack of exposure information for many of  
24 the workers in earlier years. Out of 991 workers hired before 1960, 706 had all department and job  
25 assignments listed as unknown. Thus, it would seem highly problematic to include these workers in the  
26 model. However, that leaves only 285 workers with at least some information. Possibly some additional  
27 analysis could be done on that group. However, of the 991 workers, 811 had at least one job with an  
28 unknown job assignment.

29  
30 It would be informative to calculate an overall Standardized Mortality Ratio (SMR) for the Libby  
31 worker full- and sub- cohorts for lung cancer. Comparison should be made with both Montana and U.S.  
32 data. The later cohort also had lower levels of exposure to asbestos, which would be closer to the lower  
33 levels found in the environment.

34  
35 *Question 4. Mortality from lung tumors and mesothelioma in the Libby worker cohort was selected to*  
36 *serve as the basis for the derivation of the IUR. Please comment on whether this selection is*  
37 *scientifically supported and clearly described. If a different health endpoint is recommended for*  
38 *deriving the IUR, please identify this endpoint and provide scientific support for this choice.*

39  
40 Lung cancer and mesothelioma are entirely appropriate endpoints for derivation of the IUR. They are  
41 scientifically supported and clearly described. Mesothelioma is caused by asbestos exposure. While it is  
42 possible to consider an alternative model focused on mesothelioma alone to derive the IUR, the number  
43 of deaths from mesotheliomas is small and this would likely understate the overall cancer risk.

44  
45 Since determining the cancer outcome from mortality rather than incidence data may have resulted in an  
46 undercount of both cancer outcomes, the discussion would benefit from more detail on how the use of  
47 incidence data could impact the derived IUR. In addition, the mesothelioma outcome may be

1 underrepresented because the cohort has been followed for 25 to 46 years, and lag times from exposure  
2 to detectable disease onset range from 15 to greater than 60 years. Mesothelioma also may have been  
3 underreported on death certificates. Under-represented outcomes could lead to an underestimated IUR.  
4 While there is sufficient information for derivation of the IUR, revisiting derivation of the IUR after  
5 additional follow up is warranted. It was recommended at the SAB meeting that additional follow-up of  
6 both the occupationally and environmentally exposed populations would be helpful.  
7

8 The report mentions laryngeal (n = 2) and ovarian (n = 0) cancer deaths in the text. The International  
9 Agency for Research on Cancer (IARC) concluded that there was sufficient evidence in humans that  
10 some types of asbestos were causally associated with cancer of the larynx and the ovary as cited in the  
11 publication by Straif et al.(2009).  
12

13 Tables 5-6 and 5-8 are mistitled, since the tables include the number of deaths from mesothelioma and  
14 lung cancer as well as demographic and exposure data. The titles should either be changed and  
15 additional causes of death included in the tables or new tables should be created that focus on the causes  
16 of death.  
17

18 It also would have been useful to know the other major categories of mortality in this cohort. This could  
19 include the numbers of COPD, cardiovascular, colorectal cancer and other cancer deaths. It would be  
20 helpful to have a clearer comparison of the Libby asbestos risk assessment with other amphibole  
21 asbestos cancer risk assessments or reviews, including the earlier EPA assessment in 1986. This should  
22 be summarized more clearly and indicate whether other federal agencies or groups have conducted  
23 similar quantitative risk assessments.  
24

25 An overall summary set of tables or figures describing the major cohorts (Libby workers, community,  
26 Marysville plant), and the studies/exposure information associated with each would be helpful for the  
27 readers of the document.  
28

1 **3.2.4.4. Use of Laboratory Animal and Mechanistic Studies**

2 *Question 5. The database of laboratory animal and mechanistic studies of Libby Amphibole asbestos is*  
3 *summarized in this draft assessment (see Section 4.2 and 4.3, details in Appendix D) to inform the*  
4 *mechanisms of the biological response to Libby Amphibole asbestos and support the epidemiology*  
5 *studies used for derivation of the IUR. Please comment on the use of laboratory animal and mechanistic*  
6 *information in the draft assessment.*

7  
8 The SAB agreed, with some exceptions, that the database of laboratory animal and mechanistic  
9 studies pertaining to LAA is appropriately presented for support of the analysis of the human effects  
10 observed. These studies are informative in identifying similar mechanism and progression of  
11 pathological changes in animals as are seen in humans, and help in establishing that similar  
12 pathological endpoints are seen with other amphibole fibers. Although the mechanistic studies fall  
13 short of delineating a complete mechanism of action, they are useful in identifying some common  
14 themes and potential key mechanisms in asbestos toxicity and will undoubtedly be valuable in  
15 guiding future research on this topic.

16  
17 It is now widely accepted that the toxicity and carcinogenicity of mineral and synthetic vitreous  
18 fibers is governed by fiber dimensions, *in vivo* durability, and dose, and that all long amphibole  
19 fibers are very durable *in vivo*. Thus, the differences in biological potency among the various  
20 amphibole fiber types are due primarily to their differences in dimensions, especially in their fiber  
21 length distributions. The SAB noted that the text in Sections 4.2 and 4.3, and the tables cited therein,  
22 are deficient in not citing all that is known about the dimensions of the administered fibers.

23  
24 **Recommendations:**

- 25
- 26 • Section 4.2 should start with a discussion of the relevance of routes of exposure, and then  
27 should proceed to discuss inhalation data, followed by a discussion of data from other, less  
28 relevant routes of exposure.
  - 29
  - 30 • Areas of needed improvement in the report include: (1) a discussion on known determinants  
31 of fiber toxicity; and (2) the differences in fiber size distributions between LAA and other  
32 known amphiboles.
  - 33
  - 34 • Section 4.6.2.2 should be modified to reflect that there are insufficient data to determine if a  
35 mutagenic mode of action for LAA is supported.
  - 36

1 **3.2.5. Inhalation Reference Concentration (RfC)**

2 **3.2.5.1. Estimates of Human Exposure Concentration**

3 *Question 1. Exposures to Libby Amphibole asbestos for workers in the Marysville, OH facility were*  
4 *reconstructed based on industrial hygiene data collected in the facility from 1972 to 1994. Exposures*  
5 *from 1957 to 1971 were estimated based on extrapolation from the available industrial hygiene data.*  
6 *The information used for the exposure reconstruction was based on employee interviews, court and*  
7 *company records, and the expert judgment of the researchers. Is the methodology used for the exposure*  
8 *reconstruction reported in Appendix F and the subsequent development of exposure estimates used in*  
9 *the analyses scientifically supported and clearly described?*

10  
11 The approach described in the Appendix F of the EPA document is detailed and specific. The strengths  
12 and weaknesses of the approach are clearly laid out. Large uncertainties are associated with the  
13 *unmeasured* pre-1972 exposures: subjectivity of workers' estimating relative concentrations, and  
14 unsupported weighting of Libby/South Carolina fiber concentrations. Hence the report appropriately  
15 eliminates this set of estimates and adheres to only measured exposures for its derivation of RfC.

16  
17 The development of cumulative exposure estimates for the workers in a retrospective study has as its  
18 goal the estimation of the area under the curve of the plot of each individual worker's annual exposure  
19 concentration vs. time (calendar year), producing a summary metric of cumulative fibers/cc-years. In  
20 Appendix F of the EPA document, the authors report using the natural-log-transformed exposure data to  
21 calculate the geometric mean for the job groups for use in developing the cumulative exposure metric.  
22 This approach could introduce bias by decreasing the significance of the highest exposures if the  
23 sampling data represent a random sample of the true underlying distribution of exposures. However,  
24 most company industrial hygienists historically have focused sampling on evaluating compliance using a  
25 methodology that targets the worst case or "most exposed" workers (NIOSH, 1977; Mulhausen and  
26 Damiano, 1998). In such a case, use of the mean of the unlogged data, or preferably the minimum  
27 variance unbiased estimator (MVUE) of the mean (Attfield and Hewett, 1992), would overestimate the  
28 most likely exposure of the average worker. The EPA should re-evaluate the raw exposure data and  
29 review pertinent sampling documentation to bolster its use of the geometric mean to represent the job  
30 group exposures, rather than an estimate of the arithmetic mean, and consider whether a sensitivity  
31 analysis using the MVUE of the mean is warranted in the development of the cumulative exposure  
32 metric.

33  
34 There should be a table summarizing the changes in proportion of each type of vermiculite used (South  
35 Carolina, Libby and African) at the Marysville plant throughout the time frame represented by the  
36 cohort. This section should explicitly discuss the fact that Libby vermiculite usage ended in 1980, and  
37 that the fiber counts used in the cumulative exposure calculation for the production workers, though  
38 small, are generally 1.5 to 6.3 times higher than background. These fibers are presumably from  
39 combinations of African/Virginia/South Carolina vermiculite that were used from 1980 to 2000.  
40 Likewise, the description of the calculation of the cumulative human equivalent exposure concentration  
41 (CHEEC) in Section 5.2.3.1 would benefit by addition of a version of the material on page F-19 to  
42 clarify the correction factors and breathing rate adjustments made due to extended work hours during  
43 some seasons. The approach used has the typical drawbacks of oversimplification of breathing rate (one  
44 size fits all) but is consistent with previous EPA approaches.

1 The SAB recommends that the EPA consider sensitivity analyses of additional exposure metrics such as:  
2 no exposure since 1980 in any cohort members [based on end date of processing of Libby vermiculite),  
3 and alternative weighting schemes (particularly ones weighting earlier life exposures more heavily given  
4 the importance of time since first exposure, e.g., residence time weighting (RTW)]. These sections also  
5 could be enhanced by showing relationships between the exposure metrics, such as by scatterplots of  
6 unlagged CHEEC vs. other measures (separately by cohort) and by adding more explanation about the  
7 effects of lagging.

### 8 **3.2.5.2. Exposure-Response Modeling**

9 *Question 2. Exposure-response modeling was conducted using the incidence of localized pleural*  
10 *thickening in workers and cumulative exposure to estimate the point of departure (POD) for derivation*  
11 *of the RfC. EPA's estimate of the POD is based upon a Michaelis-Menten model applied to the*  
12 *subcohort of workers examined in 2002-2005 and first exposed to Libby Amphibole asbestos in 1972*  
13 *(when measurements of fiber levels in the workplace began) or later with cumulative exposure as the*  
14 *explanatory variable. Is the selection of the model scientifically justified and clearly described? Has the*  
15 *modeling and the choice of a benchmark response (BMR) for the POD of 10% extra risk of localized*  
16 *pleural thickening been clearly described and appropriately conducted according to EPA's Draft*  
17 *Benchmark Dose Technical Guidance (U.S. EPA, 2000b)?*  
18

19 This response focuses on the primary analysis of the Marysville subcohort. Additional comments on the  
20 analysis of this cohort can be found in response to Question 4 in Section 3.2.5.4. The SAB found that the  
21 various exposure-response models that were examined were reasonably well described. However, the  
22 SAB recommends a clearer description of how the "best" model was chosen. It appears that EPA fits a  
23 series of quantal response models, retained models with adequate fit according to the Hosmer-  
24 Lemeshow test (presumably based on  $p > 0.1$ , but, if so this should be stated). Then, among the retained  
25 models, the authors selected the model with the lowest Akaike Information Criteria (AIC). From a  
26 statistical standpoint, this methodology is scientifically justified. However, it is not clear if it actually  
27 follows the decision tree for selection of the POD in the EPA's *Benchmark Dose Technical Guidance*  
28 (USEPA, 2012); the decision tree states that the POD from the model with the smallest AIC should be  
29 selected if, among models that adequately fit the data, the lower 95% confidence limit of the benchmark  
30 doses (BMDLs) all are sufficiently close given the needs of the assessment. The lower 95% confidence  
31 limit of the benchmark concentrations (BMCLs) from the candidate models differ by more than a factor  
32 of three. If the EPA can defend this range as being "sufficiently close," then their choice of the POD is  
33 in line with the technical guidance; if not, then according to the decision tree, the most conservative  
34 (smallest) BMCL should be used as the POD which comes from the log-probit model with lag 15  
35 exposure. Thus the authors need a clearer description of why the Michaelis-Menten model was chosen  
36 as the "best" model.  
37

38 The SAB recommends that a thoughtful approach to model selection be used, including consideration of  
39 biological/epidemiological plausibility, combined with careful examination of the data and application  
40 of the AIC. For example, model fit (visual comparison of model predictions to data and/or local  
41 smoother estimates from data) in the region of the benchmark response rate (BMR) should play an  
42 important role in model selection. Likewise, the fitted Michaelis-Menten model has an upper plateau of  
43 60% LPT incidence, while a study of highly exposed asbestos insulation workers reported a prevalence  
44 of 85% (Lilis et al., 1991a). The Marysville cohort does not support precise estimation of the plateau.  
45 Thus, EPA should consider fixing the plateau at a level justified by the literature.  
46

