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EPA-SAB...

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. 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:

- The SAB supports the derivation of an inhalation reference concentration (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, and include additional X-ray anomalies (diffuse pleural thickening and asbestosis) in future analyses.
- The SAB agrees that localized pleural thickening is an appropriate health endpoint for the derivation of the RfC and one that is predictive of risk for other asbestos-related diseases, including asbestosis, mesothelioma, and lung cancer. The SAB has identified additional references and recommends that the agency conduct a more detailed review of the literature to further support this conclusion.
- For exposure-response modeling of non-cancer endpoints, the SAB recommends that a clearer description be provided of how the "best" model was chosen. The EPA should consider model

1 features and balance plausibility, localized fit, and technical guidance when choosing the best
2 model and explain decisions in more detail; the SAB suggests this may lead to selecting the
3 Dichotomous-Hill model with the plateau fixed at a literature-based value. The SAB also
4 recommends examining other exposure metrics besides the simple cumulative exposure, such as
5 time weighting of exposures. In addition, more justification is needed for the selection of 10
6 percent extra risk as the benchmark response which is not consistent with EPA's guideline for
7 epidemiological data.

- 8 • A composite uncertainty factor of 100 was applied by the EPA to the point of departure to obtain
9 the RfC. Although the default value for the intraspecies uncertainty factor is 10, and there may
10 be few specific data to support departure from this default, there is concern for the impact on
11 susceptible subpopulations, especially women and children. The SAB also recommends that the
12 EPA consider additional data and analysis to further support the application of a database
13 uncertainty factor of 10.
- 14 • The SAB agrees that the weight of evidence for LAA supports the descriptor "Carcinogenic to
15 Humans by the Inhalation Route," in accordance with EPA's *Guidelines for Carcinogen Risk
16 Assessment*. The SAB views the mode of carcinogenic action of LAA as complex, and therefore
17 the default linear extrapolation at low doses is appropriate.
- 18 • The SAB supports the selection of the Libby worker cohort for the derivation of the inhalation
19 unit risk (IUR) and agrees that the use of the subcohort post-1959 for quantification is
20 reasonable due to the lack of exposure information for many of the workers in earlier years. The
21 SAB finds it appropriate to use lung cancer and mesothelioma as endpoints for the derivation of
22 the IUR. However, the SAB recommends a more detailed discussion and justification of how the
23 use of mortality data rather than incidence data may have resulted in an undercount of both
24 cancer outcomes.
- 25 • The SAB agrees that the agency clearly described the methods they selected to conduct the
26 exposure-response modeling for lung cancer and mesothelioma. However, the SAB suggests that
27 the agency provide a broader justification for its choice of statistical models to characterize the
28 exposure-response function. The SAB recommends that the EPA evaluate the time dependence
29 of disease by providing tabulation of mesothelioma mortality rates and lung cancer standardized
30 mortality ratios by time since first exposure, duration of exposure, and period of first exposure
31 for both the full cohort and subcohort.
- 32 • There are several competing models—Weibull and the two stage clonal expansion (TSCE)—that
33 might have provided very different estimates of risk than the Poisson and Cox models, but these
34 competing models are not discussed in the document. Use of the TSCE model, for example,
35 could allow for a more direct evaluation of, and possibly justification for, age-dependency of the
36 IUR.
- 37 • The SAB believes the agency has been overly constrained by reliance on model fit statistics as
38 the primary criterion for model selection. The SAB recommends graphical display of the fit to
39 the data for both the main models and a broader range of models in the draft document to
40 provide a more complete and transparent view of model fit.
- 41 • The EPA has summarized many sources of uncertainty, sometimes quantitatively, as well as the

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1 direction and magnitude of the likely impact of each source of uncertainty. The SAB identifies
2 an additional source of uncertainty, namely that of model uncertainty, that might not be
3 accounted for in the use of the 95 percent upper confidence limit on the inhalation unit risk
4 (IUR) and the combined IUR. The SAB recommends that model uncertainty be evaluated using
5 a straightforward and transparent approach by estimating risks using a more complete set of
6 plausible models for the exposure-response relationship, including the Cox and Poisson models.
7 This sensitivity analysis, while not a full uncertainty analysis, would make explicit the
8 implications of these key model choices.

9 The SAB appreciates the opportunity to provide the EPA with advice on this important subject. The
10 SAB urges the agency to move expeditiously to finalize this IRIS document for LAA. We look
11 forward to receiving the agency's response.

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13 Sincerely,
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21 Enclosure
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NOTICE

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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 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 Adverse Effect Level
NRC	National Research Council
NTP	National Toxicology Program
OR	odds ratio
ORD	Office of Research and Development
PCM	phase contrast microscopy
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

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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
WDS	wavelength dispersive spectroscopy
XRD	X-ray diffraction

1. EXECUTIVE SUMMARY

The Science Advisory Board (SAB) Libby Amphibole Asbestos Review Panel reviewed the draft *IRIS Toxicological Review of Libby Amphibole Asbestos* (hereafter referred to as the draft document) and responded to 24 charge questions from the EPA. 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., amphibole) and a specific composition or a range of compositions (e.g., winchite or tremolite). Given that these factors affect a mineral's physical and chemical behavior, they may in principle be factors to consider for potential hazard. However, this level of detail is not typically available for toxicity studies to allow its application to the evaluation of LAA *per se*. However, 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 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 Libby Amphibole 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 correct and clarify these issues.

Hazard Identification: Noncancer Health Effect

Selection of Critical Studies and Effects

The SAB supports the EPA's selection of the Marysville, Ohio, cohort for development of the RfC. The SAB finds it reasonable to select the subcohort for the main analysis (118 workers who began work in 1972 or later when exposure data were available and who had X-rays from the 2002-2005 exam), with

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1 the full cohort of 434 workers used for additional substantiating analysis. However, the SAB believes
2 additional analyses/cohorts are needed to strengthen and support the RfC. The SAB suggests that the
3 EPA include any X-ray abnormalities as the outcome [localized pleural thickening (LPT), diffuse pleural
4 thickening (DPT), or asbestosis]. The SAB also suggests that the EPA conduct analogous analyses (to
5 the extent the data permit) of pleural abnormalities among the Libby workers cohort and the
6 Minneapolis Exfoliation Community cohort.

7
8 The SAB agrees that the radiographic evidence of LPT in humans is the appropriate adverse critical
9 effect for the derivation of the RfC. LPT has the appropriate specificity and is not confounded by
10 cigarette smoking. It is physiologically important due to its measurable relationship to altered lung
11 function and is a structural, pathologic alteration of the pleura. The reported findings are compatible
12 with the animal data showing tissue injury and inflammation. Moreover, the presence of LPT itself is
13 predictive of risk for other asbestos-related diseases, including asbestosis, mesothelioma and lung cancer
14 – a point that the EPA should include as well. However, the SAB has identified additional relevant
15 publications and recommends that the agency conduct a more detailed review of the literature to further
16 support this conclusion.

17 *Use of Animal and Mechanistic Studies*

18
19
20 In general, the SAB finds the laboratory animal studies listed in Tables 4-15 and 4-16 and summarized
21 in Appendix D to be appropriate and complete. Laboratory animal studies using a variety of non-
22 inhalation routes of exposure have been used to ascertain the potential fibrogenic and carcinogenic
23 potential of LAA. While inhalation is regarded as the most physiologically relevant means of fiber
24 exposure in animals, there is no published study using this route of exposure for delivery of LAA to
25 experimental animals. Therefore, the deposition of particles and fibers cannot be adequately addressed.
26 However, inhalation studies have been conducted with tremolite. The relative potency of inhaled LAA
27 should be compared with that of tremolite in rodents to add new information for refining the RfC for
28 LAA.

29
30 Limited mechanistic studies using *in vitro* assay systems have utilized non-specific endpoints (e.g., pro-
31 inflammatory cytokines, enzyme release and oxidative stress markers), and will probably not shed much
32 light on the mechanisms of LAA-induced disease.

33 **Carcinogenicity**

34 *Weight of Evidence Characterization*

35
36
37
38 The SAB agrees that the weight of evidence for LAA supports the descriptor “Carcinogenic to Humans
39 by the Inhalation Route,” in accordance with EPA’s *Guidelines for Carcinogen Risk Assessment*. The
40 occupational studies showed dose-related increased risks of lung cancer and mesothelioma among
41 workers exposed by inhalation, although the number of mesothelioma cases are small. The case series in
42 the community, while supportive, does not provide the same level of evidence for an association, or for
43 the strength of the association. Effects from short term intra-tracheal instillation studies in mice and rats
44 include altered gene expression, collagen induction, and inflammatory response, and are consistent with
45 the early-stage pathological change induced by other amphibole fibers. The EPA also has provided

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1 supporting evidence of the carcinogenic potential of LAA from studies with tremolite fibers, in light of
2 LAA being about 6% tremolite by composition.

3
4 *Mode of Action*

5
6 The SAB agrees that the weight of evidence for the mode of action (MOA) of LAA based on laboratory
7 studies is weak, although there are abundant MOA data for other amphiboles such as crocidolite and
8 tremolite that are likely similar to the MOA for LAA. The SAB views the mode of action of LAA as
9 complex and supports the EPA's conclusion that there is insufficient information to identify the mode of
10 carcinogenic action of LAA, and that the use of the default linear extrapolation at low doses is
11 appropriate.

12
13 *Selection of Critical Study and Endpoint*

14
15 The SAB agrees that the selection of the Libby cohort for the derivation of the inhalation unit risk (IUR)
16 is scientifically supported and clearly described. This cohort has been studied thoroughly previously,
17 with detailed work histories and a job exposure matrix. This cohort had elevated asbestos exposure, a
18 wide range of measurements of asbestos exposure, and available cancer mortality data. Limitations of
19 this cohort include limited smoking information, and the endpoints of mortality based on death
20 certificates could undercount cancer endpoints, especially mesothelioma. The study population may not
21 be representative of the larger population since most of its members are white males exposed as adults,
22 and because it contains more cigarette smokers than the larger population.

23
24 The SAB finds the use of the subcohort post-1959 is reasonable due to the lack of exposure information
25 in many of the workers in earlier years; out of 991 workers hired before 1960, 706 had all department
26 and job assignments listed as unknown.

27
28 The SAB agrees that lung cancer and mesothelioma should be used as endpoints for derivation of the
29 IUR. Since determining the cancer outcome from mortality rather than incidence data may have resulted
30 in an undercount of both cancer outcomes, the SAB recommends more detailed discussion on how the
31 use of mortality data could impact the derived IUR. It also would have been useful to know other major
32 categories of mortality in this cohort.

33
34 *Use of Laboratory Animal and Mechanistic Studies*

35
36 The SAB agrees that the database of laboratory animal and mechanistic studies pertaining to LAA is
37 appropriately presented for support of the analysis of the human effects observed. However, the SAB
38 finds the document deficient in not citing all that is known about the dimensions of the administered
39 fibers, as it is now widely accepted that differences in biological potency among the various amphibole
40 fiber types are due primarily to differences in dimensions, especially in fiber length distributions. The
41 SAB also recommends that Section 4.6.2.2 be modified to reflect that there are insufficient data to
42 determine the mode of action for LAA.

