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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 of varying elemental composition that have been identified in the Rainy Creek complex near Libby, MT. In response to ORD's request, the SAB convened an expert panel to conduct this review. The SAB Panel 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 have provided 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. SAB major comments and recommendations are provided below:

- The SAB supports the derivation of an inhalation reference concentration (RfC) based on radiographic evidence of localized pleural thickening in an occupationally exposed Marysville OH cohort. The SAB finds the selection of the subcohort of 118 workers who began work in 1972 or later when exposure data were available and who had X-ray exams, with the full cohort of 434 workers used for confirmatory analyses to be clear and reasonable. However, the SAB finds that additional analyses are needed to strengthen and support the RfC. The SAB recommends that EPA include any X-ray abnormalities (localized pleural thickening, diffuse pleural thickening, or asbestosis) as the health outcome. The SAB also recommends that EPA conduct confirmatory analyses (to the

- 1 extent data permit) of pleural abnormalities using the recently published studies on the
2 Libby workers cohort and the Minneapolis Exfoliation community cohort.
- 3 • The SAB agrees that localized pleural thickening has the appropriate specificity, and has
4 a measurable relationship to altered lung function, and is a structural pathologic
5 alteration of the pleura. The presence of localized pleural thickening itself is predictive
6 of risk for other asbestos-related diseases, including asbestosis, mesothelioma and lung
7 cancer. The SAB has identified and provided the EPA with additional references and
8 recommends that the agency to conduct a more detailed review of the literature to further
9 support this conclusion.
 - 10 • For exposure-response modeling of non-cancer endpoints, the SAB recommends that a
11 clearer description be provided of how the “best” model was chosen. The SAB also
12 recommends examining other exposure metrics besides the simple cumulative exposure,
13 such as time weighting of exposures. In addition, more justification is needed for the
14 selection of 10% extra risk as the benchmark response which is not consistent with
15 EPA’s guideline for epidemiological data.
 - 16 • A composite uncertainty factor of 100 was applied to the point of departure to obtain the
17 RfC. The SAB supports the intraspecies uncertainty factor of 10 to account for human
18 variability and sensitive subpopulations. However, the SAB recommends that the EPA
19 consider additional data and analysis for the application of a database uncertainty factor
20 of 10.
 - 21 • The SAB agrees that the weight of evidence for LAA supports the descriptor
22 “Carcinogenic to Humans by the Inhalation Route”, in accordance with EPA’s
23 *Guidelines for Carcinogen Risk Assessment*. The SABs also supports the EPA’s
24 conclusion that there is insufficient information to identify the mode of carcinogenic
25 action of LAA, and therefore the default linear extrapolation at low doses is appropriate.
 - 26 • The SAB supports the selection of the Libby worker cohort for the derivation of the
27 inhalation unit risk (IUR) and agrees that the use of the subcohort post 1959 for
28 quantification is reasonable due to the lack of exposure information for many of the
29 earlier workers. The SAB finds the use of lung cancer and mesothelioma as endpoints to
30 be appropriate for the derivation of the IUR. However, the SAB recommends a more
31 detailed discussion on how the use of mortality data rather than incidence data may have
32 resulted in an undercount of both cancer outcomes.
 - 33 • The SAB agrees that the agency clearly described the methods they selected to conduct
34 the exposure-response modeling for lung cancer and mesothelioma. However, the SAB
35 suggests that the agency provide a broader justification for its choice of statistical models
36 to characterize the exposure response function. The SAB recommends that the Agency

1 evaluate the time dependence of disease by providing tabulation of mesothelioma
2 mortality rates and lung cancer standardized mortality ratios by time since first exposure,
3 duration of exposure, and period of first exposure for both the full and subcohort.