1 The SAB recommends that model features should also be considered in choosing a model. For example,  
2 the dichotomous Hill model is attractive because it allows estimation of an exposure slope parameter,  
3 allowing the exposure effect to scale as covariates are added, the exposure metric changed, or the  
4 plateau fixed. The SAB also recommends examining other exposure metrics besides the simple  
5 cumulative exposure, such as time weighting of exposures. The SAB suggests a thoughtful approach  
6 may lead to selecting the dichotomous Hill model with the plateau fixed at a literature-based value.  
7

8 The authors explain that their choice of a 10% Extra Risk (ER) as the BMR is in line with the EPA's  
9 *Benchmark Dose Technical Guidance*. However, that rate is generally considered to apply specifically to  
10 the analysis of quantal datasets from animal studies (which is the context in which it was developed). In  
11 the EPA's *Benchmark Dose Technical Guidance*, it is mentioned that a BMR of 1% ER is typically used  
12 for human quantal response data as epidemiologic data that often have greater sensitivities than bioassay  
13 data. The authors should explain what features of the dataset or outcome variable led them to choose a  
14 BMR that is considerably greater than the norm for epidemiologic data.  
15

#### 16 **Recommendations:**

- 18 • Consider model features and balance plausibility, localized fit, and EPA technical guidance when  
19 choosing the best model and explain decisions in more detail. The SAB suggests a thoughtful  
20 approach may lead to selecting the dichotomous Hill model with the plateau fixed at a literature-  
21 based value.
- 22 • Evaluate the impact of different time weightings of the exposure metric.
- 23 • Either lower the BMR to be more consistent with common practice for epidemiological data or  
24 provide more justification for the 10% BMR used to calculate the POD.

#### 25 **3.2.5.3. Alternative Modeling Approaches**

26 *Question 3. EPA's assessment also provides the results of alternative modeling approaches to derive a*  
27 *POD for localized pleural thickening. This modeling used the full Marysville worker data set with*  
28 *exposures from 1957 and later and a Cumulative Normal Michaelis-Menten model that incorporates*  
29 *both cumulative exposure and time from first exposure as explanatory variables. Please comment on*  
30 *whether EPA's rationale for presenting these alternative approaches is scientifically justified and*  
31 *clearly described. Please identify and provide the rationale if a different approach for identifying the*  
32 *most appropriate population within the cohort of Marysville workers is recommended as the basis for*  
33 *estimating a POD.*  
34

35 The SAB notes that this question applies to the full Marysville cohort. The SAB agrees that the rationale  
36 for performing additional analyses of the full Marysville cohort is scientifically justified, and that the  
37 analysis of the entire cohort increases the number of cases of LPT available for analysis and  
38 substantiates the RfC estimated using the subcohort. However, the SAB did not find the rationale for the  
39 analysis methods to be well justified. First, it was not clear about the scientific basis of using time since  
40 first exposure (TSFE) as a covariate. In particular, what is TSFE supposed to be measuring? Is it  
41 intended to be another measure of exposure? There is some suggestion in the draft document that it is a  
42 surrogate measure of intensity since people with larger TSFEs would be more likely to have been  
43 exposed to higher levels of LAA present during the early time periods. If TSFE is a surrogate of  
44 intensity, why did the EPA choose to use it rather than date of first exposure?  
45

1 The SAB also finds that the method for incorporating TSFE into the full cohort analysis is not well  
2 justified, and recommends that the analysis be revised. Currently, the EPA uses TSFE as a predictor for  
3 the plateau in the Cumulative Normal Michaelis-Menten model. The plateau provides the maximum  
4 proportion of the population that would experience LPT given sufficient exposure and time to develop  
5 the disease. No biological justification is given for why this maximum proportion would vary with  
6 TSFE. The SAB believes that in this dataset a more natural way to incorporate TSFE into the model  
7 would be to allow it to affect the rate of change in the probability of LPT; by including it directly in the  
8 linear predictor portion of the model alongside cumulative exposure; and/or by using an alternative  
9 exposure metric such as residence time weighting (RTW) that more heavily weights exposure in the  
10 distant past. The functional form of TSFE could then be selected using standard approaches (e.g.,  
11 comparing AICs). Since adding TSFE to the model should affect the coefficient of cumulative exposure,  
12 the EPA should consider a dichotomous Hill model which allows the slope to be estimated, as an  
13 alternative to the Michaelis-Menten model. Finally, the SAB recommends following the approaches for  
14 the subcohort analysis, such as fixing the plateau using literature values as recommended in the response  
15 to charge question 2 in Section 3.2.5.2 of this report.

16  
17 The SAB notes that it may be preferable to base the RfC on an analysis of incidence rather than  
18 prevalence data. Because of the nature of the dataset, the Marysville cohort does not support a direct  
19 analysis of incidence. While it may be possible to fit an alternative model derived from integration of a  
20 plausible incidence model (e.g., see Berry et al., 1979; Berry and Lewinsohn, 1979; Paris et al., 2008),  
21 this approach will require a number of untestable assumptions, particularly given the small size of the  
22 Marysville cohort. In lieu of conducting such an analysis, the SAB recommends that an explicit  
23 acknowledgement be added to the report regarding the implications of various model alternatives.

24  
25 ***Recommendations:***

- 26
- 27 • Improve the scientific justification for using TSFE in the full cohort analysis which includes a  
28 clear explanation of its meaning.
  - 29 • Revise the full cohort analysis with assessments to determine whether it is appropriate to use (a)  
30 the dichotomous Hill model, (b) TSFE in the linear predictor alongside cumulative exposure  
31 and/or use an alternative exposure metric that explicitly incorporates TSFE, and (c) the  
32 approaches recommended for the subcohort such as a fixed plateau. As appropriate, such  
33 analyses should include assessment of the functional form of TSFE.
  - 34 • The SAB encourages EPA to present BMCL estimates from a set of reasonable and plausible  
35 models, and selections of data, which will both inform selection of a preferred model and  
36 illustrate the range of model uncertainty.
- 37

1 **3.2.5.4. Potential Confounders and Covariates**

2 *Question 4. EPA has evaluated potential confounders and covariates where data are available.*  
3 *Specifically, EPA has explored the influence of age, body mass index, smoking status, time since first*  
4 *exposure, gender, and alternative exposure metrics on model fit and evaluated their association with the*  
5 *modeled health outcomes (see Section 5.3). Are these analyses clearly described and appropriately*  
6 *conducted? Are the results of these analyses appropriately considered in the RfC derivation?*  
7 *Additionally, there is a possibility of exposure-dependent censoring in participant selection for the*  
8 *update of the Marysville cohort (Rohs et al., 2008) but no evidence of selection bias. Does the SAB have*  
9 *any specific recommendations for evaluating and, if appropriate, quantitatively addressing exposure-*  
10 *dependent censoring in these analyses?*

11  
12 The SAB recommends a revised strategy for evaluation of covariates. The target of inference for the  
13 analyses of the Marysville cohort is the POD (BMCL). The evaluation of the various covariates should  
14 be made with respect to this target of inference. The SAB suggests the covariates fall into two classes:  
15 *exposure-related covariates* (various exposure metrics and TSFE) and *non-exposure-related covariates*  
16 (age, body mass index (BMI), gender, and smoking status). We provide recommended revised strategies  
17 for considering these two classes of covariates that follow directly from consideration of the target of  
18 inference.

19  
20 Non-exposure-related covariates: A decision on whether to control for the non-exposure-related  
21 covariates should account for how the EPA wishes to determine and apply the RfC. The SAB suggests a  
22 BMCL most directly applicable to all members of the general population is most appropriate. This  
23 implies that the BMCL should be estimated from a model that includes exposure covariate(s), but that is  
24 otherwise unadjusted. This is the same approach used in the current draft document; only the rationale  
25 for the approach is different. As sensitivity analyses, the SAB believes it would be informative to  
26 examine how the BMCL varies across subgroups defined by covariate values (e.g., older males or  
27 smokers). Because the Marysville subcohort is a small dataset, it is difficult to conduct this evaluation  
28 exclusively in the subcohort. Therefore the SAB suggests the EPA use the *full* cohort for the model  
29 selection and parameter estimation components of sensitivity analyses incorporating these covariates.  
30 For this activity the EPA would use their selected final model after excluding all exposure variables  
31 (e.g., the dichotomous Hill model with fixed background, fixed plateau, and after dropping exposure  
32 variables). After fitting a model with a specific set of non-exposure-related covariates in the full cohort,  
33 one can estimate a “risk score” (i.e., the linear predictor for the non-exposure-related covariates). This  
34 risk score would be included as a single term (as either an unscaled offset or scaled by its estimated  
35 coefficient) in the subcohort analysis. Similar to the approach presented in Table E-5, these analyses  
36 can be used to produce a new table of subgroup-specific conditional BMCLs; these values will give  
37 some evidence of how the target of inference varies by subgroup. In addition, weighted averages of the  
38 conditional BMCLs can be computed to reflect population average BMCLs for specific covariate  
39 distributions in target populations. For instance, Gaylor et al. (1998) gives a formula for the upper tail of  
40 a 95% confidence interval, this formula can be extended to obtain BMCLs for weighted averages.

41  
42 Exposure-related covariates: The inclusion of exposure-related covariates in the model is fundamental to  
43 the inference. The EPA has done excellent preliminary work, and the SAB has provided  
44 recommendations in Sections 3.2.5.2 and 3.2.5.3 of this report about how to revise the approach. In  
45 addition the SAB recommends that the EPA consider taking several further steps. First, alternative  
46 exposure metrics should be assessed directly in the subcohort dataset to determine whether they fit the  
47 data better. In particular, alternative metrics (such as residence time weighted exposure) that more

1 heavily weight more distant exposure may be more biologically plausible because individuals exposed at  
2 an earlier age might be more susceptible to the damaging effects of asbestos. Second, TSFE should be  
3 considered for addition to the model. Since TSFE is complete and equally well estimated across all  
4 members of the cohort, the full cohort can be used to determine how to model this variable (similar to  
5 the approach recommended for the sensitivity analyses discussed above, this would be done using the  
6 model intended for the subcohort, but omitting exposure variables other than TSFE). Then, the  
7 functional form of TSFE selected using the full cohort can be added to the subcohort analysis, either as  
8 an unscaled offset term or as a scaled covariate. Given biological understanding of the disease process,  
9 for models with both estimated exposure and TSFE included, it would be appropriate to report the  
10 BMCL conditional on a large TSFE.

11 Additional comments on covariates:

- 12
- 13 • BMI: In section 5.2.3.3.1., it would be helpful if the justification for considering BMI as a
- 14 covariate were briefly explained. It is included elsewhere, but readers may have missed it.
- 15 • TSFE:
  - 16 ○ TSFE deserves careful consideration for both biological and dataset-specific reasons. It is
  - 17 an important determinant of LPT both because individuals' lung tissues exposed at an
  - 18 earlier age might be more susceptible to the damaging effects of asbestos and because
  - 19 asbestos' effect over time is increasingly damaging. It is correlated with exposure in this
  - 20 dataset since subjects with the longest TSFE were exposed in the early years of the cohort
  - 21 when exposures were higher. It is also more accurately estimated than exposure.
  - 22 ○ The SAB does not agree with the use of the Cumulative Normal Michaelis–Menten
  - 23 model to adjust for TSFE because it makes the assumption that the TSFE only affects the
  - 24 plateau. This has not been justified biologically or in the context of features of this
  - 25 particular dataset. Instead, the SAB recommends that EPA consider alternative
  - 26 approaches to account for TSFE.
- 27 • Smoking:
  - 28 ○ Smoking is included in the follow-up by Rohs et al. (2008). However, the ever/never
  - 29 categorization of smoking is much less informative than the pack-year analysis of
  - 30 smoking used in the earlier study by Lockett et al. (1984).
  - 31 ○ There is an important discussion of the evidence linking pleural changes and smoking in
  - 32 footnote 34 on page 5-46. This information could be moved into the body of the report,
  - 33 and amplified somewhat. A table summarizing the relevant studies (irrespective of type
  - 34 of amphibole asbestos) summarizing the evidence regarding the role of smoking would
  - 35 be useful.
- 36 • Gender: There is little discussion of gender, except in places where the number of females is
- 37 listed as too few to analyze in any detail. The SAB did not regard this as a serious concern
- 38 because it is reasonable to assume that females and males have similar probabilities of
- 39 developing LPT.