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1 **Inhalation Reference Concentration (RfC)**

2
3 *Estimates of Human Exposure Concentration*

4
5 The approach described (in Appendix F of the EPA document) for exposure reconstruction is detailed
6 and specific. Due to large uncertainties associated with the unmeasured pre-1972 exposures, the SAB
7 agrees that the draft document appropriately eliminates this set of estimates and adheres only to
8 exposure estimates based on measured concentrations for the derivation of the RfC. Alternatively, the
9 SAB suggests that EPA search for phase contrast microscopy (PCM) measurements from relevant
10 exfoliation plants during the 1960s and use these for pre-1972 exposures.

11
12 In Appendix F, natural-log-transformed exposure data were used to calculate the geometric mean for the
13 job groups for use in developing the cumulative exposure metric (fiber/cc-years). The EPA should re-
14 evaluate the raw exposure data and review pertinent sampling documentation to bolster its use of the
15 geometric mean to represent the job group exposures, rather than an estimate of the arithmetic mean, and
16 consider whether a sensitivity analysis using the minimum variance unbiased estimator (MVUE) of the
17 mean is warranted in the development of the cumulative exposure metric. The SAB recommends that the
18 EPA consider sensitivity analyses of additional exposure metrics, such as no exposure since 1980 in any
19 cohort members, and alternative weighting schemes (e.g., residence time weighting).

20
21 *Exposure-Response Modeling*

22
23 The SAB recommends that the document provide a clearer description of how the “best” model was
24 chosen. According to EPA’s *Benchmark Dose Technical Guidance*, the point of departure (POD) from
25 the model with the smallest AIC should be selected if, among models that adequately fit the data, the
26 lower 95% confidence limits of the benchmark doses (BMDLs) are all sufficiently close given the needs
27 of the assessment. Otherwise, the most conservative BMDL should be used as the POD. The benchmark
28 concentrations (BMCLs) from the candidate models differ by more than a factor of three. If the EPA can
29 defend this range as being “sufficiently close,” then its choice of the POD is consistent with the
30 technical guidance; if not, then according to the decision tree, the most conservative (smallest) BMCL
31 should be used as the POD which comes from the log-probit model with lag 15 exposure.

32
33 While not recommending a dogmatic following of the EPA’s *Benchmark Dose Technical Guidance*, the
34 SAB suggests that a thoughtful approach and discussion of model selection, including consideration of
35 biological/epidemiologic plausibility, combined with careful examination of the data, should play
36 important roles along with the AIC in determining the choice of models. Likewise, the fitted Michaelis-
37 Menten model has an upper plateau of 60% LPT incidence, which is lower than the reported prevalence
38 of 85% reported in a study of highly exposed asbestos insulation workers. The Marysville cohort does
39 not support precise estimation of the plateau. Thus, the EPA should consider fixing the plateau level.

40
41 The SAB recommends that model features also should be considered when choosing a model. The SAB
42 suggests examining other exposure metrics besides the simple cumulative exposure, such as time
43 weighting of exposures. The SAB suggests a thoughtful approach may lead to selecting the dichotomous
44 Hill model with the plateau fixed at a literature-based value. In addition, the document uses a 10% Extra
45 Risk (ER) as the benchmark response level (BMR) which is in line with EPA’s *Benchmark Dose*
46 *Technical Guidance* for the analysis of quantal datasets from animal studies. However, according to this

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1 technical guidance, a BMR of 1% ER is typically used for human quantal response data since larger
2 ERs, such as 10%, would often involve upward extrapolation. The authors of the draft document should
3 explain what features of the dataset or outcome variable led them to choose a BMR that is considerably
4 greater than the norm for epidemiological data.

5 6 *Alternative Modeling Approach*

7
8 The SAB agrees that the rationale for performing additional analyses of the full Marysville cohort is
9 scientifically justified: the analysis of the entire cohort increases the number of cases of LPT available
10 for analysis and substantiates the RfC estimated using the subcohort. However, the rationale for the
11 agency's analysis methods is not well justified. The scientific basis for the use of time since first
12 exposure (TSFE) as a covariate is not clear. The SAB also finds the method for incorporating TSFE into
13 the full cohort analysis is not well justified and recommends that the analysis be revised. In the draft
14 document, the EPA uses TSFE as a predictor for the plateau in the Cumulative Normal Michaelis-
15 Menten model. The plateau provides the maximum proportion of the population that would experience
16 LPT given sufficient exposure and time to develop the disease. No biological justification is given for
17 why this maximum proportion would vary with TSFE. The SAB recommends that the EPA replace the
18 Michaelis-Menten model with a dichotomous Hill model that allows the slope to be estimated. The SAB
19 also recommends following the approaches for the subcohort analysis, such as fixing the plateau using
20 literature values.

21 22 *Evaluation of Potential Confounders and Covariates*

23
24 The SAB recommends a revised strategy for evaluation of confounders and covariates. The quantity of
25 interest in the analyses of the Marysville cohort is the POD (BMCL). The evaluation of the various
26 covariates should be made with respect to this target. The SAB suggests that the covariates fall into two
27 classes: *exposure-related covariates* (alternative exposure metrics and TSFE) and *non-exposure-related*
28 *covariates* [age, body mass index (BMI), gender, and smoking status]. The SAB also provides
29 recommended revised strategies for considering these two classes of covariates that follow directly from
30 consideration of the quantity of interest.

31
32 In addition, the SAB recommends the justification for considering BMI as a covariate be briefly
33 explained. TSFE is an important determinant of LPT because individuals' lung tissues exposed at an
34 earlier age might be more susceptible to the damaging effects of asbestos, and because asbestos' effect
35 over time is increasingly damaging. It is correlated with exposure since subjects with the longest TSFE
36 were exposed in the early years of the cohort when exposure levels were higher. The SAB does not
37 agree with the use of the Cumulative Normal Michaelis-Menten model to adjust for TSFE because it
38 makes the assumption that it only affects the plateau which lacks biological support. Instead, the SAB
39 recommends that alternative exposure metrics and approaches be used to account for TSFE. The SAB
40 suggests the discussion on the evidence linking pleural changes and smoking be moved into the body of
41 the report. The SAB does not consider gender to be a serious concern as it is reasonable to assume that
42 females and males have similar risks of LPT.

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1 *Conversion from Cumulative Occupational Exposure to Lifetime Exposure*

2
3 The modeled POD is based on cumulative exposure estimates for the worker cohort examined. The SAB
4 recommends using the full 70-year lifetime when converting cumulative to continuous exposure rather
5 than 60 (70 minus the lag of 10 used for exposure in the POD derivation); i.e., do not correct for the lag
6 of 10 for a 10-year lagged exposure. Lagging does not have real meaning in the context of time to event
7 in this prevalence dataset, and using a divisor of 60 instead of 70 in deriving the RfC is less protective.

8
9 *Selection of Uncertainty Factors*

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

29
30 *Characterization of Uncertainties*

31
32 Overall, the SAB found the discussion on uncertainties in the methodology and approach on the
33 derivation of the RfC to be thorough, detailed and logical. However, the RfC uncertainty assessment can
34 be strengthened. A key consideration of any assessment is whether the estimated RfC is too high to be
35 adequately protective of public health. The SAB recommends that additional work be done to
36 substantiate the RfC estimate through additional sensitivity analyses and discussion of results and
37 insights from other datasets and studies. In sensitivity analyses, EPA can consider alternative exposure
38 metrics (prioritizing residence time weighted metrics and excluding exposures after 1980), methods to
39 fine-tune the RfC estimate from the subcohort (particularly fixing rather than estimating the plateau),
40 and added sensitivity analyses for the full cohort. An additional source of uncertainty—the uncertainty
41 in the RfC due to relying on a single study— also should be considered.

42
43 With respect to exposure assessment, analytical methods and environmental conditions are substantial
44 contributors to uncertainty because of differences between the 1970s and today. PCM was the only
45 method for measuring airborne fiber concentrations until the 1980s. At the 1970's study site, the vast
46 majority of fibers were almost certainly LAA, so PCM's inability to identify asbestos did not create

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1 much uncertainty. Today, even ambient air sampling will yield fiber concentrations that exceed the RfC.
2 Thus, it is important that transmission electron microscopy (TEM) be used to identify and count asbestos
3 fibers longer than 5, 10, and 20 μm in air samples for RfC purposes.
4

5 **Inhalation Unit Risk (IUR)**

6 *Exposure-Response Modeling*

7
8
9 The SAB supports the agency's reliance on the Libby worker subcohort for derivation of IUR because of
10 its focus on good quality exposure data, specific for LAA. However, it is important to acknowledge that
11 this small subcohort may have its own limitations as a basis for modeling exposure-response
12 relationships. When selecting the models with which to characterize exposure-response relationships, a
13 larger population over a lifetime should be considered.
14

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

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

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

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

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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 or
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 thought 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 Kopylev manuscript also provides a figure of 1.39 in Table 3,
35 which is the mean later reported in the EPA document. The EPA method appears to be scientifically
36 supported but is not clearly described. The SAB recommends that this section be expanded to provide a
37 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

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1 more straightforward and transparent treatment of model uncertainty would be to estimate risks using a
2 more complete set of plausible models for the exposure-response relationship, including the Poisson
3 model. This sensitivity analysis would make explicit the implications of these key model choices.
4

5 *Long-Term Research Needs*
6

7 The SAB also provides recommendations for long-term research needs on epidemiology, mode of
8 action, and future development of a transmission electron microscopy method that provides equivalent
9 data to phase contrast microscopy.
10

2. INTRODUCTION

1
2
3 EPA's Office of Research and Development requested the Science Advisory Board (SAB) to review the
4 *Draft IRIS Toxicological Review of Libby Amphibole Asbestos* (hereafter referred to as the draft
5 document). The draft document is based on a comprehensive review of the available scientific literature
6 on the health effects of Libby Amphibole asbestos (LAA), a term used to refer to the mixture of
7 amphibole mineral fibers of varying elemental composition (e.g., winchite, richerite and tremolite) that
8 have been identified in the Rainy Creek complex near Libby, Montana. The draft document provides the
9 scientific and quantitative basis for toxicity values that will be entered into EPA's online Integrated Risk
10 Information System (IRIS) database. Specifically, this draft IRIS assessment provides an overview of
11 sources of exposure to LAA, and characterizes the hazard posed by exposure to LAA for carcinogenicity
12 and noncancer health effects based on the available scientific evidence. The assessment includes the
13 derivation of a chronic inhalation reference concentration (RfC) and an inhalation unit risk (IUR) that
14 can be combined with exposure information in a risk assessment to estimate noncancer hazard and
15 carcinogenic risk, respectively, in humans. The assessment does not address oral exposure to LAA.
16

17 In response to the agency's request, the SAB convened an expert panel (the Libby Amphibole Asbestos
18 Review Panel) to conduct the review. The SAB panel discussed its responses to the EPA's charge
19 questions (see Appendix A) during a February 6-8, 2012 face-to-face meeting and on public
20 teleconferences on May 1, May 8, and July 25, 2012. There were two general charge questions on the
21 organization, presentation, and clarity of the draft document, as well as specific charge questions that
22 focus on: mineralogy and toxicokinetics, hazard assessment of non-cancer and cancer health effects,
23 exposure-response assessment for derivation of an RfC for non-cancer endpoints, cancer weight of
24 evidence classification, mode of action of LAA carcinogenicity, as well as exposure-response
25 assessment for derivation of an IUR for LAA.
26

27 The Executive Summary highlights the SAB's major findings and recommendations. The SAB's full
28 responses to the charge questions are detailed in Section 3 and brief recommendations on long-term
29 research needs are provided in Section 4.
30

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, Fiber Toxicokinetics, 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, e.g., 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.