- 4 • There are several competing models- Weibull, and the two stage clonal expansion
5 (TSCE) - that could have been used instead of or in addition to the Poisson and Cox
6 models that might have provided very different estimates of risk, but these are not
7 discussed in the document. Use of the TSCE model, for example, could allow for a more
8 direct evaluation of, and possibly justification for, age-dependency of the IUR.
- 9 • The SAB believes the agency has been overly constrained by reliance on model fit
10 statistics as the primary criterion for model selection. The SAB recommends graphical
11 display of the fit to the data for both the main models and a broader range of models in
12 the draft document to provide a more complete and transparent view of model fit.
- 13 • The EPA has summarized many sources of uncertainty, sometimes quantitatively, as well
14 as the direction and magnitude of the likely impact of each source of uncertainty.
15 However, the SAB identifies an important source of uncertainty, namely, model
16 uncertainty, that might not be accounted for in the use of the 95% upper confidence limit
17 on the inhalation unit risk (IUR) and the combined IUR. The SAB recommends that a
18 more straightforward and transparent treatment of model uncertainty would be to
19 estimate risks using a more complete set of plausible models for the exposure-response
20 relationship, including the Cox and Poisson models. This sensitivity analysis, while not a
21 full uncertainty analysis, would make explicit the implications of these key model
22 choices.

23 The SAB appreciates the opportunity to provide the EPA with advice on this important
24 subject. The SAB urges the agency to move expeditiously to finalize this IRIS document
25 for Libby Amphibole Asbestos. We look forward to receiving the agency's response.

26
27 Sincerely,
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This draft is work in progress, does not reflect consensus advice or recommendations, has not reviewed by the chartered SAB, and does not represent EPA policy.

NOTICE

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This report has been written as part of the activities of the EPA Science Advisory Board, a public advisory committee providing extramural scientific information and advice to the Administrator and other officials of the Environmental Protection Agency. The Board is structured to provide balanced, expert assessment of scientific matters related to problems facing the Agency. This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not necessarily represent the views and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of the Federal government, nor does mention of trade names or commercial products constitute a recommendation for use.

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Abbreviations and Acronyms

AIC	Akaike Information Criteria
ADAF	age-dependent adjustment factor
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
EDS	Energy Dispersive Spectroscopy
EPA	Environmental Protection Agency
FEV1	forced expiratory volume in one second
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LAA	Libby Amphibole asbestos
LOAEL	Lowest Adverse Effect Level
MCMC	Markov Chain Monte Carlo
MOA	mode of action
NCI	National Cancer Institute
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
SMR	standardized mortality ratio
SIR	standardized incidence ratio
TEM	transmission electron microscopy
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 deliberated during a February 6-8, 2012 face-to-face meeting on responses 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 gap between the mineralogical detail embodied in the definition of mineral species and the detail available relative to specific exposures at Libby, MT. 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 this section, 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 shorten and simplify the text by limiting 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, clearance and translocation pathways, and health risks. Literature on risks associated with exposures to chrysotile should be excluded from this draft document. There also are some notable mis-statements 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 (e.g., Lippmann,2009; Mossman et al.,2011) 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 OH cohort for development of the RfC. The SAB finds the selection of the subcohort for the main analysis (118 workers who began work in 1972 or later when exposure data was available and who had X-rays from the 2002-2005 exam), with the full cohort of 434 workers used for confirmatory analysis to be clear and reasonable. However, the SAB

1 believes additional analyses/cohorts are needed to strengthen and support the RfC. The SAB suggests
2 that EPA include any X-ray abnormalities as the outcome (localized pleural thickening (LPT), diffuse
3 pleural thickening (DPT), or asbestosis). The SAB also suggests that the EPA conduct analogous
4 analyses (to the extent the data permit) of pleural abnormalities among the Libby workers cohort
5 (Larson et al.,2012), and the Minneapolis Exfoliation Community cohort (Adgate et al.,2011; Alexander
6 et al.,2012).