40

41 The SAB recommends that a table be included summarizing the results of the various sensitivity

42 analyses and how they change the POD.

43

44 Exposure-dependent censoring: The exposure-dependent censoring discussion is based on results

45 from Rohs et al. (2008) that inappropriately separated deceased non-participants from the remaining

1 non-participants. Once all non-participants are combined there is no evidence of exposure-dependent  
2 censoring.

3  
4 **Recommendations:**

- 5  
6
- Revise consideration of covariates to focus on their impact on the target of inference.
    - For non-exposure-related covariates, this only alters the presentation; no additional primary  
7 analyses are needed. Sensitivity analyses conditional on subgroups defined by covariates can be  
8 added.
    - For exposure-related covariates, additional work is needed to refine the models to consider  
9 alternative exposure metrics, as well as the inclusion of TSFE or other time-related variables in  
10 analyses of the full cohort. The SAB encourages the EPA to either fully justify analyses based on  
11 the Cumulative Normal Michaelis-Menten model in the context of this particular dataset, or  
12 replace them.
  - Remove the discussion of exposure-dependent censoring and revise the summary of Rohs et al.  
13 (2008) to combine all non-participants into a single group.  
14  
15  
16

17 **3.2.5.5. Conversion from Cumulative Occupational Exposure to Lifetime Exposure**

18 *Question 5. The modeled POD estimate is based on cumulative exposure estimates for the worker cohort*  
19 *examined. For the derivation of the RfC, this cumulative exposure is prorated over the period of*  
20 *environmental exposure (lifetime or shorter duration chronic exposure when appropriate). The RfC is*  
21 *provided in units of continuous air concentration. Is the basis of this conversion clearly explained and*  
22 *scientifically justified?*  
23

24 The SAB agrees that the conversion is clearly explained and follows standard practice. However, the  
25 SAB recommends a revision to use the full 70-year lifetime in the conversion rather than 60 (70 minus  
26 the lag of 10 used for exposure in the POD derivation). Given that the exposure metric is arbitrarily  
27 related to the prevalence data, lagging does not have real meaning in the context of time to event and  
28 using a divisor of 60 instead of 70 in deriving the RfC is less protective.  
29

30 **Recommendation:**

- 31
- Use the full 70-year lifetime when converting cumulative to continuous exposure; i.e., do not  
32 correct for the lag of 10 for a 10-year lagged exposure.  
33
- 34  
35

### 3.2.5.6. Selection of Uncertainty Factors

*Question 6. Please comment on the rationale for the selection of the uncertainty factors (UFs) applied to the POD for the derivation of the RfC. Are the UFs appropriate based on A Review of the Reference Dose and Reference Concentration Processes (U.S. EPA, 2002; Section 4.4.5) and clearly described? If changes to the selected UFs are proposed, please identify and provide scientific support. Specifically, please comment on the rationale for the selection of the database uncertainty factor (UF<sub>D</sub>) of 10 applied in the derivation of the RfC. The database uncertainty factor accounts for the lack of data on effects other than in the respiratory system, including other effects observed in community and laboratory animal studies (cardiovascular disease and autoimmune effects) that have not been well-studied (See Section 5.2.3 of the Toxicological Review); and lack of health data assessed at later time points. Is the rationale for the UF<sub>D</sub> appropriate and clearly described? Please provide the rationale if a change in the UF<sub>D</sub> is proposed.*

Uncertainty factors were selected in accordance with the usual procedures laid out in EPA risk assessment guidelines. A value of 10 was selected for UF<sub>H</sub> (human inter-individual variability) and UF<sub>D</sub> (database uncertainty), with a value of 1 for all others.

Use of a UF<sub>H</sub> of at least 10 is standard in considering health protective levels based on effects in the workforce, which is generally healthier and less diverse than the general population. In fact, arguments have been made that a factor of 10 is not sufficient to cover all sensitive sub-populations, especially children. Some treatment of the question of inter-individual variability is offered in the later summary of conclusions (Section 6 of the EPA document). There is no specific evidence on the relative sensitivity of children to the non-cancer effects of Libby asbestos, although some indications with other amphiboles suggest the possibility of enhanced effects following exposure at younger ages. Overall, it seems unlikely that a departure from the default guideline value of UF<sub>H</sub> = 10 could be justified within the existing guidelines, but concerns remain for the impact on susceptible subpopulations, especially women and children.

Selection of a UF<sub>D</sub> of 10 is explained and justified based on the limited number of studies of exposure to Libby asbestos (Libby workers, ATSDR community study and Marysville workers) and the lack of evaluation of potentially more sensitive alternative endpoints. This seems reasonable and consistent with the guidelines. In particular, this uncertainty factor would not be reduced even if improved exposure estimates allowed consideration of the full cohorts (or a larger fraction thereof). However, some additional data have recently been published for the community surrounding a Minnesota expansion plant (Adgate et al., 2011; Alexander et al., 2012).

Although there appears to be a rationale for at least an initial consideration of LAA as a unique material (to provide an unbiased comparison with other amphiboles), the current review has identified very substantial grounds for considering this material as having composition, physical properties, and biological effects that are very similar to those seen for other amphiboles. The most relevant comparison would be to tremolite, since Libby Amphibole is ~6% tremolite, an amphibole that is known to cause cancer and non-cancer effects in human populations. However, it is uncertain how other components of Libby Amphibole (richerite and winchite) interact as a mixture with tremolite to modify toxicity. This consideration of data on other amphiboles is particularly pertinent to discussions of the mode of action, as well as the exposure-response relationships, for Libby Amphibole. In light of this similarity it appears reasonable, and indeed necessary, to at least debate the question of whether the available data on non-cancer health effects of amphiboles are sufficient to mitigate the acknowledged data shortage for Libby

1 Amphibole itself. This consideration of additional data (e.g., the Minnesota cohort and data on other  
2 amphiboles) might support a lower value, such as 3, for  $UF_D$ . On the other hand, there are substantial  
3 remaining uncertainties that are not addressed by these additional data, including those raised by  
4 consideration of the severity of the endpoint and the selection of the BMR (see below). It can also be  
5 argued that a subchronic-to-chronic uncertainty factor ( $UF_S$ ) higher than 1 should be used, given that the  
6 mean and maximum exposure duration in this study are both well below the lifetime exposure of  
7 interest. Thus, the eventual selection of a value of 10 for  $UF_D$ , or similar uncertainty spread across  
8 several factors, may well be appropriate, but this needs to be evaluated explicitly once all the additional  
9 information has been incorporated in the discussion.

10  
11 There is a concern that the BMR of 10%, which was chosen for a severe endpoint, is not reflected by the  
12 choice of a LOAEL-to-NOAEL uncertainty factor ( $UF_L$ ) of 1. It is appropriate to consider either a lower  
13 BMR, or the application of a larger  $UF_L$  for this endpoint. An argument could be made that some  
14 allowance has been made for this concern in the choice of the  $UF_D$ , but it is debatable whether this is  
15 sufficient, given the other matters to which that UF is also assigned. At the very least, this question  
16 deserves more consideration and analysis that it receives in the draft assessment report.

#### 17 **Recommendations:**

- 19 • Review additional data in particular the exposure-response relationship for non-cancer endpoints  
20 in the Minneapolis community cohort.
- 21 • Determine whether this new analysis is supportive of the existing analysis based on the  
22 Marysville data, and if so whether this warrants reduction of the value of  $UF_D$  since the limited  
23 data basis for the original analysis has been expanded.
- 24 • Reassess the selection of the BMR, to reflect the severity of the chosen endpoint in the  
25 Marysville cohort and the precision available in the data. Whether or not the chosen BMR is  
26 changed, present this analysis in the document rather than simply asserting that a “default” value  
27 for the BMR was chosen. Similar consideration should be applied to the Minneapolis cohort to  
28 provide a valid comparison. This consideration needs to be linked to discussion of the selection  
29 of a value for  $UF_L$  as noted below.
- 30 • Review additional sources of uncertainty:
  - 31 ○ timescale of cohort coverage, normally addressed by  $UF_S$  if this is a significant concern  
32 rather than including this as a component of  $UF_D$  which already has several major issues to  
33 account for.
  - 34 ○ additional uncertainty resulting from target population diversity (including women and  
35 children, specific sub-populations of concern not represented in the cohort), and endpoint  
36 severity.
- 37 • Consider adjusting  $UF_D$ ,  $UF_S$  or  $UF_L$  if necessary to accurately reflect the overall uncertainties in  
38 these categories: provide specific justification for the choices made rather than claiming  
39 unsupported use of default values.

#### 40 **3.2.5.7. Characterization of Uncertainties**

41 *Question 7. Please comment on whether the document adequately describes the uncertainties and*  
42 *limitations in the methodology used to derive the RfC and whether this information is presented in a*  
43 *transparent manner.*

1 In the report there are two sections on uncertainty for the RfC: an application of uncertainty factors  
2 following standard EPA practice (Section 5.2.4), and a discussion of the uncertainties in the overall  
3 methodology and approach (Section 5.3). This response focuses on the latter. Overall the SAB found the  
4 discussion to be thorough, detailed and logical. The document can be improved by harmonizing the full  
5 set of uncertainty discussions, including both the discussion of RfC uncertainty and the related  
6 discussion of the IUR uncertainty (see the SAB response to question 5 under Section 3.2.6.5 below). In  
7 addition, the RfC uncertainty assessment can be strengthened. A key consideration of any assessment is  
8 whether the estimated RfC is adequately protective of public health. The SAB recommends that  
9 additional work be done to substantiate the RfC estimate through additional sensitivity analyses and  
10 discussion of results and insights from other datasets [e.g., cause of death for the deceased non-  
11 participants in Rohs et al. (2008) and the Minneapolis exfoliation community cohort (Alexander et al.,  
12 2012)].

13  
14 In considering other studies, the appropriate assumption is that LAA fibers have the same mechanisms  
15 of toxicity and quantitative risk relations as that of other asbestos fibers. In sensitivity analyses, consider  
16 alternative exposure metrics (prioritizing residence time weighted metrics and excluding exposures after  
17 1980), methods to fine-tune the RfC estimate from the subcohort (particularly fixing rather than  
18 estimating the plateau, allow the slope parameter to be estimated, use a lifetime of 70 regardless of the  
19 exposure metric), and added sensitivity analyses in the full cohort using suggestions from the SAB.  
20 Finally, a new uncertainty topic should be added: the uncertainty in the RfC due to relying on a single  
21 study.

22  
23 With respect to exposure assessment, analytical methods and environmental conditions are substantial  
24 contributors to uncertainty because of differences between the 1970s and today. As discussed throughout  
25 the report, PCM was the only generally accepted method for measuring airborne fiber concentrations  
26 used until the 1980's. PCM's limitations are well-detailed in the report: an inability to detect fibers  
27 smaller than 0.25  $\mu\text{m}$ , an inability to differentiate asbestos fibers from other fibers, and a limitation to  
28 counting only fibers longer than 5  $\mu\text{m}$ . Today, TEM can easily detect and positively identify airborne  
29 asbestos of all sizes. But, because the RfC is based on 1970's PCM analyses, the RfC must be  
30 implemented in a way that most closely replicates analysis in the 1970's. At the 1970's study site, the  
31 vast majority of measured fibers were almost certainly LAA, so PCM's inability to identify asbestos did  
32 not create much uncertainty. Today, even ambient air will yield fiber concentrations that exceed the  
33 RfC. The culprit fibers will likely be cellulose fibers from cotton, wood, paper or synthetic fibers, rather  
34 than asbestos. Hence, today's PCM counts will be from fibers that are unrelated to the RfC. Thus it is  
35 important that TEM be used to identify and count asbestos fibers in air samples for RfC purposes.  
36 Finally, Page 5-118, Lines 22-33 of the EPA's draft discuss the two-fold under-reporting of fibers  
37 because of PCM's poorer resolution in the 1970's, 0.44  $\mu\text{m}$  versus 0.25  $\mu\text{m}$  today. Because today's  
38 PCM analysts have no capability for discriminating fibers  $> 0.44 \mu\text{m}$ , the need for TEM analysis of  
39 samples collected for RfC purposes is even more important. A TEM protocol for PCM equivalent fibers  
40 wider than 0.44  $\mu\text{m}$  could be easily developed.