Noncancer Effect

- The SAB agrees that the selection of radiographic evidence of localized pleural thickening (LPT) in humans is the appropriate critical effect for the derivation of the RfC. LPT is a structural, pathological alteration of the pleura, and is associated with reduced lung function. The presence of LPT itself is a risk factor for other asbestos-related diseases, including asbestosis, mesothelioma and lung cancer, a point that EPA should also include. The SAB identified additional evidence and recommends a more detailed review of the literature to further support this view.
- Section 4.5 describes the radiological changes associated with pleural plaques and diffuse pleural thickening. However, it does not describe bloody pleural effusions and the severity of the pleural diseases associated with exposure to LAA as discussed in Broaddus et al. (2011).

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- 1 • The role of smoking in different asbestos-related diseases and other nonmalignant respiratory
2 diseases (e.g., COPD) could be clarified. Smoking is not considered a risk factor for LPT, but is
3 associated with reduced lung function (FEV1) (and probably also with increased small opacities
4 on chest X-rays).
- 5
- 6 • Although the Marysville subcohort represents the best available population upon which to derive
7 the RfC, the SAB recommends that EPA include any X-ray abnormalities as the outcomes (LPT,
8 diffuse pleural thickening (DPT) or asbestosis) in future analyses. The SAB also recommends
9 that EPA substantiate the results with other cohorts (e.g., the Libby workers cohort, and the
10 Minneapolis exfoliation community cohort).
- 11
- 12 • The SAB found that the various exposure-response models were reasonably well described.
13 However, the SAB would like a clearer description of how the “best” model was chosen. The
14 SAB suggests a thoughtful approach to model selection, one that considers
15 biological/epidemiologic plausibility, combined with careful examination of the data and
16 application of the Akaike Information Criteria (AIC).
- 17

18 *Cancer Effect*

- 19
- 20 • The SAB agrees that the weight of evidence for LAA supports the descriptor “Carcinogenic to
21 Humans by the Inhalation Route.” However, the agency’s position on the weight of evidence of
22 carcinogenicity via exposure to other routes (oral, dermal) should be more clearly stated.
- 23
- 24 • The SAB considers that the agency had been overly constrained by regulatory guidance
25 recommending reliance on model fit as the primary criterion for model selection and would have
26 preferred a broader discussion of biological and epidemiological criteria as well as statistical
27 criteria that were used. There are many competing models that could have been used instead of
28 the Poisson and Cox models which could have provided very different estimates of risk, but
29 these are not discussed.
- 30

31 *Relevance of Other Literature Related to Amphiboles*

- 32
- 33 • The toxicological review does not make clear the relevance of the extensive literature on the
34 health effects of other amphibole fibers. There are numerous publications on the mode of action
35 of other amphiboles, inhalation studies in rodents, and epidemiological studies of populations
36 exposed to amphiboles environmentally. Literature on epidemiological studies of other
37 amphiboles are particularly useful for model selection for dose-response assessment of LAA.

38 *Early Lifestage Susceptibility*

- 39
- 40 • There is inconsistency in the tone of the conclusions in Section 4.7.1.1 (Lifestage Susceptibility)
41 and in Section 6.3.3 (Applications to Early Lifetime and Partial Lifetime Environmental
42 Exposure Scenarios for IUR) to either support or refute early lifestage susceptibility. We
43 recognize that no firm conclusion can be drawn about differential risk of adverse health effects
44 after early life stage exposure to LAA compared to exposure during adulthood, due to the limited
45 and inconclusive studies on other forms of asbestos. However, the limited evidence pointing to

1 excess risk for exposures during childhood that is available needs to be considered when
2 considering a margin of safety.

3 ***Recommendations***

- 4
- 5 • The draft document would benefit from greater usage of graphs and figures to highlight
6 conclusions. A figure describing the two major occupational groups studied, including their time-
7 lines of exposure, would be very helpful.
8
- 9 • Add discussion of known amphibole fiber toxicity determinants [dose, durability, dimension
10 (especially length), surface chemistry].
11
- 12 • Add some additional causes of death (e.g., COPD) to full- and sub-cohorts (Table 5-6, 5-8).
13
- 14 • The section on susceptible populations could be better organized and more succinctly
15 summarized. The section should especially focus on childhood asbestos exposure, the asbestos
16 susceptibility issue most relevant to this EPA document, and probably the topic where there is at
17 least some (albeit limited) data.
18
- 19 • Encourage the continued monitoring of relevant Libby residents for early onset asbestos
20 associated diseases.
21
- 22 • Re-evaluate other models that might be a better fit for determination of early lifestage
23 susceptibility.
24
- 25 • The draft document could be enhanced with quantitative comparison of the environmental
26 exposures that have taken place in other geographic regions of the world (i.e., the Anatolia
27 region of Turkey and Greece) (Sichletidis et al., 2006; Constantopoulos, 2008; Gogou et al.,
28 2009; Carbone et al., 2011; Metintas et al., 2008, 2010, 2012) with the Libby, Montana,
29 community with regard to airborne tremolite. This comparison should include numbers of fibers
30 and fiber size distribution in relation to of health effects.
31
- 32 • The final proposed IUR should be compared with those calculated for other types of amphibole
33 asbestos. A table comparing these results with the results from the earlier 1988 EPA analysis
34 (USEPA, 1988) on asbestos would be helpful.

35 **3.1.2. Additional Literature**

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

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

40
41 Adgate, JL; Cho, SJ; Alexander, BH; Ramachandran, G; Raleigh, KK; Johnson, J; Messing, RB;
42 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, V.C. *et al.* Libby vermiculite exposure and risk of developing asbestos-related lung and pleural
9 diseases. *Curr. Opin. Pulmonary Med.* 18:161-167, 2012. 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, SH.
15 (2012). Long-term response of rats to single intratracheal exposure of libby amphibole or amosite. *J Toxicol*
16 *Environ Health A* 75: 183-200. <http://dx.doi.org/10.1080/15287394.2012.641203>.

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

21
22 Shannahan, JH; Nyska, A; Cesta, M; Schladweiler, MC; Vallant, BD; Ward, WO; Ghio, AJ; Gavett, SH;
23 Kodavanti, UP. (2012a). 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, J.H. *et al.* Transcriptional activation of inflammasome components by Libby amphibole and
28 the role of iron. *Inhalation Toxicology* 24:60-69, 2012. PMID: 22168577

29
30 Webber, J.S., D.J. Blake, T.J. Ward, and J.C. Pfau. 2008. Separation and Characterization of Respirable Amphibole
31 Fibers from Libby, Montana. *Inhal. Toxicol.* 20:8: 733 - 740.

32
33 Zeka A, Gore R, Kriebel D. The two-stage clonal expansion model in occupational cancer
34 epidemiology: results from three cohort studies. *Occupational and Environmental Medicine* 68:618-24.

35 **3.2. Chemical-Specific Charge Questions**

36 **3.2.1. Mineralogy**

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

39
40 Section 2, Geology and Mineralogy of Libby Amphibole Asbestos, provides a discussion of the
41 mineralogical and geological aspects of Libby Amphibole. In general, the SAB finds that this section
42 provides an important foundation for understanding the nature of Libby Amphibole asbestos (LAA) as
43 related to evaluation of potential exposures. There are places where the clarity and accuracy of the
44 section can be improved, and these are detailed below.

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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. However, the SAB recognizes that this level of
7 detail is not typically available for toxicity studies to allow its application to the evaluation of LAA *per*
8 *se*. In general, however, the observed unique aspects of amphibole asbestos support the evaluation of
9 LAA through comparison with other amphiboles based on particle morphology and amphibole
10 designation. Nevertheless, the SAB encourages a rigorous and accurate description of LAA in Section 2,
11 perhaps while noting the potential ambiguities in the use of mineral-species names in other studies.
12

13 Comments on the subsections follow:
14

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

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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 the most
30 biologically potent according to the Stanton-Pott hypothesis. The fact that only a third of the
31 Transmission Electron Microscopy (TEM)-visible Libby fibers were PCM-visible is buried in
32 McDonald et al. (1986). Furthermore, Text Box 2-2 does not adequately contrast the capability
33 of EM versus PCM. EM's capability to yield elemental composition via Energy Dispersive
34 Spectroscopy (EDS) and Wavelength Dispersive X-ray Spectroscopy (WDS) provides
35 information to identify different asbestos types. PCM, in contrast, cannot even determine if the
36 fiber is mineral. Furthermore, the Selected Area Electron Diffraction (SAED) capability of TEM
37 allows determination of crystalline structure, e.g., amphibole versus serpentine. Finally, Box 2-2
38 incorrectly states that scanning electron microscopy (SEM) "produces three-dimensional (3-D)
39 images". Rather, SEM produces 2-D images that reveal surface structure of particles.
40
- 41 • The electron microscopy section on page 2-11 could be clarified. SEM and TEM provide higher
42 magnification to allow better particle morphological analysis. Electron diffraction allows
43 mineralogical assessment. Energy dispersive X-ray analysis allows elemental composition
44 determination, which can corroborate the mineralogical determination. X-ray diffraction (XRD)
45 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 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 that, fortunately, are not included in the well-crafted Section 6 on Major Conclusions in the Characterization of Hazard and Exposure-Response.
 - The authors of the earlier sections, in cleaning up the text, 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 um. 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: (1) on surface fluids drawn onto the mucociliary escalator by surface tension, and (2) 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.

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- 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 tremolite, which is very similar to Libby amphibole. Also, this section should discuss the tremolite inhalation study of Bernstein et al. (2003, 2005) that is cited in Table 4-16, as well as the more recent study by Bernstein et al. (2011) that demonstrated pleural translocation in rats using non-invasive means following airborne amosite asbestos exposure. The study examined animals for up to one year following a short 1-week exposure to amphibole and characterized the size of fibers that were present in parietal pleura. Non-cancer inflammatory pleural changes were demonstrated associated with fiber translocation. This paper shows rapid translocation of fibers to the pleura (at least of rodents) and it should be referenced for completeness on toxicokinetic issues. Furthermore, the results of the various studies cited in this section are almost all very difficult to interpret with respect to the toxic effects that were, or were not, reported, since no information was provided on the key dosimetric factor of fiber dimensions.