#### 41 42 **Recommendations**

- 43
- 44 • Harmonize the uncertainty discussions across the document
- 45 • Add a new uncertainty topic: Uncertainty due to reliance on a single study
- 46 • Substantiate the RfC estimate through
- 47 ○ Additional sensitivity analyses of the subcohort

- 1           ○ Discussion of results from other studies
- 2           ○ Additional sensitivity analysis of the full cohort
- 3           ○ Summarize in tabular form the results of the various sensitivity analyses and model
- 4           alternatives, to show how they affect the POD
- 5       • Use TEM to identify and count asbestos fibers longer than 5, 10, and 20  $\mu\text{m}$  in air samples for
- 6       RfC purposes

### 7   **3.2.6. Inhalation Unit Risk (IUR)**

#### 8   **3.2.6.1. Exposure-Response Modeling**

9   *Question 1. Exposure-response modeling was conducted separately for lung cancer and mesothelioma*  
10 *mortality. The POD estimates for these endpoints are based upon analysis of the subcohort of workers*  
11 *first exposed after 1959 when the exposure data were judged to be better characterized. The exposure-*  
12 *response modeling included consideration of a variety of exposure metrics that varied with time and*  
13 *incorporated different lag and decay parameters. Based on the results of the exposure-response*  
14 *modeling, a life table analysis was used to determine the PODs for each type of cancer for the various*  
15 *exposure metrics. Have the exposure-response modeling and determination of the PODs from life table*  
16 *analysis been appropriately conducted and clearly described? If a different approach to exposure-*  
17 *response analysis is recommended as the basis for the estimating the IUR, please identify the*  
18 *recommended methods and provide a rationale for this choice.*

19  
20 In general, the EPA clearly described the methods it had selected to conduct the exposure-response  
21 modeling for lung cancer and mesothelioma. The risk calculations in the life tables appeared correct but  
22 would benefit from clearer explanations. Some suggestions for clarifications are noted below.

23  
24 The agency was overly constrained by reliance on model fit as the primary criterion for model selection  
25 and recommends a broader discussion of biological and epidemiological criteria as well. For the  
26 mesothelioma data, for example, the Peto model was disregarded due to a poorer fit than the Poisson  
27 model. The results for this analysis are not shown, and given the particular interest in this model, should  
28 have been. A parametric survival model (e.g., Weibull) could have also been used to obtain estimates of  
29 absolute risk. It would also be appropriate to compare the results of the final model against those from  
30 fitting a two-stage clonal expansion (TSCE) model. Use of the (TSCE) model would allow for a more  
31 direct evaluation of, and possibly justification for, age-dependency of the IUR. The Richardson (2008)  
32 paper provides a publicly available and transparent approach to application of the TSCE. Ultimately,  
33 there are many competing models that could have been used instead of the Poisson and Cox models  
34 (e.g., parametric survival models, accelerated failure time models, additive models) that could have  
35 provided very different estimates of risk, but they were not discussed.

36  
37 Data exists that suggests that the lifetime risk of developing the mesothelioma increases the earlier in  
38 life that exposure is first received. The Peto model (Peto, 1979; Peto et al., 1982) was developed to  
39 explain such observations in the empirical data. While the Peto model has been more widely used for  
40 risk assessment, most notably in the previous IRIS summary for asbestos, it has also only been formally  
41 fitted to data in a limited number of cohorts (HEI-AR, 1991). Ongoing analysis of incidence of  
42 mesothelioma appears to be consistent with the exposure-response relationship described in the Peto  
43 model. The draft report needs to do a more complete job of justifying why this and other epidemiologic  
44 evidence should be excluded as a basis for selection of a plausible model for predicting mesothelioma  
45 risk. Chapters 2 and 3, for example, consider toxicological and other evidence developed with exposures

1 to asbestos that are not strictly LAA. Did EPA have a reason to believe that the cohorts used in the  
2 development of the Nicholson/Peto model, and the exposures they experienced, were so  
3 unrepresentative of the LAA exposures that they should be assumed to provide no information about the  
4 time course of the development of disease?  
5

6 The SAB recognizes that the agency's effort to focus on good quality exposures specific to LAA has led  
7 to reliance solely on the Libby worker subcohort. This rationale is understandable, but at the same time,  
8 it is important to acknowledge that this small subcohort may have its own limitations as a basis for  
9 modeling exposure-response relationships for a larger population over a lifetime. As a sensitivity  
10 analysis to evaluate the potential impact of omitting the Libby workers hired before 1959, the SAB  
11 recommends analyzing the entire Libby cohort using interval statistics (Nguyen et al. 2012; Manski  
12 2003; *inter alia*) or other traditional approaches for data censoring in predictors (cf. Küchenhoff et al.,  
13 2007). It can be misleading to use midpoint substitution (as described in Section 5.4.6.1.2) that assumes  
14 poorly measured or missing predictors have some constant value. Interval statistics and traditional  
15 censoring approaches to measurement uncertainty would, in essence, replace point values with interval  
16 ranges. When the intervals are narrow, as they might be for 21% of the early hires for which jobs titles  
17 are available, there might be a good deal of recoverable information present. When the intervals are  
18 much wider, there would be accordingly less information. Whatever empirical information may be  
19 present, it is worth evaluating whether its inclusion is better than leaving out the data entirely, which in  
20 principle amounts to replacing them with intervals that are completely vacuous, from zero to infinity.  
21 This approach can produce an interval range for the final outputs, which would provide the explicit  
22 quantitative uncertainty statement as recommended by previous National Academy of Science reviews.  
23

24 The SAB recognizes that the agency did conduct sensitivity analyses with several analyses of the Libby  
25 cohort data, including those that used different models (Tables 5-20 for lung cancer and 5-21 for  
26 mesothelioma). A limitation of these analyses is that they all rely on the assumption that the effect of  
27 exposure can be modeled as a function of cumulative dose. This assumption is consistent with the  
28 agency's *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005), which states that "unless there is  
29 evidence to the contrary in a particular case, the cumulative dose received over a lifetime, expressed as  
30 an average daily exposure prorated over a lifetime, is recommended as appropriate measure of exposure  
31 to a carcinogen." EPA therefore did not address the fundamental question about whether any one model  
32 can or should be assumed to represent the exposure-response relationship for LAA. Therefore, one  
33 cannot be confident that the "true" exposure-response relationship for LAA is really "accounted for" by  
34 use of the upper confidence limit (UCL) on the slope (per fiber/cc) or, ultimately, the combined IUR  
35 from mesothelioma and lung-cancer mortality (see related discussion in response to question 3 and 5 in  
36 Section 3.2.5).  
37

38 This issue is of particular concern for the estimation of mesothelioma risks from partial lifetime  
39 exposures, where risk is essentially assumed to be independent of when in the course of a lifetime  
40 exposure occurs. For example, one year of exposure to a given concentration in childhood yields the  
41 same lifetime average daily dose as one year of the same exposure in adulthood. This assumption is not  
42 consistent with the relevant body of evidence on the development of asbestos-related disease. Therefore,  
43 there is some probability — not well characterized — that this approach underestimates the relative  
44 effect of early exposure, but exaggerates the effect of exposure later in life.  
45

46 ***Recommendations:***  
47

- 1 • Expand the discussion of model selection to explain the reliance on model fit criteria for model  
2 selection. In particular, why should the broader epidemiologic evidence on the time course of  
3 disease not argue at least for the presentation of more than one statistical model?
- 4 • Provide in an appendix the details of the Nicholson/Peto model fit for which the text currently  
5 states “data not shown.”
- 6 • In a tabular form, summarize the fit results, POD estimates, and IUR estimates from the full  
7 range of models considered in order to show the dependence of the IUR estimate on model  
8 selection.
- 9 • Present the fit to data graphically for both the main models and for a broader range of models.  
10 This step would provide a more thorough and transparent view of fit, particularly in the region of  
11 the BMR, than is allowed by examining summary statistical values alone.
- 12 • Allow evaluation of the time dependence of disease by providing tabulations of mesothelioma  
13 mortality rates and lung cancer SMRs by time since first exposure, duration of exposure and  
14 period of first exposure (for both the full and sub-cohorts of Libby workers).
- 15 • Consider developing an ancillary analysis of the full Libby data set, including hires before 1959,  
16 using interval statistics or other traditional censoring methods (not simple midpoint substitution).
- 17 • Consider adding a discussion of assumptions made in the calculation of the final IUR.

18  
19 **Clarifications requested:**

- 20  
21 • Poisson regression analyses: the mathematical form of the regression function should be given,  
22 and discussion of whether the potential for over-dispersion was assessed.
- 23 • Cox proportional hazards modeling: the reasons should be given for not conducting a Bayesian  
24 analysis as was done for the Poisson regression model for mesothelioma.
- 25 • Life-table analysis: the method used to estimate the hazard function for the exposed population  
26 should be clearly spelled out in the text. Was it based on a nonparametric estimate of the baseline  
27 hazard from the sub-cohort? Given that the SEER data were used to calculate the background  
28 incidence of lung cancer, it would seem more appropriate to use those data to estimate the  
29 baseline hazard and then to use the regression coefficient obtained from the Cox model applied  
30 to the sub-cohort data to obtain the hazard of the exposed group. Thus, the reasons for not using  
31 the SEER data to estimate the baseline hazard should be explained.

32 **3.2.6.2. Potential Confounding by Smoking**

33 *Question 2. Smoking is a strong independent risk factor for lung cancer and may be an important*  
34 *confounder of the lung cancer mortality analysis. Data on individual smoking habits and history were*  
35 *largely missing and could not be used to control for potential confounding in regression analyses.*  
36 *However, EPA used three approaches to evaluate the confounding issue, including restriction of the*  
37 *cohort and two analytic evaluations of the potential for confounding by smoking (see Section 5.4.3.6.5).*  
38 *Please comment on whether the methods and analyses are clearly presented and scientifically justified.*  
39 *If additional analyses are recommended, please identify the methods and scientific rationale.*

40  
41 The SAB recognizes the challenges in controlling for smoking given the lack of data on smoking  
42 histories for the cohort. The agency has taken reasonable steps to identify the potential for confounding  
43 using independent approaches. However, statements in the document (on p. 5-96 and again on p. 5-127)  
44 that— because the proportional hazards assumption is satisfied in the subcohort— there is no evidence of  
45 confounding by smoking, are too strong. Reaching this conclusion requires some strong assumptions,

1 including one that the decline in smoking prevalence observed in the general U.S. population also  
2 occurred in the Libby cohort.

3  
4 The agency's use of the Richardson (2010) method for exploring possible confounding for smoking was  
5 appropriate. However, the conclusion that there is no evidence for confounding by smoking relies more  
6 heavily on the  $p$ -values, which are marginally non-significant, than it needs to. More compelling is the  
7 observation of a negative association with COPD. However, the fact that the coefficients for exposure in  
8 the COPD Cox models were negative is strong evidence against positive confounding; smoking is  
9 positively related to COPD risk and thus if positive confounding is occurring, then one would also  
10 expect the relationship between asbestos exposure and COPD risk to be positive. It is possible, however,  
11 that negative confounding is occurring in which case the risk of lung cancer associated with asbestos  
12 exposure would be understated.

13  
14 ***Recommendations:***

- 15  
16
- The numbers of COPD deaths ( $n$ ) in the sub-cohort that were the basis for the analysis should be presented in the text.
  - The statements about the evidence against confounding by smoking given by restriction of the cohort should be qualified by the assumptions required to justify them, or deleted.
  - The SAB had no recommendations for further analyses.
  - The reference to three methods is confusing. There are actually only two, the restricted cohort and the Richardson analysis for which two exposure metrics are explored.
- 17  
18  
19  
20  
21  
22  
23

1 **3.2.6.3. Quantification of Inhalation Unit Risk**

2 *Question 3. In order to derive an IUR which represents the combined risk of mortality from lung cancer*  
3 *or mesothelioma, a cancer-specific unit risk for each tumor type was calculated according to the*  
4 *Guidelines for Carcinogen Risk Assessment (U.S., EPA, 2005; Sections 3.2 and 3.3) by linear*  
5 *extrapolation from the corresponding POD (i.e., the lower 95% confidence limit on the exposure*  
6 *associated with 1% extra risk of lung cancer or 1% absolute risk of mesothelioma mortality). The IUR*  
7 *was then determined as a combined upper bound risk estimate for mortality considering both cancers.*  
8 *Has this approach been appropriately conducted and clearly described?*  
9

10 The SAB found the description of the procedure used to be clear but considered the justification for the  
11 independence assumption to be lacking in depth. The EPA should provide a discussion of the potential  
12 consequences of assuming that the estimated IURs for mesothelioma and lung cancer mortality are  
13 independent, noting the possibility that the upper bound on the IUR may be understated if the risks are  
14 positively correlated. The document may refer to the 1994 NRC report, which suggested that treating  
15 different tumor occurrences as independent is "not likely to introduce substantial error in assessing  
16 carcinogenic potency". However, the document should acknowledge that this statement was made in the  
17 context of animal bioassays and that human populations are more heterogeneous in risk factors related to  
18 mesothelioma and lung cancer mortality. If any risk factors are shared across outcomes and not  
19 accounted for in the modeling, the risk estimates generated by the different models are likely correlated.  
20 Given the small size of the data set, and lack of an appropriate statistical method, this correlation cannot  
21 be estimated reliably. One approach might be to undertake bounding analysis on the lifetime risk  
22 estimates using, for example, the Fréchet inequality for disjunctions (Fréchet, 1935) that makes no  
23 assumption about the nature of the dependence. This analysis could reveal how large the impact of  
24 dependence might be. At the very least, the restrictive assumption of independence must be mentioned  
25 and the potential consequences of a violation of this assumption must be discussed.

26  
27 **Recommendation:**

28  
29 The EPA should acknowledge that the assumption of independence is a theoretical limitation of the  
30 analysis, and should provide a fuller justification for this assumption. EPA has cited the NRC (1994)  
31 analysis as suggesting the impact of issue is likely to be relatively small. This view is also echoed in the  
32 EPA's (2005) *Guidelines for Carcinogen Risk Assessment*. These provide the basis for a default  
33 assumption. However, it would be preferable if this assessment discussed the evidence base and  
34 rationale for lung cancer and mesothelioma specifically. As a sensitivity analysis, the EPA should  
35 consider quantitatively accounting for dependence in the risks of mesothelioma and lung cancer  
36 mortality either using a method that models the dependence explicitly, or a bounding study that  
37 evaluates the numerical consequences of the assumption of independence.

38 **3.2.6.4. Adjustment for Mesothelioma Mortality Under-ascertainment**

39 *Question 4. Please comment on the adjustment for mesothelioma mortality under ascertainment. Is this*  
40 *adjustment scientifically supported and clearly described? If another adjustment approach is*  
41 *recommended as the basis for the IUR, please identify that approach and provide the scientific*  
42 *rationale.*  
43

44 The number of mesothelioma deaths was adjusted for under-ascertainment stemming from inadequate  
45 coding used in death certificates. The procedure used is not described in any detail, but can be found in  
46 the Kopylev et al. (2011) reference. A total of 18 mesotheliomas were observed in the Libby cohort

1 from 1980 to 2006. The estimated number of 24 mesotheliomas was obtained after using a Monte Carlo  
2 analysis. The ratio of 24 to 18 yields the median of 1.33. The Kopylev manuscript also provides a figure  
3 of 1.39 in Table 3, which is the mean later reported in the EPA report. The EPA method appears to be  
4 scientifically supported, but is not clearly described. This section should be expanded and a much more  
5 detailed statement of how the numbers were arrived at should be provided.

6  
7 No additional adjustment approach is described in the EPA report. The authors should provide an  
8 additional estimate using the 37% figure mentioned on page 46 of the Kopylev et al. (2011) reference.  
9 This is the percentage of mesothelioma cases that would be missed using previous histopathological  
10 analyses of cancer registry data. Using 37% would yield an estimate of about 29 mesothelioma cases  
11 instead of 24. The median ratio would then be 1.61 instead of 1.33. This number, and its related mean,  
12 should be utilized to provide a separate analysis of unit risk for comparison purposes.

### 13 **3.2.6.5. Characterization of Uncertainties**

14 *Question 5. Please comment on whether the document adequately describes the uncertainties and*  
15 *limitations in the methodology used to derive the IUR and whether this information is presented in a*  
16 *transparent manner.*

17  
18 The SAB commends the EPA for summarizing (in Section 5.4.6.1 of the draft document) the many  
19 sources of uncertainty considered in the course of this document and evaluating, at least qualitatively,  
20 and sometimes quantitatively, the direction and magnitude of the likely impact of each source of  
21 uncertainty.

22  
23 However, the SAB noted that most of what the document has accomplished is through targeted  
24 sensitivity analyses that examine one assumption at a time, while holding all others more or less  
25 constant. For example, the agency has indeed done a thorough job of exploring sensitivity of the IURs to  
26 a range of investigator analyses of lung cancer (Table 5-20) and mesothelioma (Table 5-21) for the  
27 Libby worker subcohort, and to a wide range of assumptions about the exposure metrics to be used in  
28 the basic models (e.g., Table 5-9). The basic underlying models chosen for lung cancer and for  
29 mesothelioma are the same.

30  
31 The sensitivity analyses in the document are individually well described, appear well-done and provide  
32 reassurance, under the assumptions of the basic models and approaches chosen to estimate the IUR, that  
33 the particular exposure metric and lag, for example, do not appear to make a big difference in the value  
34 of the IUR. However, they are currently presented somewhat in isolation, and thus do not take into  
35 account the magnitude and likelihood of multiple sources of uncertainty in the same analysis or address  
36 the overall distribution of uncertainty in the IUR. Consequently, the SAB did not think that the  
37 following statement had been fully justified:

38  
39 “the EPA’s selected combined IUR of mesothelioma and lung-cancer mortality accounts for  
40 both the demonstrated cross- metric uncertainty as well as several additional uncertainties,  
41 which could have resulted in underestimates of the mesothelioma and lung-cancer mortality  
42 risks” (p 5-105, lines 1-5).

43  
44 As noted in response to question 1 in Section 3.2.6.1 above, the SAB identified that model uncertainty is  
45 an important source of uncertainty that might well not be accounted for by using the 95% UCL on the

1 IUR and the combined IUR — or at least that had not been represented by the sensitivity analyses  
2 provided.

3  
4 **Recommendations:**

- 5
- 6 • The SAB recommends that a more straightforward and transparent treatment of model uncertainty  
7 would be to estimate risks using a more complete set of plausible models for the exposure- response  
8 relationship (discussed in response to question 1 in Section 3.2.6.1), including the Poisson models.  
9 This sensitivity analysis would make the implications of these key model choices explicit.
  - 10  
11 • The SAB recommends that, as an initial step in conducting an integrated and comprehensive  
12 uncertainty analysis, the agency provide a tabular presentation and narrative evaluation of the IUR  
13 estimates based on a reasonable range of data selections (e.g., all or part of the earlier hires as well as  
14 the “preferred” subcohort), model forms and input assumptions (as discussed, in the response to  
15 question 1 in Section 3.2.5.) These input assumptions should include *inter alia* exposure metrics and  
16 externally defined parameters, as discussed in the response to question 1 in Section 3.2.5. As noted  
17 in the current cancer risk assessment guidelines (EPA, 2005, page 3-29):

18  
19 *The full extent of model uncertainty usually cannot be quantified; a partial characterization can*  
20 *be obtained by comparing the results of alternative models. Model uncertainty is expressed*  
21 *through comparison of separate analyses from each model, coupled with a subjective probability*  
22 *statement, where feasible and appropriate, of the likelihood that each model might be correct*  
23 *(NRC, 1994).*

24 The preferred model or models will be selected as a judgment based on quality of fit, and biological  
25 plausibility (including consistency with available mechanistic data). EPA (2005) provides a number of  
26 suggestions for comparing and synthesizing multiple estimates (Section 3.3.5, page 3-24 *et seq.*) EPA’s  
27 Cancer Guidelines provides the following suggestions (primarily addressing animal data, but equally  
28 applicable in principle to epidemiological results):

- 29
- 30 • Combining data from different datasets in a joint analysis;
  - 31 • Combining responses that operate through a common mode of action;
  - 32 • Presenting a range of results from multiple datasets (in this case, the dose-response assessment  
33 includes guidance on how to choose an appropriate value from the range);
  - 34 • Choosing a single dataset if it can be justified as most representative of the overall response in  
35 humans,
  - 36 • A combination of these options.

37 Ideally, different estimates might be quantitatively incorporated in an overall estimate by modeling the  
38 joint distributions of the major sources of uncertainty it has identified in its evaluation. However, the  
39 SAB recognizes the challenge of conducting such an analysis, and notes that simplified approaches such  
40 as using the geometric mean of several consistent and plausible upper bound estimates, or selection of a  
41 single preferred value based on health protection are frequently used in practice.

42  
43 There is uncertainty associated with a composite IUR for mesothelioma and lung cancer, because it  
44 relies on an assumption of independence of the endpoints. Other methods that do not require this  
45 assumption should be explored (See response to question 1 in Section 3.2.6.1)

## 4. LONG-TERM RESEARCH NEEDS

### 4.1. Epidemiology

It would be informative and very important for NIOSH and ATSDR to continue monitoring mortality among Libby workers (including those residing in Libby and nearby towns such as Troy, Montana) and residents of Libby and nearby towns such as Troy, respectively, to determine the number of new lung cancers, mesotheliomas, and non-malignant pulmonary diseases (i.e., asbestosis) in these two populations.

The last occupational ascertainment was through 2006; an additional five years of data should now be available. In addition to a dose-response evaluation, an overall SMR should be calculated for lung cancer in this population by comparison to both the Montana and U.S. populations.

The previous ATSDR community SMR mortality survey was from 1979-1998. It should now be extended through 2011 and should include an analysis specific for community, non-occupationally exposed, individuals. Early-life exposure to LAA could possibly be obtained from surrogate interview information from the community population. Smoking, occupational, and residential histories should be obtained for the lung cancer, mesothelioma, and non-malignant respiratory disease (i.e., asbestosis) categories. Data concerning previous Libby residents who had moved away (and died in other states) would need to be obtained by means of a special effort of ATSDR.

A community cross-sectional respiratory health screening was conducted in Libby by ATSDR in 2000 and 2001. A non-malignant respiratory health update since then would be useful. The appropriate smoking, occupational, and residential histories should be included.

### 4.2. Mode of Action

It would be valuable for future research on LAA mode of action to focus on biomarkers that are more clearly and specifically related to non-cancer endpoints (i.e., asbestosis) or cancer endpoints (e.g., mesothelioma). Critical genotoxicity studies including mutagenesis and chromosomal aberration studies have not been investigated with LAA. Inhalation studies in animal models that can provide mechanistic and dose-response relationship should be conducted.

### 4.3. Future Development of a TEM Method for PCM Equivalency

EPA needs to develop a transmission electron microscopy (TEM) method that provides equivalent data to phase contrast microscopy (PCM). This TEM method development must first recognize fundamental differences between TEM and PCM analysis. Areas that need better definition include differences in analyzable areas, changes in PCM resolution over time, measuring complex fibrous structures, measuring obscured fibers, defining TEM analysis parameters more succinctly, recognition of several other measurement characteristics of importance (such as surface area), defining inter-laboratory variations and their causes, as well as other areas related to analysis.