3.2.3. Noncancer Health Effects of Libby Amphibole Asbestos

3.2.3.1. Selection of Critical Studies and Effects

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

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

Although the SAB agrees that the Marysville subcohort represents the best population upon which to base the RfC, there was discussion about the need for additional analyses/cohorts to strengthen and support the RfC given this groundbreaking effort. One suggestion is to use the Marysville cohort but include any X-ray abnormalities as the outcome (LPT, DPT, or asbestosis). In addition, cause of death might be assessed for those who died between the two exams. Another suggestion for providing support and perspective to the Marysville findings is to conduct analogous analyses (to the extent the data permit) of pleural abnormalities among the Libby workers cohort (Larson et al., 2012) and among the Minneapolis exfoliation community cohort (Adgate et al., 2011; Alexander et al., 2012). The Libby workers have higher, well characterized occupational exposures compared to the Marysville cohort. The Minneapolis cohort of non-workers generally had estimated exposures at the lower end of the Marysville cohort but included women and children, thus providing a cohort more representative of the general

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1 population. However, because the Minneapolis cohort had estimated, not measured exposures, it would
2 not be suitable for the primary RfC analysis. Similarly, because the Libby workers have both
3 environmental and occupational exposures, this cohort should not be used for primary RfC analysis.
4

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

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

18 While other health endpoints might have been considered candidates for the critical effect for deriving
19 the RfC, such as diffuse pleural thickening and small opacity profusion, the use of LPT is appropriate
20 and well supported. LPT is found at a significantly elevated prevalence in the community of exposed
21 individuals. Localized pleural thickening has the appropriate specificity and is not confounded by
22 cigarette smoking. LPT is physiologically important due to its measurable relationship to altered lung
23 function. LPT is a structural, pathologic alteration of the pleura. Furthermore the findings reported in
24 this section are compatible with the animal data showing tissue injury and inflammation. Additionally,
25 the presence of LPT itself is predictive of risk for other asbestos-related diseases, including asbestosis,
26 mesothelioma and lung cancer, a point that the EPA should include.
27

28 Due to the landmark action of developing an RfC for LAA, the SAB discussed the need for the inclusion
29 of a more detailed review of the literature to support the presence of a relationship between localized
30 pleural thickening and both pathologic and physiologic abnormalities. There is additional literature that
31 addresses and demonstrates the relationship between LPT and reduced lung function that should be
32 included. Published studies suggested by the SAB (Lilis et al., 1991b; Paris et al., 2009; Clin et al.,
33 2011) should be considered and included, along with those referenced in the American Thoracic Society
34 (ATS) Statement entitled, *Diagnosis and Initial Management of Nonmalignant Diseases Related to*
35 *Asbestos: Official Statement of the American Thoracic Society* (ATS, 2004) (Ohlson et al., 1984; 1985;
36 Jarvolm and Sanden, 1986; Hjortsberg et al., 1988; Oliver et al., 1988; Bourbeau et al., 1990; Schwartz
37 et al., 1990; Miller et al., 1992; Van Cleemput et al., 2001; Miller, 2002; Whitehouse, 2004; Sichletidis
38 et al., 2006; Wilken et al., 2011). Consistent with that Statement, it is the view of the SAB that large
39 cohort studies have shown significant reduction in lung function, including diminished diffusing
40 capacity and vital capacity associated with (or in those with) LPT.
41

42 The SAB also suggests that the EPA consider looking at LPT, DPT and small opacity profusion score
43 together as an outcome. There is evidence that LPT is not always the first adverse effect that is detected
44 on chest radiographs, and some individuals with LAA exposure can develop either DPT or increased
45 profusion of small opacities without developing evidence of LPT. Combining outcomes is appropriate

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1 for this policy-oriented analysis since the goal is to define an exposure level below which LAA is
2 unlikely to have adverse health effects.

3
4 **Recommendations:**

- 5
6 • Include a more detailed review of the literature to support the selection of LPT through detailing
7 the studies that show the relationship between localized pleural thickening and both pathologic
8 and physiologic abnormalities, and also risk of other asbestos-related diseases.
- 9 • In addition to LPT, include an analysis that uses all radiographic outcomes (LPT, DPT and small
10 opacities), recognizing this change will have little impact on the current analysis. .

11 **3.2.3.2. Use of Animal and Mechanistic Studies**

12 *Question 3. The database of laboratory animal and mechanistic studies of Libby Amphibole asbestos is*
13 *summarized in the draft assessment (see Section 4.2 and 4.3, details in Appendix D) to inform the*
14 *mechanisms of the biological response to Libby Amphibole asbestos and support the epidemiology*
15 *studies used for derivation of the RfC. Please comment on whether the laboratory animal and*
16 *mechanistic information presented is used appropriately in the draft assessment.*
17

18 The EPA Toxicological Review discusses the different types of minerals present in LAA and it is
19 uncertain how the various components relate to adverse health effects, although it is made clear that
20 tremolite is a highly carcinogenic and profibrogenic amphibole. LAA contains ~6% tremolite and
21 there is clear evidence from human and animal studies that tremolite causes adverse health effects in
22 humans and experimental animals. However, since LAA also contains winchite (84%) and richterite
23 (~11%), it would be prudent to determine whether these mineral forms contribute to the adverse
24 health effects of LAA or whether there are interactive effects of winchite or richterite that modify the
25 toxicity of tremolite. The SAB recommends that this issue be highlighted since it is well-known that
26 tremolite is highly toxic, profibrogenic, and causes malignant mesothelioma (MM). However, the
27 contribution of winchite or richterite to adverse health effects is apparently unknown.

28
29 In general, the laboratory animal studies listed in Tables 4-15 and 4-16 and summarized in Appendix
30 D are appropriate and complete. Laboratory animal studies utilizing various stocks and strains of
31 mice and rats as well as hamsters, by a variety of non-inhalation routes of exposure, have been used
32 to ascertain the potential fibrogenic and carcinogenic potential of the LAA. While inhalation is
33 regarded as the most physiologically relevant means of fiber exposure in animals, there is no
34 published study with this route of fiber administration in experimental animals. However, there has
35 been intratracheal instillation of LAA in short term studies with mice and rats that resulted in airway
36 inflammatory change consistent with earlier changes seen in tremolite-exposed animals. The lack of
37 any inhalation data in rats or mice is an important issue since the deposition of particles and fibers
38 cannot be adequately addressed using intratracheal instillation of a bolus of fibers delivered in
39 aqueous suspension. For example, the development of pleural lesions may be quite different when
40 comparing fibrogenic or carcinogenic fibers or other particles by inhalation versus instillation. While
41 inhalation studies have been conducted with tremolite (e.g., Bernstein et al., 2005), the relative
42 potency of inhaled LAA should be compared to that of tremolite. This could add new information
43 for refining the RfC for LAA.
44

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

17
18 As discussed under a separate section in this SAB review, the inhalation reference concentration
19 (RfC) is intended to define an exposure level at or below which there is unlikely to be any adverse
20 health effects. Given the complexities and limited data available in the literature on both animal and
21 mechanistic studies of LAA, the SAB agrees that a conservative approach that is protective of public
22 health to derive the RfC is appropriate.

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 In environmental toxicology, human epidemiological data supersede animal and other laboratory
31 studies in the identification of a human carcinogen/toxicant. For Libby Amphibole asbestos, the
32 SAB agrees with the EPA that, while there are no concrete laboratory studies that unequivocally
33 demonstrate carcinogenicity of the fiber mix, there are strong epidemiological data that support the
34 notion that LAA fiber is closely linked to cancer incidence in humans under occupational settings.
35 The occupational studies appeared most persuasive at showing dose-related increased risks of lung
36 cancer and mesothelioma among workers exposed by inhalation. However, the number of
37 mesothelioma cases is small. The case series in the community, while supportive, do not provide the
38 same level of evidence for an association or for the strength of the association. Nonetheless, the
39 epidemiologic evidence from the occupational studies does support the choice of descriptor
40 "carcinogenic to humans by the inhalation route" for LAA under the conditions of exposure in those
41 studies.
42

43 On the other hand, the only solid evidence that the LAA is carcinogenic to animals is in hamsters
44 injected intraperitoneally with a single 25-mg dose of the fiber mix, which is not a physiologically

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

11 **3.2.4.2. Mode of Action**

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

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

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

39 **3.2.4.3. Selection of Critical Study and Endpoint**

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

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

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

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

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

37

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1 *Question 4. Mortality from lung tumors and mesothelioma in the Libby worker cohort was selected to*
2 *serve as the basis for the derivation of the IUR. Please comment on whether this selection is*
3 *scientifically supported and clearly described. If a different health endpoint is recommended for*
4 *deriving the IUR, please identify this endpoint and provide scientific support for this choice.*
5

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

10
11 Since determining the cancer outcome from mortality rather than incidence data may have resulted in an
12 undercount of both cancer outcomes, the discussion would benefit from more detail on how the use of
13 incidence data could impact the derived IUR. In addition, the mesothelioma outcome may be
14 underrepresented because the cohort has been followed for 25 to 46 years and lag times from exposure
15 to detectable disease onset range from 15 to greater than 60 years. Mesothelioma also may have been
16 underreported on death certificates. Under-represented outcomes could lead to an underestimated IUR.
17 While there is sufficient information for derivation of the IUR, revisiting derivation of the IUR after
18 additional follow up is warranted. It was recommended at the SAB meeting that additional follow-up of
19 both the occupationally and environmentally exposed populations would be helpful.
20

21 The report mentions laryngeal (n = 2) and ovarian (n = 0) cancer deaths in the text. The International
22 Agency for Research on Cancer (IARC) concluded that there was sufficient evidence in humans that
23 some types of asbestos were causally associated with cancer of the larynx and the ovary (Straif et al.,
24 2009).
25

26 Tables 5-6 and 5-8 are mistitled since the tables include the number of deaths from mesothelioma and
27 lung cancer as well as demographic and exposure data. The titles should either be changed and
28 additional causes of death included in the tables or new tables should be created that focus on the causes
29 of death.
30

31 It also would have been useful to know the other major categories of mortality in this cohort. This could
32 include the numbers of COPD, cardiovascular, colorectal cancer and other cancer deaths.
33

34 It would be helpful to have a clearer comparison of the Libby asbestos risk assessment with other
35 amphibole asbestos cancer risk assessments or reviews, including the earlier EPA assessment in 1986.
36 Have non-U.S. agencies or groups attempted similar quantitative risk assessments? This should be
37 summarized more clearly.
38

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

42 **3.2.4.4. Use of Laboratory Animal and Mechanistic Studies**

43 *Question 5. The database of laboratory animal and mechanistic studies of Libby Amphibole asbestos is*
44 *summarized in this draft assessment (see Section 4.2 and 4.3, details in Appendix D) to inform the*
45 *mechanisms of the biological response to Libby Amphibole asbestos and support the epidemiology*

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1 *studies used for derivation of the IUR. Please comment on the use of laboratory animal and mechanistic*
2 *information in the draft assessment.*
3

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

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

20 **Recommendations:**

- 21
- 22 • Section 4.2 should start with a discussion of the relevance of routes of exposure, and then
23 should proceed to discuss inhalation data, followed by a discussion of data from other, less
24 relevant routes of exposure.
25
- 26 • Areas of needed improvement in the report include: (1) a discussion on known determinants
27 of fiber toxicity; and (2) the differences in fiber size distributions between LAA and other
28 known amphiboles.
29
- 30 • Section 4.6.2.2 should be modified to reflect that there are insufficient data to determine if a
31 mutagenic mode of action for LAA is supported.

32 **3.2.5. Inhalation Reference Concentration (RfC)**

33 **3.2.5.1. Estimates of Human Exposure Concentration**

34 *Question 1. Exposures to Libby Amphibole asbestos for workers in the Marysville, OH facility were*
35 *reconstructed based on industrial hygiene data collected in the facility from 1972 to 1994. Exposures*
36 *from 1957 to 1971 were estimated based on extrapolation from the available industrial hygiene data.*
37 *The information used for the exposure reconstruction was based on employee interviews, court and*
38 *company records, and the expert judgment of the researchers. Is the methodology used for the exposure*
39 *reconstruction reported in Appendix F and the subsequent development of exposure estimates used in*
40 *the analyses scientifically supported and clearly described?*
41

42 The approach described in the Appendix F of the EPA document is detailed and specific. The strengths
43 and weaknesses of the approach are clearly laid out. Large uncertainties are associated with the
44 *unmeasured* pre-1972 exposures: subjectivity of workers' estimating relative concentrations, and

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1 unsupported weighting of Libby/South Carolina fiber concentrations. Hence the report appropriately
2 eliminates this set of estimates and adheres to only measured exposures for its derivation of RfC.
3 Alternatively, the EPA might search for PCM measurements from exfoliation plants during the 1960s
4 and use these for re-examining the pre-1972 exposures.