Other areas of analysis may include but not limited to: differences between PCM reticule areas and TEM grid opening areas that create biases; TEM rules with regard to fibers obscured by grid bars which create positive bias in TEM results; measurement of obscured, complex arrangements of fibers by TEM that

1 differ from PCM counts; TEM measurement errors associated with fibers of various widths; differences  
2 between laboratories with interpretation of TEM counting rules; differences in  
3 magnification/orientations used for analysis; and other issues which create variation between analyses.  
4

## REFERENCES

- 1  
2  
3  
4 Albert, RE; Lippmann M; Briscoe W. (1969) The characteristics of bronchial clearance in humans and  
5 the effects of cigarette smoking. *Arch. Environ. Health* 18:738-755.  
6  
7 Amandus, HE; Wheeler, R. (1987). The morbidity and mortality of vermiculite miners and millers  
8 exposed to tremolite-actinolite: Part II. *Mortality. Am J Indian Med*11: 15-26.  
9  
10 ATS (2004). Diagnosis and initial management of nonmalignant disease of asbestos. *American J*  
11 *Respiratory Critical Care Med* 170: 691-715.  
12  
13 ATSDR. (2000). Health consultation: mortality from asbestosis in Libby, Montana, Atlanta, GA.  
14  
15 ATSDR. (2001). Year 2000 medical testing of individuals potentially exposed to asbestiform minerals  
16 associated with vermiculite in Libby, Montana: A report to the community. Atlanta, GA.  
17  
18 Ates,G; Yildiz, T; Akyildiz, L; Topcu, F; Erturk, B.(2010). Environmental asbestos-related pleural  
19 plaque in southeast of Turkey. *Arch Environ Occup Health.* 65(1):34-7.  
20  
21 Attfield, MD and Hewett, P. (1992). Exact expressions for the bias and variance of estimators of the  
22 mean of a lognormal distribution. *Am Ind Hyg Assoc J* 53: 432-435.  
23  
24 Below, JE; Cox, NJ; Fukagawa, NK.; Hirvonen, A.; Testa, JR. (2011). Factors that impact susceptibility  
25 to fiber-induced health effects. *J Toxicol Environ Health, Part B* 14:246-266.  
26  
27 Berman, DW. (2011). Apples to apples: The origin and magnitude of differences in asbestos cancer risk  
28 estimates derived using varying protocols. *Risk Analysis* 31: 1308-1326.  
29  
30 Bernstein, DM; Chevalier, J; Smith, P (2003). Comparison of Calidria chrysotile asbestos to pure  
31 tremolite: Inhalation biopersistence and histopathology following short-term exposure.  
32 *Inhalation Toxicology* 15: 1387-1419.  
33  
34 Bernstein, D, Rogers, R; Smith, P. (2005). The biopersistence of Canadian chrysotile asbestos following  
35 inhalation: final results through 1 year after cessation of exposure. *Inhalation Toxicology* 17: 1-  
36 14.  
37  
38 Bernstein, DM; Rogers, RA; Sepulveda, R; Donaldson, K; Schuler, D; Gaering, S; Kunzendorf, P;  
39 Chevalier, J; and Holm, SE. (2011). Quantification of the pathological response and fate in the  
40 lung and pleura of chrysotile in combination with fine particles compared to amosite-asbestos  
41 following short-term inhalation exposure. *Inhalation Toxicology* 23(7):372-391.  
42  
43 Berry, G and Lewinsohn, HC. (1979). Dose-response relationships for asbestos-related disease:  
44 implications for hygiene standards. Part 1: morbidity. *Annals New York Academy of Sciences*  
45 330: 185-194.  
46

- 1 Berry, G; Gilson, JC; Holmes, S; Lewinsohn, HC; and Roach, SA. (1979). Asbestosis: a study of dose-  
2 response relationships in an asbestos textile factory. *British J of Industrial Medicine* 36: 98-112.  
3
- 4 Bourbeau, J; Ernst, P; Chrome, J; Armstrong, B; Becklake, MR. (1990). The relationship between  
5 respiratory impairment and asbestos-related pleural abnormality in an active work force. *Am Rev*  
6 *Respir Dis* 142: 837-842.  
7
- 8 Broaddus, VC; Everitt, JI.; Black, B; Kane, AB. (2011). Non-neoplastic and neoplastic pleural endpoints  
9 following fiber exposure. *J Toxicol Environ Health, Part B* 14:153-178.  
10
- 11 Brody, AR; Hill, LH; Adkins, B Jr; O'Connor, RW. (1981). Chrysotile asbestos inhalation in rats:  
12 deposition pattern and reaction of alveolar epithelium and pulmonary macrophages. *Am. Rev.*  
13 *Respir. Dis.* 123:670-679.  
14
- 15 Brody, AR; Roe, MW. (1983). Deposition pattern of inorganic particles at the alveolar level in the lungs  
16 of rats and mice. *Am. Rev. Respir. Dis.* 128:724-729.  
17
- 18 Brody, AR; Liu, JY; Brass, D; Corti, M. (1997). Analyzing the genes and peptide growth factors  
19 expressed in lung cells in vivo consequent to asbestos exposure and in vitro. *Environ Health*  
20 *Perspect.* 105 Suppl 5:1165-71  
21
- 22 Clin, B; Paris, C; Ameille, J; Brochard, P; Conso, F; Gislard, A; Laurent, F; Letourneux, M; Luc, A;  
23 Schorle, E; Pairon, JC. (2011). Do asbestos-related pleural plaques on HRCT scans cause  
24 restrictive impairment in the absence of pulmonary fibrosis. *Thorax* 66: 985-991.  
25
- 26 Carbone, M; Baris, YI; Bertino, P; Brass, B; Comertpay, S; Dogan, AU; Gaudino, G; Jube, S; Kanodia,  
27 S; Partridge, CR; Pass, HI; Rivera, ZS; Steele, I; Tuncer, M; Way, S; Yang, H; Miller, A.(2011).  
28 Erionite exposure in North Dakota and Turkish villages with mesothelioma. *Proc Natl Acad Sci*  
29 *U S A.* 108(33):13618-23. Epub 2011 Jul 25.  
30
- 31 Constantopoulos, SH. (2008). Environmental mesothelioma associated with tremolite asbestos: lessons  
32 from the experiences of Turkey, Greece, Corsica, New Caledonia and Cyprus. *Regul Toxicol*  
33 *Pharmacol.*52(1 Suppl):S110-5. Epub 2007 Nov 13.  
34
- 35 Davis, JMG; Addison, J; Bolton, RE; Donaldson, K; Jones, AD; Miller, BG. (1985) Inhalation studies  
36 on the effects of tremolite and brucite dust in rats. *Carcinogenesis* 6: 667-674.  
37
- 38 Fréchet, M. (1935). Généralisations du théorème des probabilités totales. *Fundamenta Mathematica* 25:  
39 379-387.  
40
- 41 Gaylor, D ; Ryan, L; Krewski, D ; Zhu, Y (1998). Procedures for calculating benchmark doses for health  
42 risk assessment. *Regulatory Toxicology and Pharmacology* 28 : 150-164.  
43
- 44 Gogou, E; Kerenidi, T; Chamos, V; Zintzaras ,E; Gourgoulianis, KI. (2009). Mesothelioma mortality in  
45 Greece from 1983 to 2003. *Int J Clin Pract.*63:944-948. Epub 2007 Jun 15.  
46

- 1 HEI-AR, (1991). HEI Special Report "Asbestos in Public and Commercial Buildings." Health Effects  
2 Institute, Cambridge, MA. <http://pubs.healtheffects.org/view.php?id=13>  
3
- 4 Hjortsberg, U; Orbaek, P; Arborellius, M; Ranstam, J; Welinder, H (1988). Railroad workers with  
5 pleural plaques. I. Spirometric and nitrogen washout investigation on smoking and nonsmoking  
6 asbestos-exposed workers. *American J. of Industrial Medicine* 14: 649-656.  
7
- 8 Jarvold, B and Sanden, A (1986). Pleural plques and respiratory function. *American J. Industrial*  
9 *Medicine* 10: 419-426.  
10
- 11 Kamp, DW, Weitzman ,SA (1999).The molecular basis of asbestos induced lung injury. *Thorax*.  
12 54(7):638-52.  
13
- 14 Klein, JP and Moeschberger, ML (2003). *Survival Analysis: Techniques for Censored and Truncated*  
15 *Data*. New York: Springer.  
16
- 17 Kopylev, L; Sullivan, PA; Vinikoor, LC; Bateson, TF. (2011). Monte Carlo analysis of impact of  
18 underscertainment of mesothelioma cases on underestimation of risk. *The Open Epidemiology*  
19 *Journal* 4: 45-53.  
20
- 21 Küchenhoff, H; Bender, R; Langner, I. (2007) Effect of Berkson measurement error on parameter  
22 estimates in Cox regression models. *Lifetime Data Analysis* 13(2):261–72.  
23
- 24 Larson, TC; Antao, VC; Bove, FJ; Cusack, C. (2012). Association Between Cumulative Fiber Exposure  
25 and Respiratory Outcomes Among Libby Vermiculite Workers. *J Occup Environ Med* 54: 56-63.  
26
- 27 Leake, BE; Woolley, AR; Arps, CES; Birch, WD; Gilbert, MC; Grice, JD; Hawthorne, FC; Kato, A;  
28 Kisch, HJ; Krivovichev, VG; Linthout, K; Laird, J; Mandarino, JMaresch, WV; Nickel, EH;  
29 Rock, NMS; Schumacher, JC; Smith, DC; Shephenson, NCN; Ungaretti, L; Whittake, EJW;  
30 Youzhi, G. (1997). Nomenclature of amphiboles: Report of the Subcommittee on Amphiboles of  
31 the International Mineralogical Association Commission on New Minerals and Mineral Names.  
32 *Mineral Mag* 61: 295-321.  
33
- 34 Lilis, R; Miller, A; Godbold, J; Chan, E; Selikoff, IJ. (1991a). Radiographic abnormalities in asbestos  
35 insulators: effects of duration from onset of exposure and smoking: relationships of dyspnea with  
36 parenchymal and pleural fibrosis. *Am J Ind Med* 20:1-15.  
37
- 38 Lilis, R; Miller, A; Godbold, J; Chan, E; Selikoff, IJ. (1991b). Pulmonary function and pleural fibrosis:  
39 quantitative relationships with an integrative index of pleural abnormalities. *Am J Ind Med* 29:  
40 145-161.  
41
- 42 Lippmann, M. (2009). Asbestos and other mineral fibers. In: M. Lippmann, Ed., *Environmental*  
43 *Toxicants: Human Exposures and Their Health Effects, 3rd Ed.*, John Wiley, New York, NY,  
44 2009, pp. 395-458.  
45

- 1 Lockey, JE; Brooks, SM; Jarabek, AM; Khoury, PR; McKay, RT; Carson, A; Morrison, JA; Wiot, JF;  
2 Spitz, HB. (1984). Pulmonary changes after exposure to vermiculite contaminated with fibrous  
3 tremolite. *Am Rev Respir Dis* 129: 952-958.  
4
- 5 Manski, CF. (2003). *Partial Identification of Probability Distributions*. Springer, New York.  
6
- 7 McDonald, JC; McDonald,AD; Armstrong, B; Sebastien, P (1986). Cohort study of mortality of  
8 vermiculite miners exposed to tremolite. *Occup Environ Medical* 43:436-444.  
9
- 10 McDonald, JC; Harris, J; Armstrong, B. (2004). Mortality in a cohort of vermiculite miners exposed to  
11 fibrous amphibole in Libby, Montana. *Occup Environ Med* 61: 363-366.  
12
- 13 Meeker, GP; Bern, AM; Brownfield, IK; Lowers, HA; Sutley, SJ; Hoefen, TM; Vance, JS. (2003) The  
14 composition and morphology of amphiboles from the Rainy Creek Complex, near Libby,  
15 Montana. *American Mineralogist* 88: 1955-1969.  
16
- 17 Metintas, S; Metintas, M; Ak ,G, Kalyoncu C.(2012). Environmental asbestos exposure in rural Turkey  
18 and risk of lung cancer. *Int J Environ Health Res*. Feb 2. [Epub ahead of print]  
19
- 20 Metintas, M; Hillerdal, G; Metintas, S; Dumortier, P. (2010) Endemic malignant mesothelioma:  
21 exposure to erionite is more important than genetic factors. *Arch Environ Occup Health*.  
22 65(2):86-93.  
23
- 24 Metintas, M; Metintas, S; Ak G, Erginel S; Alatas F; Kurt E; Ucgun I; Yildirim H.(2008). Epidemiology  
25 of pleural mesothelioma in a population with non-occupational asbestos exposure. *Respirology*  
26 13(1):117-21.  
27
- 28 Miller, A; Lilis, R; Godbold, J; Chan, E; Selikoff, IJ. (1992). Relationship of pulmonary function to  
29 radiographic interstitial fibrosis in 2,611 long term asbestos insulators: an assessment of the  
30 International Labour Organization profusion score. *Am Rev Respir Dis* 145: 263-270.  
31
- 32 Miller, A. (2002) Pleural plaques and lung function. *Am J Respir Crit Care Med*.165(2):305-6.  
33
- 34 Mossman, BT; Lounsbury, KM; Reddy, SP. (2006). Oxidants and signaling by mitogen-activated  
35 protein kinases in lung epithelium. *Am J Respir Cell Mol Biol*. 34(6):666-9.  
36
- 37 Mossman, BT; Lippmann, M; Hesterberg, TW; Kelsey, KT; Barchowsky, A; Bonner, JC. (2011).  
38 Pulmonary endpoints (lung carcinomas and asbestosis) following inhalation exposure to  
39 asbestos. *J Toxicol Environ Health, Critical Reviews, Part B* 14:76-121.  
40
- 41 Mulhausen, J and Damiano, J. (1998) *A Strategy for Assessing and Managing Occupational Exposures*.  
42 *2nd edition*, AIHA Press.  
43
- 44 Neri, M; Ugolini, D; Dianzani, I; Gemignani, F; Landi, S; Cesario, A; Magnani, C; Mutti, L; Puntoni, R;  
45 Bonassi, S. (2008) Genetic susceptibility to malignant pleural mesothelioma and other asbestos-  
46 associated diseases. *Mutation Research* 659:126-136.  
47