5
6 The development of cumulative exposure estimates for the workers in a retrospective study has as its
7 goal the estimation of the area under the curve of the plot of each individual worker's annual exposure
8 concentration vs. time (calendar year), producing a summary metric of cumulative fibers/cc-years. In
9 Appendix F of the EPA document, the authors report using the natural-log-transformed exposure data to
10 calculate the geometric mean for the job groups for use in developing the cumulative exposure metric.
11 This approach could introduce bias by decreasing the significance of the highest exposures if the
12 sampling data represent a random sample of the true underlying distribution of exposures. However,
13 most company industrial hygienists historically have focused sampling on evaluating compliance using a
14 methodology that targets the worst case or "most exposed" workers (NIOSH, 1977; Mulhausen and
15 Damiano, 1998). In such a case, use of the mean of the unlogged data, or preferably the minimum
16 variance unbiased estimator (MVUE) of the mean (Attfield and Hewett, 1992), would overestimate the
17 most likely exposure of the average worker. The EPA should re-evaluate the raw exposure data and
18 review pertinent sampling documentation to bolster its use of the geometric mean to represent the job
19 group exposures, rather than an estimate of the arithmetic mean, and consider whether a sensitivity
20 analysis using the MVUE of the mean is warranted in the development of the cumulative exposure
21 metric.

22
23 In the text, there should be a table summarizing the changes in proportion of each type of vermiculite
24 used (South Carolina, Libby and African) at the Marysville plant throughout the time frame represented
25 by the cohort. This section should explicitly discuss the fact that Libby vermiculite usage ended in 1980
26 and that the fiber counts used in the cumulative exposure calculation for the production workers, though
27 small, are generally 1.5 to 6.3 times higher than background. These fibers are presumably from
28 combinations of African/Virginia/South Carolina vermiculite that were used from 1980 to 2000.
29 Likewise, the description of the calculation of the cumulative human equivalent exposure concentration
30 (CHEEC) in section 5.2.3.1 would benefit by addition of a version of the material on page F-19 to
31 clarify the correction factors and breathing rate adjustments made due to extended work hours during
32 some seasons. The approach used has the typical drawbacks of oversimplification of breathing rate (one
33 size fits all) but is consistent with previous EPA approaches.

34
35 The SAB recommends that the EPA consider sensitivity analyses of additional exposure metrics such as:
36 no exposure since 1980 in any cohort members (based on end date of processing of Libby vermiculite),
37 and alternative weighting schemes (particularly ones weighting earlier life exposures more heavily given
38 the importance of time since first exposure, e.g., RTW – residence time weighting). These sections also
39 could be enhanced by showing relationships between the exposure metrics, such as by scatterplots of
40 unlagged CHEEC vs. other measures (separately by cohort) and by adding more explanation about the
41 effects of lagging.

42 **3.2.5.2. Exposure-Response Modeling**

43 *Question 2. Exposure-response modeling was conducted using the incidence of localized pleural*
44 *thickening in workers and cumulative exposure to estimate the point of departure (POD) for derivation*
45 *of the RfC. EPA's estimate of the POD is based upon a Michaelis-Menten model applied to the*

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1 *subcohort of workers examined in 2002-2005 and first exposed to Libby Amphibole asbestos in 1972*
2 *(when measurements of fiber levels in the workplace began) or later with cumulative exposure as the*
3 *explanatory variable. Is the selection of the model scientifically justified and clearly described? Has the*
4 *modeling and the choice of a benchmark response (BMR) for the POD of 10% extra risk of localized*
5 *pleural thickening been clearly described and appropriately conducted according to EPA's Draft*
6 *Benchmark Dose Technical Guidance (U.S. EPA, 2000b)?*
7

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

25 That said, the SAB does not recommend a dogmatic following of the EPA's *Benchmark Dose Technical*
26 *Guidance*. Rather, the SAB recommends that a thoughtful approach to model selection be used,
27 including consideration of biological/epidemiologic plausibility, combined with careful examination of
28 the data and application of the Akaike Information Criteria (AIC). For example, model fit (visual
29 comparison of model predictions to data and/or local smoother estimates from data) in the region of the
30 benchmark response rate (BMR) should play an important role in model selection. Likewise, the fitted
31 Michaelis-Menten model has an upper plateau of 60% LPT incidence, while a study of highly exposed
32 asbestos insulation workers reported a prevalence of 85% (Lilis et al., 1991a). The Marysville cohort
33 does not support precise estimation of the plateau. Thus, EPA should consider fixing the plateau at a
34 level justified by the literature.
35

36 The SAB recommends that model features should also be considered in choosing a model. For example,
37 the dichotomous Hill model is attractive because it allows estimate of an exposure slope parameter,
38 allowing the exposure effect to scale as covariates are added, the exposure metric changed, or the
39 plateau fixed. The SAB also recommends examining other exposure metrics besides the simple
40 cumulative exposure, such as time weighting of exposures. The SAB suggests a thoughtful approach
41 may lead to selecting the dichotomous Hill model with the plateau fixed at a literature-based value.
42

43 The authors explain that their choice of a 10% Extra Risk (ER) as the BMR is in line with the EPA's
44 *Benchmark Dose Technical Guidance*. However, that rate is generally considered to apply specifically to
45 the analysis of quantal datasets from animals studies (which is the context in which it was developed). In
46 the EPA's *Benchmark Dose Technical Guidance*, it is mentioned that a BMR of 1% ER is typically used

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1 for human quantal response data as epidemiologic data that often have greater sensitivities than bioassay
2 data. The authors should explain what features of the dataset or outcome variable led them to choose a
3 BMR that is considerably greater than the norm for epidemiologic data.
4

5 **Recommendations:**
6

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

14 **3.2.5.3. Alternative Modeling Approaches**

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

24 The SAB notes that this question applies to the full Marysville cohort. The SAB agrees that the rationale
25 for performing additional analyses of the full Marysville cohort is scientifically justified, and that the
26 analysis of the entire cohort increases the number of cases of LPT available for analysis and
27 substantiates the RfC estimated using the subcohort. However, the SAB did not find the rationale for the
28 analysis methods to be well justified. First, there was general confusion among the SAB members about
29 the scientific basis of using time since first exposure (TSFE) as a covariate. In particular, what is TSFE
30 supposed to be measuring? Is it intended to be another measure of exposure? There is some suggestion
31 in the draft document that it is a surrogate measure of intensity since people with larger TSFEs would be
32 more likely to have been exposed to higher levels of LAA present during the early time periods. If TSFE
33 is a surrogate of intensity, why did the EPA choose to use it rather than date of first exposure?
34

35 The SAB also finds that the method for incorporating TSFE into the full cohort analysis is not well
36 justified and recommends that the analysis be revised. Currently, the EPA uses TSFE as a predictor for
37 the plateau in the Cumulative Normal Michaelis-Menten model. The plateau provides the maximum
38 proportion of the population that would experience LPT given sufficient exposure and time to develop
39 the disease. No biological justification is given for why this maximum proportion would vary with
40 TSFE. The SAB concludes that a more natural way to incorporate TSFE into the model would be to
41 allow it to affect the rate of change in the probability of LPT; by including it directly in the linear
42 predictor portion of the model alongside cumulative exposure; and/or by using an alternative exposure
43 metric such as residence time weighting (RTW) that more heavily weights exposure in the distant past.
44 The functional form of TSFE could then be selected using standard approaches (e.g., comparing AICs).
45 Since adding TSFE to the model should affect the coefficient of cumulative exposure, the EPA should

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1 replace the Michaelis-Menten model with a dichotomous Hill model which allows the slope to be
2 estimated. Finally, the SAB recommends following the approaches for the subcohort analysis, such as
3 fixing the plateau using literature values as recommended in the response to charge question 2 in Section
4 3.2.5.2 of this report.

5
6 The SAB notes that it may be preferable to base the RfC on an analysis of incidence rather than
7 prevalence data. Because of the nature of the dataset, the Marysville cohort does not support a direct
8 analysis of incidence. While it may be possible to fit an alternative model derived from integration of a
9 plausible incidence model (e.g., see Berry et al., 1979; Berry and Lewinsohn, 1979; Paris et al., 2008),
10 this approach will require a number of untestable assumptions, particularly given the small size of the
11 Marysville cohort. In lieu of conducting such an analysis, the SAB recommends that an explicit
12 acknowledgement be added to the report regarding the implications of various model alternatives.

13 14 **Recommendations:**

- 15
- 16 • Improve the scientific justification for using TSFE in the analysis which includes a clear
17 explanation of its meaning.
- 18 • Revise the full cohort analysis using (a) the dichotomous Hill model, (b) TSFE in the linear
19 predictor alongside cumulative exposure and/or use an alternative exposure metric that explicitly
20 incorporates TSFE, and (c) using the approaches recommended for the subcohort such as a fixed
21 plateau. As appropriate, such analyses should include assessment of the functional form of
22 TSFE.

23 **3.2.5.4. Potential Confounders and Covariates**

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

33
34 The SAB recommends a revised strategy for evaluation of covariates. The target of inference for the
35 analyses of the Marysville cohort is the POD (BMCL). The evaluation of the various covariates should
36 be made with respect to this target of inference. The SAB suggests the covariates fall into two classes:
37 *exposure-related covariates* (alternative exposure metrics and TSFE) and *non-exposure-related*
38 *covariates* (age, body mass index (BMI), gender, and smoking status). We provide recommended
39 revised strategies for considering these two classes of covariates that follow directly from consideration
40 of the target of inference.

41
42 Non-exposure-related covariates: A decision on whether to control for the non-exposure-related
43 covariates should account for how the EPA wishes to determine and apply the RfC. The SAB suggests a
44 BMCL most directly applicable to all members of the general population is most appropriate. This
45 implies that the BMCL should be estimated from a model that includes exposure covariate(s) but that is

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1 otherwise unadjusted. This is the same approach used in the current draft document; only the rationale
2 for the approach is different. As sensitivity analyses, the SAB suggests it would be informative to
3 understand how the BMCL varies conditional on subgroups defined by covariate values (e.g., older
4 males or smokers). Because the Marysville subcohort is a small dataset, it is difficult to conduct this
5 evaluation exclusively in the subcohort. Therefore the SAB suggests EPA use the *full* cohort for the
6 model selection and parameter estimation components of sensitivity analyses incorporating these
7 covariates. For this activity the EPA would use their selected final model after excluding all exposure
8 variables (e.g., the dichotomous Hill model with fixed background, fixed plateau, and after dropping
9 exposure variables). After fitting a model with a specific set of non-exposure-related covariates in the
10 full cohort, one can estimate a “risk score” (i.e., the linear predictor for the non-exposure-related
11 covariates). This risk score would be included as a single term (as either an unscaled offset or scaled by
12 its estimated coefficient) in the subcohort analysis. These analyses can be used to produce a new table of
13 subgroup-specific conditional BMCLs; these values will give some evidence of how the target of
14 inference varies by subgroup. In addition, weighted averages of the conditional BMCLs can be
15 computed to reflect population average BMCLs for specific covariate distributions in target populations.
16

17 Exposure-related covariates: The inclusion of exposure-related covariates in the model is fundamental to
18 the inference. EPA has done excellent preliminary work and the SAB has provided recommendations in
19 Sections 3.2.5.2 and 3.2.5.3 of this report about how to revise the approach. In addition the SAB
20 recommends that the EPA consider taking several further steps. First, alternative exposure metrics
21 should be assessed directly in the subcohort dataset to determine whether they fit the data better. In
22 particular, alternative metrics (such as residence time weighted exposure) that more heavily weight more
23 distant exposure may be more biologically plausible because individuals exposed at an earlier age might
24 be more susceptible to the damaging effects of asbestos. Second, TSFE should be considered for
25 addition to the model. Since TSFE is complete and equally well estimated across all members of the
26 cohort, the full cohort can be used to determine how to model this variable. (Similar to the approach
27 recommended for the sensitivity analyses discussed above, this would be done using the model intended
28 for the subcohort, but omitting exposure variables other than TSFE). Then the linear predictor for TSFE
29 can be added to the subcohort analysis, either as an unscaled offset term or as a scaled covariate. Given
30 biological understanding of the disease process, for models with both estimated exposure and TSFE
31 included, it would be appropriate to report the BMCL conditional on a large TSFE.

32 Additional comments on covariates:
33

- 34 • BMI: In section 5.2.3.3.1., it would be helpful if the justification for considering BMI as a
35 covariate were briefly explained. It is included elsewhere, but readers may have missed it.
- 36 • TSFE:
 - 37 ○ TSFE deserves careful consideration for both biological and dataset-specific reasons. It is
38 an important determinant of LPT both because individuals’ lung tissues exposed at an
39 earlier age might be more susceptible to the damaging effects of asbestos and because
40 asbestos’ effect over time is increasingly damaging. It is correlated with exposure in this
41 dataset since subjects with the longest TSFE were exposed in the early years of the cohort
42 when exposures were higher. It is also more accurately estimated than exposure.
 - 43 ○ The SAB does not agree with the use of the Cumulative Normal Michaelis–Menten
44 model to adjust for TSFE because it makes the biologically implausible assumption that

1 the TSFE only affects the plateau. Instead, the SAB recommends that alternative
2 exposure metrics and approaches be used to account for TSFE.

- 3 • Smoking:
 - 4 ○ Smoking is included in the follow-up by Rohs et al. (2008). However, the ever/never
 - 5 categorization of smoking is much less informative than the pack-year analysis of
 - 6 smoking used in the earlier study by Lockey et al. (1984).
 - 7 ○ There is an important discussion of the evidence linking pleural changes and smoking in
 - 8 footnote 34 on page 5-46. This information could be moved into the body of the report,
 - 9 and amplified somewhat. A table summarizing the relevant studies (irrespective of type
 - 10 of amphibole asbestos) summarizing the evidence regarding the role of smoking would
 - 11 be useful.
- 12 • Gender: There is little discussion of gender, except in places where the number of females is
- 13 listed as too few to analyze in any detail. The SAB did not regard this as a serious concern
- 14 because it is reasonable to assume that females and males have similar probabilities of
- 15 developing LPT.
- 16 • The SAB recommends that a table be included summarizing the results of the various sensitivity
- 17 analyses and how they change the POD.
- 18 • Exposure-dependent censoring: The exposure-dependent censoring discussion is based on results
- 19 from Rohs et al. (2008) that inappropriately separated deceased non-participants from the
- 20 remaining non-participants. Once all non-participants are combined there is no evidence of
- 21 exposure-dependent censoring.

22 **Recommendations:**

- 23 • Revise consideration of covariates to focus on their impact on the target of inference.
 - 24 ○ For non-exposure-related covariates, this only alters the presentation; no additional primary
 - 25 analyses are needed. Sensitivity analyses conditional on subgroups defined by covariates can be
 - 26 added.
 - 27 ○ For exposure-related covariates, additional work is needed to refine the models to consider
 - 28 alternative exposure metrics and inclusion of TSFE. The analyses based on the Cumulative
 - 29 Normal Michaelis-Menten model should be removed from the document.
- 30 • Remove the discussion of exposure-dependent censoring and revise the summary of Rohs et al. to
- 31 combine all non-participants into a single group.

32 **3.2.5.5. Conversion from Cumulative Occupational Exposure to Lifetime Exposure**

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

39
40
41 The SAB agrees that the conversion is clearly explained and follows standard practice. However, the
42 SAB recommends a revision to use the full 70-year lifetime in the conversion rather than 60 (70 minus
43 the lag of 10 used for exposure in the POD derivation). Given that the exposure metric is arbitrarily
44 related to the prevalence data, lagging does not have real meaning in the context of time to event and
45 using a divisor of 60 instead of 70 in deriving the RfC is less protective.

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Recommendation:

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

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_D) 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_D appropriate and clearly described? Please provide the rationale if a change in the UF_D 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_H (human inter-individual diversity) and UF_D (database uncertainty), with a value of 1 for all others. This results in a relatively low value for the resulting RfC (comparable to the 10⁻⁵ lifetime risk level predicted by the cancer unit risk), which is the consequence of a relatively severe and sensitive critical endpoint. The remaining uncertainty is substantial, but not unusual in comparison with other RfC derivations.

In considering the use of these uncertainty factors, it is important to note first that these are defined, and their values in various specific situations specified, in the RfC risk assessment guidelines (U.S. EPA 2002 and others). The uncertainty factors are used to ensure that the RfC meets its definition as a level at which there is reasonable confidence that no adverse health effects will occur. In other words, it is not a minimal effect level and there is no explicit prediction of a dose-response relationship at specific levels above the RfC. Risk managers are tasked with evaluating the significance of exposures above the RfC based on other criteria, including characterization of severity, dose-response, and uncertainty provided in the Toxicological Review. It has also been pointed out that wherever possible the uncertainty factors should be replaced by data-based calculations (for example, toxicokinetic or toxicodynamic models and distributions of population characteristics). While this is sound advice in principle, there are no obvious opportunities to apply this approach in the current case.

Use of a UF_H 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

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1 suggest the possibility of enhanced effects following exposure at younger ages. Overall, it seems
2 unlikely that a departure from the default guideline value of $UF_H = 10$ could be justified within the
3 existing guidelines, but concerns remain for the impact on susceptible subpopulations, especially women
4 and children.

5
6 Selection of a UF_D of 10 is explained and justified based on the limited number of studies of exposure to
7 Libby asbestos (Libby workers, ATSDR community study and Marysville workers) and the lack of
8 evaluation of potentially more sensitive alternative endpoints. This seems reasonable and consistent with
9 the guidelines. In particular, this uncertainty factor would not be reduced even if improved exposure
10 estimates allowed consideration of the full cohorts (or a larger fraction thereof). However, some
11 additional data have recently been published for the community surrounding a Minnesota expansion
12 plant (Adgate et al., 2011; Alexander et al., 2012).

13
14 Although there appears to be a rationale for at least an initial consideration of LAA as a unique material
15 (to provide an unbiased comparison with other amphiboles), the current review has identified very
16 substantial grounds for considering this material as having composition, physical properties, and
17 biological effects that are very similar to those seen for other amphiboles. The most relevant comparison
18 would be to tremolite, since Libby Amphibole is ~6% tremolite, an amphibole that is known to cause
19 cancer and non-cancer effects in human populations. However, it is uncertain how other components of
20 Libby Amphibole (richerite and winchite) interact as a mixture with tremolite to modify toxicity. This
21 consideration of data on other amphiboles is particularly pertinent to discussions of the mode of action,
22 as well as the exposure-response relationships, for Libby Amphibole. In light of this similarity it appears
23 reasonable, and indeed necessary, to at least debate the question of whether the available data on non-
24 cancer health effects of amphiboles are sufficient to mitigate the acknowledged data shortage for Libby
25 Amphibole itself. This consideration of additional data (e.g., the Minnesota cohort and data on other
26 amphiboles) might support a lower value, such as 3, for UF_D . On the other hand, there are substantial
27 remaining uncertainties that are not addressed by these additional data, including those raised by
28 consideration of the severity of the endpoint and the selection of the BMR (see below). It can also be
29 argued that a subchronic-to-chronic uncertainty factor (UF_S) higher than 1 should be used, given that the
30 mean and maximum exposure duration in this study are both well below the lifetime exposure of
31 interest. Thus, the eventual selection of a value of 10 for UF_D , or similar uncertainty spread across
32 several factors, may well be appropriate, but this needs to be evaluated explicitly once all the additional
33 information has been incorporated in the discussion.

34
35 There is a concern that the BMR of 10%, which was chosen for what is undoubtedly a fairly severe
36 endpoint, is not reflected by the choice of a UF_L of 1. It is appropriate to consider either a lower BMR,
37 or the application of a larger uncertainty factor (UF_L) for this endpoint. An argument could be made that
38 some allowance has been made for this concern in the choice of the UF_D , but it is debatable whether this
39 is sufficient, given the other matters to which that UF is also assigned. At the very least, this question
40 deserves more consideration and analysis that it receives in the draft assessment report.

41
42 ***Recommendations:***

- 43
- 44 • Review additional data identified since the draft report was prepared, and in particular the
45 exposure-response relationship for non-cancer endpoints in the Minneapolis community cohort.
 - Determine whether this new analysis is supportive of the existing analysis based on the

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1 Marysville data, and if so whether this warrants reduction of the value of UF_D since the limited
2 data basis for the original analysis has been expanded.

- 3 • Reassess the selection of the BMR, to reflect the severity of the chosen endpoint in the
4 Marysville cohort and the precision available in the data. Whether or not the chosen BMR is
5 changed, present this analysis in the document rather than simply asserting that a “default” value
6 for the BMR was chosen. Similar consideration should be applied to the Minneapolis cohort to
7 provide a valid comparison. This consideration needs to be linked to discussion of the selection
8 of a value for UF_L as noted below.
- 9 • Review additional sources of uncertainty:
 - 10 ○ timescale of cohort coverage, normally addressed by UF_S if this is a significant concern
11 rather than including this as a component of UF_D which already has several major issues to
12 account for.
 - 13 ○ additional uncertainty resulting from target population diversity (including women and
14 children, specific sub-populations of concern not represented in the cohort), and endpoint
15 severity.
- 16 • Consider adjusting UF_D , UF_C or UF_L if necessary to accurately reflect the overall uncertainties in
17 these categories: provide specific justification for the choices made rather than claiming
18 unsupported use of default values.