- 1 NIOSH (1977). Leidel, Bush & Lynch Occupational Exposure Sampling Strategy Manual. NIOSH 77-  
2 173 CDC.  
3
- 4 Nguyen, HT; Kreinovich, V; Wu, B.; Xiang, G. (2012) *Computing Statistics under Interval and Fuzzy*  
5 *Uncertainty*. Springer, Berlin.  
6
- 7 NRC (1994). *Science and Judgement in Risk Assessment*. Washington, DC: National Academy Press  
8 [Chapter 11, Appendix I-1, Appendix I-2] [http://www.nap.edu/catalog.php?recird\\_id=2125](http://www.nap.edu/catalog.php?recird_id=2125)  
9
- 10 Ohlson, G; Rydman, T; Sundell, L; Bodin L; Hogstedt, C (1984). Decreased lung function in long-term  
11 asbestos cement workers: a cross-sectional study. *American J Industrial Medicine* 14: 649-656.  
12
- 13 Ohlson, CG; Bodin, L; Rydman, T; et al. (1985) Ventilatory derangements in former asbestos cement  
14 workers: a four year follow up. *Brit J Ind Medicine* 42: 612-616.  
15
- 16 Oliver, LC; Eisen, EA; Greene, R; Sprince, NL (1988) Asbestos-related pleural plaques and lung  
17 function. *American J. of Industrial Medicine* 14:649-656.  
18
- 19 Paris, C; Martin, A; Letourneux, M; Wild, P. (2008). Modelling prevalence and incidence of fibrosis and  
20 pleural plaques in asbestos-exposed populations for screening and follow-up: a cross-sectional  
21 study. *Environ Health Global Sci Source* 7: 30. <http://dx.doi.org/10.1186/1476-069X-7-30>.  
22
- 23 Paris, C; Thierry S; Brochard P, et al. (2009) Pleural plaques and asbestosis: dose- and time-response  
24 relationships based on HRCT data. *Eur Respir j.* 34:72-79.  
25
- 26 Peto, J. (1979). Dose-response relationships for asbestos-related disease: Implications for hygiene  
27 standards. Part II: Mortality. *Ann NY Acad Sci* 330: 195-204.  
28
- 29 Peto, J; Seidman, H; Selikoff, IJ. (1982). Mesothelioma mortality in asbestos workers: implications for  
30 models of carcinogenesis and risk assessment. *Br J Cancer* 45: 124-135.  
31
- 32 Reid, A; Berry, G; Heyworth, J; de Klerk, NH; Musk, AW. (2009). Predicted mortality from malignant  
33 mesothelioma among women exposed to blue asbestos at Wittenoom, Western Australia. *Occup*  
34 *Environ Med* 66: 169-174.  
35
- 36 Reid, A; Heyworth J; de Klerk NH; Musk B (2008) . Cancer incidence among women and girls  
37 environmentally and occupationally exposed to blue asbestos at Wittenoom, Western Australia.  
38 *Int J Cancer* 122(10):2337-44.  
39
- 40 Reid, A; Berry, G; de Klerk, N; Hansen, J; Heyworth, J; Ambrosini, G; Fritschi, L; Olsen, N; Merler, E;  
41 Musk, A (2007) Age and sex differences in malignant mesothelioma after residential exposure to  
42 blue asbestos (crocidolite). *Chest* 131: 376-382.  
43
- 44 Richardson, DB. (2010). Occupational exposures and lung cancer: Adjustment for unmeasured  
45 confounding by smoking. *Epidemiology* 21: 181-186.  
46

- 1 Richardson, DB (2008). Multistage Modeling of Leukemia in Benzene Workers: A simple Approach to  
2 fitting the 2-stage Clonal Expansion Model. *Am J. Epi.* DOI:10.1093/aje/kwn284  
3
- 4 Robledo, R; Mossman, B. (1999). Cellular and molecular mechanisms of asbestos-induced fibrosis. *J*  
5 *Cell Physiol.* 180(2):158-66.  
6
- 7 Rohs, A; Lockey, J; Dunning, K; Shukla,R; Fan, H; Hilbert,T; Borton,E; Wiot, J; Meyer, C; Shipley, R;  
8 Lemasters, G; Kapil, V. (2008). Low-level fiber-induced radiographic changes caused by Libby  
9 vermiculite: A 25-year follow-up study. *Am. J Respir Crit Care Med* 177: 630-637.  
10
- 11 Sanchez, MS; Gunter, ME; Dyar, MD. (2008) Characterization of historical amphibole samples from the  
12 former vermiculite mine near Libby, Montana, U.S.A. *European Journal of Mineralogy* 20:  
13 1043-1053.  
14
- 15 Schwartz, DA, Fuortes, LJ; Galvin, JR; Burmeister, LF; Schmidt, LE; Leistikow, BN; LaMarte, FP;  
16 Merchant, JA. (1990). Asbestos-induced pleural fibrosis and impaired lung function. *Am Rev*  
17 *Respir Dis.* 141(2):321-6.  
18
- 19 Sichletidis, L; Chloros, D; Chatzidimitriou, N; Tsiotsios, I; Spyratos, D; Patakas, D. (2006). Diachronic  
20 study of pleural plaques in rural population with environmental exposure to asbestos. *Am J Ind*  
21 *Med.* 49(8):634-41.  
22
- 23 Straif, K; Benbrahim-Tallaa, L; Baan, R; Grosse, Y; Secretan, B; El Ghissassi, F; Bouvard, V; Guha, N;  
24 Freeman, C; Galichet, L; Coglianò, V. (2009). A review of human carcinogens: Part C: Metals,  
25 arsenic, dusts, and fibres. *Lancet Oncol* 10: 453-454.  
26
- 27 Sussman ,RG; Cohen, BS; Lippmann, M. (1991a). Asbestos fiber deposition in a human  
28 tracheobronchial cast. I. *Exp. Inhal. Toxicol.* 3:145-160.  
29
- 30 Sussman, RG; Cohen, BS; Lippmann, M. (1991b). Asbestos fiber deposition in a human  
31 tracheobronchial cast. II. Empirical model. *Inhal. Toxicol.* 3:161-179.  
32
- 33 Testa, JR; Cheung, M; Pei, J; Below, JE; Tan, Y; Sementino, E; Cox, NJ; Dogan, AU; Pass, HI, Trusa  
34 S.; Hesdroffer, M.; Nasu, M; Powers, A; Rivera, Z; Comertpay, S; Tanji, M; Gaudino, G.; Yang,  
35 H; Carbone, M (2011) Germline BAP1 mutations predispose to malignant mesothelioma. *Nature*  
36 *Genetics* 43:1022-1025.  
37
- 38 USEPA (2012). Benchmark Dose Technical Guidance. Risk Assessment Forum, EPA/100/R-12/001 .  
39
- 40 USEPA (2005). *Guidelines for Carcinogen Risk Assessment.* Risk Assessment Forum. EPA/630/P-  
41 03/001B.  
42
- 43 USEPA (2002). *A review of the reference dose and reference concentration processes.* Risk Assessment  
44 Forum. EPA/630/P-02/002F  
45
- 46 USEPA (1994). *Methods for derivation of inhalation reference concentrations and application of*  
47 *inhalation dosimetry.* EPA/600/8-90/066F

- 1  
2 USEPA (1988). IRIS summary for Asbestos (CASRN 1332-21-4), Washington, DC.  
3 <http://www.epa.gov/iris/subst/0371.htm>.  
4
- 5 Van Cleemput, J; De Raeve, H; Verschakelen, JA; Rombouts J; Lacquet, LM; Nemery, B (2001),  
6 Surface of localized pleural plaques quantitated by computed tomography scanning: no relation  
7 with cumulative asbestos exposure and no effect on lung function. *Am J. Respiratory Crit Care*  
8 *Medicine* 163: 705-710.  
9
- 10 Veblen, DR and Wylie, AG. (1993). Mineralogy of amphiboles and 1:1 layer silicates. In, G.D. Guthrie  
11 Jr. and B.T. Mossman, Eds., *Health effects of mineral dusts*, Vol 28, pp 61-137. Reviews in  
12 Mineralogy, Mineralogical Society of America, Washington, DC.  
13
- 14 Warheit, DB; Hartsky, MA. (1990). Species comparisons of alveolar deposition patterns of inhaled  
15 particles. *Exp. Lung Res.* 16:83-99.  
16
- 17 Webber, JS; Blake, DJ; Ward, TJ; and Pfau, JC (2008) Separation and characterization of respirable  
18 amphibole fibers from Libby, Montana. *Inhal Toxicol* 20: 733-740.  
19
- 20 Weill, D; Dhillon, G; Freyder, L; Lefante, J; Glindmeyer, H. (2011). Lung function, radiological  
21 changes and exposure: analysis of ATSDR data from Libby, Montana. USA. *Eur Respir J* 38:  
22 376-383.  
23
- 24 Weiner, SJ; Neragi-Miandoab, S. (2009) Pathogenesis of malignant pleural mesothelioma and the role of  
25 environmental and genetic factors. *J Cancer Res Clin Oncol* 135:15-27.  
26
- 27 Whitehouse, AC. (2004) Asbestos-related pleural disease due to tremolite associated with progressive  
28 loss of lung function: Serial observations in 123 miners, family members, and residents of Libby,  
29 Montana. *Am J Industr Med* 46:219-225.  
30
- 31 Wilken, D; Garrido, MV; Manuwald, U; Bauer X (2011). Lung function in asbestos-exposed workers, a  
32 systematic review and meta-analysis. *J Occup Med Tox.* 6:21-37.  
33
- 34 Zeka, A; Gore, R; Kriebel, D. (2011). The two-stage clonal expansion model in occupational cancer  
35 epidemiology: results from three cohort studies. *Occupational and Environmental Medicine*  
36 68:618-24.  
37

## APPENDIX A: EPA'S CHARGE QUESTIONS

### EPA Charge to the SAB for the IRIS Toxicological Review of Libby Amphibole Asbestos

August 2011

#### Introduction

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the draft Toxicological Review of Libby Amphibole asbestos that will appear on the Agency's online database, the Integrated Risk Information System (IRIS). IRIS is prepared and maintained by the EPA's National Center for Environmental Assessment (NCEA) within the Office of Research and Development (ORD). An existing IRIS assessment for asbestos which includes a carcinogenicity assessment was posted on IRIS in 1988. The draft on which EPA is now seeking review is the first IRIS assessment specific to Libby Amphibole asbestos<sup>1</sup>.

IRIS is a human health assessment program that evaluates qualitative and quantitative risk information on effects that may result from exposure to specific chemical substances found in the environment. Through the IRIS Program, EPA provides quality science-based human health assessments to support the Agency's regulatory activities. Combined with specific exposure information, government and private entities use IRIS to help characterize public health risks of chemical substances in site-specific situations in support of risk management decisions.

Libby Amphibole asbestos, found in vermiculite ore deposits near Libby, Montana, is comprised of a mixture of related mineral forms of amphibole asbestos: primarily winchite, richterite and tremolite with trace amounts of magnesioriebeckite, edenite, and magnesio-arfvedsonite. Health effects from exposure to Libby Amphibole asbestos are a potential concern for Libby residents, as well as workers and others who may have handled vermiculite mined in Libby, Montana. Additionally, vermiculite from Libby, Montana was incorporated into various consumer products, some of which may remain in place (e.g., vermiculite attic insulation in homes).

The external review draft Toxicological Review of Libby Amphibole asbestos is based on a comprehensive review of the available scientific literature on the health effects of Libby Amphibole asbestos and was developed in adherence with general guidelines for risk assessment set forth by the National Research Council in 1983 (NRC, 1983)<sup>2</sup> and numerous guidelines and technical reports published by EPA (see Section 1 of the assessment)<sup>3</sup>. Specifically, this draft IRIS assessment provides an overview of sources of exposure to Libby Amphibole asbestos, characterizes the hazard posed by exposure to Libby Amphibole asbestos for carcinogenicity and noncancer health effects based on the available scientific evidence, and presents a qualitative and quantitative health assessment, including the

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<sup>1</sup> The term "Libby Amphibole asbestos" is used in this document to identify the mixture of amphibole mineral fibers of varying elemental composition (e.g., winchite, richterite, tremolite, etc.) that have been identified in the Rainy Creek complex near Libby, Montana.

<sup>2</sup> NRC (1983). *Risk Assessment in the federal government: managing the process*. Washington DC: National Academy Press.