19 3.2.5.7. Characterization of Uncertainties

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

23
24 In the report there are two sections on uncertainty for the RfC: an application of uncertainty factors
25 following standard EPA practice (Section 5.2.4), and a discussion of the uncertainties in the overall
26 methodology and approach (Section 5.3). This response focuses on the latter. Overall the SAB found the
27 discussion to be thorough, detailed and logical. The document can be improved by harmonizing the full
28 set of uncertainty discussions, including both the discussion of RfC uncertainty and the related
29 discussion of the IUR uncertainty (see the SAB response to question 5 under Section 3.2.6.5 below). In
30 addition, the RfC uncertainty assessment can be strengthened. A key consideration of any assessment is
31 whether the quantity of interest (here the estimated RfC) is too high to be adequately protective of public
32 health. The SAB recommends that additional work be done to substantiate the RfC estimate through
33 additional sensitivity analyses and discussion of results and insights from other datasets [e.g., cause of
34 death for the deceased non-participants in Rohs et al. (2008) and the Minneapolis exfoliation community
35 cohort (Alexander et al., 2012)].

36
37 In considering other studies, the appropriate assumption is that LAA fibers have the same mechanisms
38 of toxicity and quantitative risk relations as that of other asbestos fibers. In sensitivity analyses, consider
39 alternative exposure metrics (prioritizing residence time weighted metrics and excluding exposures after
40 1980), methods to fine-tune the RfC estimate from the subcohort (particularly fixing rather than
41 estimating the plateau, allow the slope parameter to be estimated, use a lifetime of 70 regardless of the
42 exposure metric), and added sensitivity analyses in the full cohort using suggestions from the SAB.
43 Finally, a new uncertainty topic should be added: the uncertainty in the RfC due to relying on a single
44 study.

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1 With respect to exposure assessment, analytical methods and environmental conditions are substantial
2 contributors to uncertainty because of differences between the 1970s and today. As discussed throughout
3 the report, PCM was the only method for measuring airborne fiber concentrations until the 1980's.
4 PCM's limitations are well-detailed in the report: an inability to detect fibers smaller than 0.25 μm , an
5 inability to differentiate asbestos fibers from other fibers, and a limitation to counting only fibers longer
6 than 5 μm . Today, TEM can easily detect and positively identify airborne asbestos of all sizes. But,
7 because the RfC is based on 1970's PCM analyses, the RfC must be implemented in a way that most
8 closely replicates analysis in the 1970's. At the 1970's study site, the vast majority of fibers were almost
9 certainly LAA, so PCM's inability to identify asbestos did not create much uncertainty. Today, even
10 ambient air will yield fiber concentrations that exceed the RfC. The culprit fibers will likely be cellulose
11 fibers from cotton, wood, paper or synthetic fibers, rather than asbestos. Hence, today's PCM counts
12 will be from fibers that are unrelated to the RfC. Thus it is important that TEM be used to identify and
13 count asbestos fibers in air samples for RfC purposes. Finally, Page 5-118, Lines 22-33 of the report
14 discuss the two-fold under-reporting of fibers because of PCM's poorer resolution in the 1970's, 0.44
15 μm versus 0.25 μm today. Because today's PCM analysts have no capability for discriminating fibers >
16 0.44 μm , the need for TEM analysis of samples collected for RfC purposes is even more important. A
17 TEM protocol for PCME fibers wider than 0.44 μm could be easily developed.

18 **Recommendations**

- 21 • Harmonize the uncertainty discussions across the document
- 22 • Add a new uncertainty topic: Uncertainty due to reliance on a single study
- 23 • Substantiate the RfC estimate through
 - 24 ○ Additional sensitivity analyses of the subcohort
 - 25 ○ Discussion of results from other studies
 - 26 ○ Additional sensitivity analysis of the full cohort
- 27 • Use TEM to identify and count asbestos fibers longer than 5, 10, and 20 μm in air samples for
28 RfC purposes

29 **3.2.6. Inhalation Unit Risk (IUR)**

30 **3.2.6.1. Exposure-Response Modeling**

31 *Question 1. Exposure-response modeling was conducted separately for lung cancer and mesothelioma*
32 *mortality. The POD estimates for these endpoints are based upon analysis of the subcohort of workers*
33 *first exposed after 1959 when the exposure data were judged to be better characterized. The exposure-*
34 *response modeling included consideration of a variety of exposure metrics that varied with time and*
35 *incorporated different lag and decay parameters. Based on the results of the exposure-response*
36 *modeling, a lifetable analysis was used to determine the PODs for each type of cancer for the various*
37 *exposure metrics. Have the exposure-response modeling and determination of the PODs from lifetable*
38 *analysis been appropriately conducted and clearly described? If a different approach to exposure-*
39 *response analysis is recommended as the basis for the estimating the IUR, please identify the*
40 *recommended methods and provide a rationale for this choice.*

41
42 In general, the SAB agreed that the EPA clearly described the methods it had selected to conduct the
43 exposure-response modeling for lung cancer and mesothelioma. The risk calculations in the life tables

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1 appeared correct but would benefit from clearer explanations. Some suggestions for clarifications are
2 noted below.

3
4 However, the SAB concludes that the agency was overly constrained by reliance on model fit as the
5 primary criterion for model selection and recommends a broader discussion of biological and
6 epidemiological criteria as well. For the mesothelioma data, for example, the Peto model was
7 disregarded due to a poorer fit than the Poisson model. The results for this analysis are not shown, and
8 given the particular interest in this model, should have been. A parametric survival model (e.g., Weibull)
9 could have also been used to obtain estimates of absolute risk. It would also be appropriate to compare
10 the results of the final model against those from fitting a two stage clonal expansion (TSCE) model. Use
11 of (TSCE) model would allow for a more direct evaluation of, and possibly justification for, age-
12 dependency of the IUR. The Richardson (2008) paper provides a publicly available and transparent
13 approach to application of the TSCE. Ultimately, there are many competing models that could have been
14 used instead of the Poisson and Cox models (e.g., parametric survival models, accelerated failure time
15 models, additive models) that could have provided very different estimates of risk, but they are not
16 discussed.

17
18 As discussed in more detail in individual comments, there exists a base of epidemiologic evidence for
19 mesothelioma that suggests that the lifetime risk of developing the disease increases the earlier in life
20 that exposure is first received. The Peto model (Peto, 1979; Peto et al., 1982) was developed to explain
21 these observations in the empirical data. While the Peto model has been more widely used for risk
22 assessment, most notably in the previous IRIS summary for asbestos, it has also only been formally
23 fitted to data in a limited number of cohorts (HEI-AR, 1991). Ongoing analysis of incidence of
24 mesothelioma appears to be consistent with the exposure-response relationship described in the Peto
25 model. The draft report needs to do a more complete job of justifying why this and other epidemiologic
26 evidence should be excluded as a basis for selection of a plausible model for predicting mesothelioma
27 risk. Chapters 2 and 3, for example, consider toxicological and other evidence developed with exposures
28 to asbestos that are not strictly LAA. Did EPA have a reason to believe that the cohorts used in the
29 development of the Nicholson/Peto model, and the exposures they experienced, were so
30 unrepresentative of the LAA exposures that they should be assumed to provide no information about the
31 time course of the development of disease?

32
33 The SAB recognizes that the agency's effort to focus on good quality exposures specific to LAA has led
34 to reliance solely on the Libby worker subcohort. This rationale is understandable but at the same time,
35 it is important to acknowledge that this small subcohort may have its own limitations as a basis for
36 modeling exposure-response relationships for a larger population over a lifetime. As a sensitivity
37 analysis to evaluate the potential impact of omitting the Libby workers hired before 1959, the SAB
38 recommends analyzing the entire Libby cohort using interval statistics (Nguyen et al 2012; Manski
39 2003; inter alia) or other traditional approaches for data censoring in predictors (cf. Küchenhoff et al.,
40 2007). It is inappropriate to use midpoint substitution (as described in section 5.4.6.1.2) that assumes
41 poorly measured or missing predictors have some constant value. Interval statistics and traditional
42 censoring approaches to measurement uncertainty would, in essence, replace point values with interval
43 ranges. When the intervals are narrow, as they might be for 21% of the early hires for which jobs titles
44 are available, there might be a good deal of recoverable information present. When the intervals are
45 much wider, there would be accordingly less information. Whatever empirical information may be
46 present, it is worth evaluating whether its inclusion is better than leaving out the data entirely, which in

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1 principle amounts to replacing them with intervals that are completely vacuous, from zero to infinity.
2 This approach can produce an interval range for the final outputs, which would provide the explicit
3 quantitative uncertainty statement as recommended by previous National Academy of Science reviews.
4

5 The SAB recognizes that the agency did conduct sensitivity analyses with several analyses of the Libby
6 cohort data, including those that used different models (Tables 5-20 for lung cancer and 5-21 for
7 mesothelioma). A limitation of these analyses is that they all rely on the assumption that the effect of
8 exposure can be modeled as a function of cumulative dose. This assumption is consistent with the
9 agency's *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005), which states that "unless there is
10 evidence to the contrary in a particular case, the cumulative dose received over a lifetime, expressed as
11 an average daily exposure prorated over a lifetime, is recommended as appropriate measure of exposure
12 to a carcinogen." They therefore do not address the fundamental question about whether any one model
13 can or should be assumed to represent the exposure-response relationship for LAA. Therefore, one
14 cannot be confident that the "true" exposure-response relationship for LAA is really "accounted for" by
15 use of the upper confidence limit (UCL) on the slope (per fiber/cc) or, ultimately, the combined IUR
16 from mesothelioma and lung-cancer mortality (see related discussion in response to question 3 and 5 in
17 Section 3.2.5).
18

19 This issue is of particular concern for the estimation of mesothelioma risks from partial lifetime
20 exposures where risk is essentially assumed to be independent of when in the course of a lifetime
21 exposure occurs. For example, one year of exposure to a given concentration in childhood yields the
22 same lifetime average daily dose as one year of the same exposure in adulthood. This assumption is not
23 consistent with the relevant body of evidence on the development of asbestos related disease. Therefore,
24 there is some probability — not well characterized — that this approach underestimates the relative
25 effect of early exposure, but exaggerates the effect of exposure later in life.
26

27 ***Recommendations:***
28

- 29 • Expand the discussion of model selection to explain the reliance on model fit criteria for model
30 selection. In particular, why should the broader epidemiologic evidence on the time course of
31 disease not argue at least for the presentation of more than one statistical model?
- 32 • Provide in an appendix the details of the Nicholson/Peto model fit for which the text currently
33 states "data not shown."
- 34 • Present the fit to data graphically for both the main models and for a broader range of models.
35 This step would provide a more thorough and transparent view of fit, particularly in the region of
36 the BMR, than is allowed by examining summary statistical values alone.
- 37 • Allow evaluation of the time dependence of disease by providing tabulations of mesothelioma
38 mortality rates and lung cancer SMRs by time since first exposure, duration of exposure and
39 period of first exposure (for both the full and sub-cohorts of Libby workers).
- 40 • Consider developing an ancillary analysis of the full Libby data set, including hires before 1959,
41 using interval statistics or other traditional censoring methods (not simple midpoint substitution).
- 42 • Consider adding a footnote for assumptions made in the calculation of the final IUR.
43

44 ***Clarifications requested:***
45

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- 1 • Poisson regression analyses: the mathematical form of the regression function should be given,
2 and discussion of whether the potential for over-dispersion was assessed.
- 3 • Cox proportional hazards modeling: the reasons should be given for not conducting a Bayesian
4 analysis as was done for the Poisson regression model for mesothelioma.
- 5 • Life-table analysis: the method used to estimate the hazard function for the exposed population
6 should be clearly spelled out in the text. Was it based on a nonparametric estimate of the baseline
7 hazard from the sub-cohort? Given that the SEER data were used to calculate the background
8 incidence of lung cancer, it would seem more appropriate to use those data to estimate the
9 baseline hazard and then to use the regression coefficient obtained from the Cox model applied
10 to the sub-cohort data to obtain the hazard of the exposed group. Thus, the reasons for not using
11 the SEER data to estimate the baseline hazard should be explained.