<sup>3</sup> <http://www.epa.gov/iris/backgrd.html>

1 derivations of a chronic inhalation reference concentration (RfC) and an inhalation unit risk (IUR) that  
2 can be combined with exposure information in a risk assessment to estimate noncancer hazard and  
3 carcinogenic risk, respectively, in humans. The assessment does not address oral exposure to Libby  
4 Amphibole asbestos.

## 6 **Charge Questions**

8 Below is a set of charge questions that address scientific issues in the draft human health assessment of  
9 Libby Amphibole asbestos. Please provide detailed explanations for responses to the charge questions.  
10 EPA will also consider the Science Advisory Board reviewer SAB comments on other major scientific  
11 issues specific to the hazard identification and dose response assessment of Libby Amphibole asbestos.  
12 Please identify and provide the rationale for approaches to resolve the issues where possible. Please  
13 consider the accuracy, objectivity, and transparency of EPA's analyses and conclusions in your review.

### 15 **General Charge Questions:**

- 17 1. Is the Toxicological Review logical, clear, and concise? Has EPA clearly, and in sufficient detail,  
18 presented and synthesized the scientific evidence for health hazards from Libby Amphibole asbestos?  
19
- 20 2. Please identify any additional peer-reviewed studies from the primary literature that should be  
21 considered in the assessment of noncancer and cancer health effects of Libby Amphibole asbestos.  
22

### 23 **Chemical-Specific Charge Questions:**

#### 25 I. Background

##### 26 A. Mineralogy and Toxicokinetics

27 1. In order to inform the hazard identification and dose response of Libby Amphibole asbestos,  
28 background material is included in the document briefly describing the mineralogy and toxicokinetics of  
29 asbestos and related mineral fibers (Section 2 and 3):

- 31 a. Please comment on whether the presentation of the available data on the mineralogy of Libby  
32 Amphibole asbestos is clear, concise and accurate.  
33
- 34 b. In the absence of toxicokinetic information specific to Libby Amphibole asbestos, the draft  
35 assessment contains a general summary description of fiber toxicokinetics. Please comment on whether  
36 this overview of general fiber toxicokinetics is clear, concise and accurate.  
37

#### 38 II. Hazard Identification of Libby Amphibole Asbestos

##### 39 **A. Noncancer Health Effects:**

40 1. An occupational cohort of workers in a Marysville, OH facility exposed to Libby Amphibole asbestos  
41 (Lockey et al., 1984; Rohs et al., 2008) was selected as the basis for the derivation of the reference  
42 concentration (RfC). Please comment on whether the selection of this study population is scientifically  
43 supported and clearly described. If a different study population is recommended as the basis for the RfC,  
44 please identify this study and provide scientific support for this choice.  
45

1 2. Radiographic evidence of localized pleural thickening in humans was concluded by EPA to be an  
2 adverse effect and was selected as the critical effect for the derivation of the RfC. Pleural thickening is  
3 associated with restrictive lung function, breathlessness during exercise and, for some individuals,  
4 chronic chest pain. Please comment on whether the selection of this critical effect and its  
5 characterization is scientifically supported and clearly described. If a different health endpoint is  
6 recommended as the critical effect for deriving the RfC, please identify this effect and provide scientific  
7 support for this choice.

8  
9 3. The database of laboratory animal and mechanistic studies of Libby Amphibole asbestos is  
10 summarized in the draft assessment (see Section 4.2 and 4.3, details in Appendix D) to inform the  
11 mechanisms of the biological response to Libby Amphibole asbestos and support the epidemiology  
12 studies used for derivation of the RfC. Please comment on whether the laboratory animal and  
13 mechanistic information presented is used appropriately in the draft assessment.

## 14 15 **B. Carcinogenicity:**

16 1. Under EPA's Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005;  
17 [www.epa.gov/iris/backgrd.html](http://www.epa.gov/iris/backgrd.html)), the draft IRIS assessment characterizes Libby Amphibole asbestos as  
18 "carcinogenic to humans" by the inhalation route of exposure. Please comment on whether the cancer  
19 weight of evidence characterization is scientifically supported and clearly described.

20  
21 2. Due to the limitations of the data available, the draft assessment concludes that there is insufficient  
22 information to identify the mode of carcinogenic action of Libby Amphibole asbestos. Please comment  
23 on whether this determination is appropriate and clearly described. Note that in the absence of  
24 information to establish a mode of action, a linear low dose extrapolation is recommended by the  
25 Guidelines for Carcinogen Risk Assessment (U.S., EPA, 2005; Section 3.3). If it is judged that a mode  
26 of action can be established for Libby Amphibole asbestos, please identify the mode of action and its  
27 scientific support (i.e., studies that support the key events, and specific data available to inform the  
28 shape of the exposure-response curve at low doses).

29 3. An occupational cohort of workers from Libby, Montana exposed to Libby Amphibole asbestos (i.e.,  
30 the Libby worker cohort) was selected as the basis for the derivation of the inhalation unit risk (IUR).  
31 Please comment on whether the selection of this study population is scientifically supported and clearly  
32 described. If a different study population is recommended as the basis for the IUR, please identify this  
33 study and provide scientific support for this choice.

34  
35 4. Mortality from lung tumors and mesothelioma in the Libby worker cohort was selected to serve as the  
36 basis for the derivation of the IUR. Please comment on whether this selection is scientifically supported  
37 and clearly described. If a different health endpoint is recommended for deriving the IUR, please  
38 identify this endpoint and provide scientific support for this choice.

39  
40 5. The database of laboratory animal and mechanistic studies of Libby Amphibole asbestos is  
41 summarized in this draft assessment (see Section 4.2 and 4.3, details in Appendix D) to inform the  
42 mechanisms of the biological response to Libby Amphibole asbestos and support the epidemiology  
43 studies used for derivation of the IUR. Please comment on the use of laboratory animal and mechanistic  
44 information in the draft assessment.

## 45 46 III. Exposure-Response Assessment

### 47 **A. Inhalation Reference Concentration (RfC):**

1 1. Exposures to Libby Amphibole asbestos for workers in the Marysville, OH facility were reconstructed  
2 based on industrial hygiene data collected in the facility from 1972 to 1994. Exposures from 1957 to  
3 1971 were estimated based on extrapolation from the available industrial hygiene data. The information  
4 used for the exposure reconstruction was based on employee interviews, court and company records, and  
5 the expert judgment of the researchers. Is the methodology used for the exposure reconstruction reported  
6 in Appendix F and the subsequent development of exposure estimates used in the analyses scientifically  
7 supported and clearly described?  
8

9 2. Exposure-response modeling was conducted using the incidence of localized pleural thickening in  
10 workers and cumulative exposure to estimate the point of departure (POD) for derivation of the RfC.  
11 EPA's estimate of the POD is based upon a Michaelis-Menten model applied to the subcohort of  
12 workers examined in 2002-2005 and first exposed to Libby Amphibole asbestos in 1972 (when  
13 measurements of fiber levels in the workplace began) or later with cumulative exposure as the  
14 explanatory variable. Is the selection of the model scientifically justified and clearly described? Has the  
15 modeling and the choice of a benchmark response (BMR) for the POD of 10% extra risk of localized  
16 pleural thickening been clearly described and appropriately conducted according to EPA's Draft  
17 Benchmark Dose Technical Guidance (U.S. EPA, 2000b)?  
18

19 3. EPA's assessment also provides the results of alternative modeling approaches to derive a POD for  
20 localized pleural thickening. This modeling used the full Marysville worker data set with exposures  
21 from 1957 and later and a Cumulative Normal Michaelis-Menten model that incorporates both  
22 cumulative exposure and time from first exposure as explanatory variables. Please comment on whether  
23 EPA's rationale for presenting these alternative approaches is scientifically justified and clearly  
24 described. Please identify and provide the rationale if a different approach for identifying the most  
25 appropriate population within the cohort of Marysville workers is recommended as the basis for  
26 estimating a POD.  
27

28 4. EPA has evaluated potential confounders and covariates where data are available. Specifically, EPA  
29 has explored the influence of age, body mass index, smoking status, time since first exposure, gender,  
30 and alternative exposure metrics on model fit and evaluated their association with the modeled health  
31 outcomes (see Section 5.3). Are these analyses clearly described and appropriately conducted? Are the  
32 results of these analyses appropriately considered in the RfC derivation? Additionally, there is a  
33 possibility of exposure-dependent censoring in participant selection for the update of the Marysville  
34 cohort (Rohs et al., 2008) but no evidence of selection bias. Does the SAB have any specific  
35 recommendations for evaluating and, if appropriate, quantitatively addressing exposure-dependent  
36 censoring in these analyses?  
37

38 5. The modeled POD estimate is based on cumulative exposure estimates for the worker cohort  
39 examined. For the derivation of the RfC, this cumulative exposure is prorated over the period of  
40 environmental exposure (lifetime or shorter duration chronic exposure when appropriate). The RfC is  
41 provided in units of continuous air concentration. Is the basis of this conversion clearly explained and  
42 scientifically justified?  
43

44 6. Please comment on the rationale for the selection of the uncertainty factors (UFs) applied to the POD  
45 for the derivation of the RfC. Are the UFs appropriate based on A Review of the Reference Dose and  
46 Reference Concentration Processes (U.S. EPA, 2002; Section 4.4.5) and clearly described? If changes  
47 to the selected UFs are proposed, please identify and provide scientific support. Specifically, please

1 comment on the rationale for the selection of the database uncertainty factor (UFD) of 10 applied in the  
2 derivation of the RfC. The database uncertainty factor accounts for the lack of data on effects other than  
3 in the respiratory system, including other effects observed in community and laboratory animal studies  
4 (cardiovascular disease and autoimmune effects) that have not been well-studied (See Section 5.2.3 of  
5 the Toxicological Review); and lack of health data assessed at later time points. Is the rationale for the  
6 UFD appropriate and clearly described? Please provide the rationale if a change in the UFD is  
7 proposed.

8  
9 7. Please comment on whether the document adequately describes the uncertainties and limitations in  
10 the methodology used to derive the RfC and whether this information is presented in a transparent  
11 manner.

### 12 13 **B. Inhalation Unit Risk (IUR):**

14 1. Exposure-response modeling was conducted separately for lung cancer and mesothelioma mortality.  
15 The POD estimates for these endpoints are based upon analysis of the subcohort of workers first  
16 exposed after 1959 when the exposure data were judged to be better characterized. The exposure-  
17 response modeling included consideration of a variety of exposure metrics that varied with time and  
18 incorporated different lag and decay parameters. Based on the results of the exposure-response  
19 modeling, a life table analysis was used to determine the PODs for each type of cancer for the various  
20 exposure metrics. Have the exposure-response modeling and determination of the PODs from life table  
21 analysis been appropriately conducted and clearly described? If a different approach to exposure-  
22 response analysis is recommended as the basis for the estimating the IUR, please identify the  
23 recommended methods and provide a rationale for this choice.

24  
25 2. Smoking is a strong independent risk factor for lung cancer and may be an important confounder of  
26 the lung cancer mortality analysis. Data on individual smoking habits and history were largely missing  
27 and could not be used to control for potential confounding in regression analyses. However, EPA used  
28 three approaches to evaluate the confounding issue, including restriction of the cohort and two analytic  
29 evaluations of the potential for confounding by smoking (see Section 5.4.3.6.5). Please comment on  
30 whether the methods and analyses are clearly presented and scientifically justified. If additional analyses  
31 are recommended, please identify the methods and scientific rationale.

32  
33 3. In order to derive an IUR which represents the combined risk of mortality from lung cancer or  
34 mesothelioma, a cancer-specific unit risk for each tumor type was calculated according to the Guidelines  
35 for Carcinogen Risk Assessment (U.S., EPA, 2005; Sections 3.2 and 3.3) by linear extrapolation from  
36 the corresponding POD (i.e., the lower 95% confidence limit on the exposure associated with 1% extra  
37 risk of lung cancer or 1% absolute risk of mesothelioma mortality). The IUR was then determined as a  
38 combined upper bound risk estimate for mortality considering both cancers. Has this approach been  
39 appropriately conducted and clearly described?

40  
41 4. Please comment on the adjustment for mesothelioma mortality under ascertainment. Is this adjustment  
42 scientifically supported and clearly described? If another adjustment approach is recommended as the  
43 basis for the IUR, please identify that approach and provide the scientific rationale.

44  
45 5. Please comment on whether the document adequately describes the uncertainties and limitations in  
46 the methodology used to derive the IUR and whether this information is presented in a transparent  
47 manner.