12 **3.2.6.2. Potential Confounding by Smoking**

13 *Question 2. Smoking is a strong independent risk factor for lung cancer and may be an important*
14 *confounder of the lung cancer mortality analysis. Data on individual smoking habits and history were*
15 *largely missing and could not be used to control for potential confounding in regression analyses.*
16 *However, EPA used three approaches to evaluate the confounding issue, including restriction of the*
17 *cohort and two analytic evaluations of the potential for confounding by smoking (see Section 5.4.3.6.5).*
18 *Please comment on whether the methods and analyses are clearly presented and scientifically justified.*
19 *If additional analyses are recommended, please identify the methods and scientific rationale.*
20

21 The SAB recognizes the challenges in controlling for smoking given the lack of data on smoking
22 histories for the cohort. The agency has taken reasonable steps to identify the potential for confounding
23 using independent approaches. However, statements in the document (on p. 5-96 and again on p. 5-127)
24 that— because the proportional hazards assumption is satisfied in the subcohort— there is no evidence of
25 confounding by smoking, are too strong. Reaching this conclusion requires some strong assumptions,
26 including one that the decline in smoking prevalence observed in the general U.S. population also
27 occurred in the Libby cohort.
28

29 The agency's use of the Richardson (2010) method for exploring possible confounding for smoking was
30 appropriate. However, the conclusion that there is no evidence for confounding by smoking relies more
31 heavily on the p -values, which are marginally non-significant, than it needs to. More compelling is the
32 observation of a negative association with COPD. However, the fact that the coefficients for exposure in
33 the COPD Cox models were negative is strong evidence against positive confounding; smoking is
34 positively related to COPD risk and thus if positive confounding is occurring, then one would also
35 expect the relationship between asbestos exposure and COPD risk to be positive. It is possible, however,
36 that negative confounding is occurring in which case the risk of lung cancer associated with asbestos
37 exposure would be understated.
38

39 **Recommendations:**

- 40
- 41 • The numbers of COPD deaths (n) in the sub-cohort that were the basis for the analysis should be
42 presented in the text.
- 43 • The statements about the evidence against confounding by smoking given by restriction of the
44 cohort should be qualified by the assumptions required to justify them, or deleted.
- 45 • The SAB had no recommendations for further analyses.

- Minor detail: 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.

3.2.6.3. Quantification of Inhalation Unit Risk

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

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

Recommendation:

The EPA should acknowledge that the assumption of independence is a theoretical limitation of the analysis and should provide a fuller justification for this assumption. EPA may cite the (2005) cancer risk assessment guidelines and the NRC (1994) analysis as suggesting the impact of issue is likely to be relatively small. As a sensitivity analysis, the EPA should consider quantitatively accounting for dependence in the risks of mesothelioma and lung cancer mortality either using a method which models the dependence explicitly, or a bounding study that evaluates the numerical consequences of the assumption of independence

3.2.6.4. Adjustment for Mesothelioma Mortality Under-ascertainment

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

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1 The number of mesothelioma deaths was adjusted for under-ascertainment stemming from inadequate
2 coding used in death certificates. The procedure used is not described in any detail but can be found in
3 the Kopylev et al. (2011) reference. A total of 18 mesotheliomas were observed in the Libby cohort
4 from 1980 to 2006. The estimated number of 24 mesotheliomas was obtained after using a Monte Carlo
5 analysis. The ratio of 24 to 18 yields the median of 1.33. The Kopylev manuscript also provides a figure
6 of 1.39 in Table 3, which is the mean later reported in the EPA report. The EPA method appears to be
7 scientifically supported but is not clearly described. This section should be expanded and a much more
8 detailed statement of how the numbers were arrived at should be provided.

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

16 **3.2.6.5. Characterization of Uncertainties**

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

20
21 The SAB commends the EPA for summarizing (in Section 5.4.6.1 of the draft document) the many
22 sources of uncertainty considered in the course of this document and evaluating at least qualitatively,
23 and sometimes quantitatively, the direction and magnitude of the likely impact of each source of
24 uncertainty. This is a welcome advance in the discussion of uncertainties for IRIS toxicity reviews.

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

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

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

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1
2 As noted in response to question 1 in Section 3.2.6.1 above, the SAB identified that model uncertainty is
3 an important source of uncertainty that might well not be accounted for by using the 95% UCL on the
4 IUR and the combined IUR — or at least that had not been represented by the sensitivity analyses
5 provided.

6
7 **Recommendations:**

- 8
9 • The SAB recommends that a more straightforward and transparent treatment of model uncertainty
10 would be to estimate risks using a more complete set of plausible models for the exposure- response
11 relationship (discussed in response to question 1 in Section 3.2.6.1), including the Poisson models.
12 This sensitivity analysis would make the implications of these key model choices explicit.
13
14 • The SAB recommends that, as an initial step in conducting an integrated and comprehensive
15 uncertainty analysis, the agency provide a tabular presentation and narrative evaluation of the IUR
16 estimates based on a reasonable range of data selections (e.g., all or part of the earlier hires as well as
17 the “preferred” subcohort), model forms and input assumptions (as discussed, illustratively, in the
18 response to question 1 in Section 3.2.5. These input assumptions should include inter alia exposure
19 metrics and externally defined parameters, as discussed in the response to question 1 in Section
20 3.2.5. As noted in the current cancer risk assessment guidelines (EPA, 2005, page 3-29):

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

27 The preferred model or models will be selected as a judgment based on quality of fit, plausibility
28 (including consistency with mechanistic data insofar as this is available), and public health protection.
29 EPA (2005) provides a number of suggestions for comparing and synthesizing multiple estimates
30 (Section 3.3.5, page 3-24 *et seq.*). Their suggestions (primarily addressing animal data, but equally
31 applicable in principle to epidemiological results), include:

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

39
40 Ideally, different estimates might be quantitatively incorporated in an overall estimate by modeling the
41 joint distributions of the major sources of uncertainty it has identified in its evaluation. However, the
42 SAB recognizes the challenge of conducting such an analysis, and notes that simplified approaches such
43 as using the geometric mean of several consistent and plausible upper bound estimates, or selection of a
44 single preferred value based on health protection are frequently used in practice.
45

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- 1 There is uncertainty associated with a composite IUR for mesothelioma and lung cancer, because it
- 2 relies on an assumption of independence of the endpoints. Other methods that do not require this
- 3 assumption should be explored (See response to question 1 in Section 3.2.6.1)
- 4

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 and residents of Libby and 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.

None of the above suggestions for additional research should delay the current clean-up activities of the EPA at Libby. However, if new information is obtained, a revision of the EPA document pertinent to LAA exposure could be considered.

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 (i.e., mesothelioma). Critical genotoxicity studies including mutagenesis and chromosomal aberration studies have not been reported/ examined with LAA. Inhalation studies in animal models that can provide both quantitative as well as mechanistic insight should be included.

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 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.

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1 Other areas of analysis may include but not limited to differences between PCM reticule areas and TEM
2 grid opening areas that create biases, TEM rules with regard to fibers obscured by grid bars which create
3 positive bias in TEM results, measurement of obscured, complex arrangements of fibers by TEM that
4 differ from PCM counts, TEM measurement errors associated with fibers of various widths, differences
5 between laboratories with interpretation of TEM counting rules, differences in
6 magnification/orientations used for analysis, and other issues which create variation between analyses.
7

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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 asbestos¹.

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)² and numerous guidelines and technical reports published by EPA (see Section 1 of the assessment)³. Specifically, this draft IRIS assessment provides an overview of sources of exposure to Libby Amphibole asbestos, characterizes the hazard posed by

¹ 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.

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

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

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1 exposure to Libby Amphibole asbestos for carcinogenicity and noncancer health effects based on the
2 available scientific evidence, and presents a qualitative and quantitative health assessment, including the
3 derivations of a chronic inhalation reference concentration (RfC) and an inhalation unit risk (IUR) that
4 can be combined with exposure information in a risk assessment to estimate noncancer hazard and
5 carcinogenic risk, respectively, in humans. The assessment does not address oral exposure to Libby
6 Amphibole asbestos.

8 **Charge Questions**

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

17 **General Charge Questions:**

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

25 **Chemical-Specific Charge Questions:**

27 I. Background

28 A. Mineralogy and Toxicokinetics

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

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

40 II. Hazard Identification of Libby Amphibole Asbestos

41 **A. Noncancer Health Effects:**

42 1. An occupational cohort of workers in a Marysville, OH facility exposed to Libby Amphibole asbestos
43 (Lockey et al., 1984; Rohs et al., 2008) was selected as the basis for the derivation of the reference
44 concentration (RfC). Please comment on whether the selection of this study population is scientifically

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1 supported and clearly described. If a different study population is recommended as the basis for the RfC,
2 please identify this study and provide scientific support for this choice.

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

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

17 18 **B. Carcinogenicity:**

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

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

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

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

42
43 5. The database of laboratory animal and mechanistic studies of Libby Amphibole asbestos is
44 summarized in this draft assessment (see Section 4.2 and 4.3, details in Appendix D) to inform the
45 mechanisms of the biological response to Libby Amphibole asbestos and support the epidemiology

1 studies used for derivation of the IUR. Please comment on the use of laboratory animal and mechanistic
2 information in the draft assessment.

3
4 III. Exposure-Response Assessment

5 **A. Inhalation Reference Concentration (RfC):**

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

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

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

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

42
43 5. The modeled POD estimate is based on cumulative exposure estimates for the worker cohort
44 examined. For the derivation of the RfC, this cumulative exposure is prorated over the period of
45 environmental exposure (lifetime or shorter duration chronic exposure when appropriate). The RfC is

1 provided in units of continuous air concentration. Is the basis of this conversion clearly explained and
2 scientifically justified?

3
4 6. Please comment on the rationale for the selection of the uncertainty factors (UFs) applied to the POD
5 for the derivation of the RfC. Are the UFs appropriate based on A Review of the Reference Dose and
6 Reference Concentration Processes (U.S. EPA, 2002; Section 4.4.5) and clearly described? If changes
7 to the selected UFs are proposed, please identify and provide scientific support. Specifically, please
8 comment on the rationale for the selection of the database uncertainty factor (UFD) of 10 applied in the
9 derivation of the RfC. The database uncertainty factor accounts for the lack of data on effects other than
10 in the respiratory system, including other effects observed in community and laboratory animal studies
11 (cardiovascular disease and autoimmune effects) that have not been well-studied (See Section 5.2.3 of
12 the Toxicological Review); and lack of health data assessed at later time points. Is the rationale for the
13 UFD appropriate and clearly described? Please provide the rationale if a change in the UFD is
14 proposed.

15
16 7. Please comment on whether the document adequately describes the uncertainties and limitations in
17 the methodology used to derive the RfC and whether this information is presented in a transparent
18 manner.

19
20 **B. Inhalation Unit Risk (IUR):**

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

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

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

This draft is work in progress, does not reflect consensus advice or recommendations, has not been reviewed by the chartered SAB, and does not represent EPA policy.

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

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