7
8 The SAB agrees that the radiographic evidence of localized pleural thickening (LPT) in humans is the
9 appropriate adverse critical effect for the derivation of the RfC. LPT has the appropriate specificity and
10 is not confounded by cigarette smoking. It is physiologically important due to its measurable
11 relationship to altered lung function, and is a structural, pathologic alteration of the pleura. The reported
12 findings are compatible with the animal data showing tissue injury and inflammation. Moreover, the
13 presence of LPT itself is predictive of risk for other asbestos-related diseases, including asbestosis,
14 mesothelioma and lung cancer, a point that the EPA should include as well. However, the SAB has
15 identified additional relevant publications and a more detailed review of the literature is needed to
16 further 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 the LA. While inhalation is regarded as the most physiologically relevant mean of fiber
24 exposure in animals, there is no published study using this route of exposure in experimental animals.
25 Therefore, the deposition of particles and fibers cannot be adequately addressed. However, inhalation
26 studies have been conducted with tremolite. The relative potency of inhaled LAA should be compared
27 with that of tremolite to add new information for refining the RfC for LAA.

28
29 Limited mechanistic studies using *in vitro* assay systems have utilized non-specific endpoints (e.g., pro-
30 inflammatory cytokines, enzyme release and oxidative stress markers), and will probably not shed much
31 light on the mechanisms of LAA-induced disease.

32 **Carcinogenicity**

33 *Weight of Evidence Characterization*

34
35
36
37 The SAB agrees that the weight of evidence for LAA supports the descriptor “Carcinogenic to Humans
38 by the Inhalation Route”, in accordance with EPA’s *Guidelines for Carcinogen Risk Assessment*
39 (USEPA,2005). The occupational studies showed dose-related increased risks of lung cancer and
40 mesothelioma among workers exposed by inhalation, although the numbers of cases are small,
41 particularly in the sub-cohort used from the Marysville, Ohio plant that had lower estimated levels of
42 exposure. The case series in the community, while supportive, does not provide the same level of
43 evidence for an association, or for the strength of the association. Effects from short term intra-tracheal
44 instillation studies in mice and rats include altered gene expression, collagen induction, and
45 inflammatory response, and are consistent with the early-stage pathological change induced by other

1 amphibole fibers. The EPA also has provided supporting evidence of the carcinogenic potential of LAA
2 from studies with tremolite fibers, in light of its 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 of LAA based on laboratory studies
7 is weak. The SAB views the mode of action of LA as complex and supports the EPA's conclusion that
8 there is insufficient information to identify the mode of carcinogenic action of LAA, and that the default
9 linear extrapolation at low doses is appropriate as a policy choice.

10
11 *Selection of Critical Study and Endpoint*

12
13 The SAB agrees that the selection of the Libby cohort for the derivation of the inhalation unit risk (IUR)
14 is scientifically supported and clearly described. This cohort has been studied thoroughly previously,
15 with detailed work histories and a job exposure matrix. This cohort had elevated asbestos exposure, a
16 wide range of measurements of asbestos exposure, and available cancer mortality data. Limitations of
17 this cohort include limited smoking information, and the endpoints of mortality based on death
18 certificates could undercount cancer endpoints, especially mesothelioma. The study population may not
19 be representative of the larger population since most of its members are white males exposed as adults,
20 and contains more cigarette smokers than the larger population.

21
22 The SAB finds the use of the subcohort post 1959 is reasonable due to the lack of exposure information
23 in many of the earlier workers: 706 out of 991 workers hired before 1960 had all department and job
24 assignments listed as unknown.

25
26 The SAB agrees that lung cancer and mesothelioma should be used as endpoints for derivation of the
27 IUR. Since determining the cancer outcome from mortality rather than incidence data may have resulted
28 in an undercount of both cancer outcomes, the SAB recommends more detailed discussion on how the
29 use of mortality data could impact the derived IUR. It also would have been useful to know other major
30 categories of mortality in this cohort.

31
32 *Use of Laboratory Animal and Mechanistic Studies*

33
34 The SAB agrees that the database of laboratory animal and mechanistic studies pertaining to LA is
35 appropriately presented for support of the analysis of the human effects observed. However, the SAB
36 finds the document deficient in not citing all that is known about the dimensions of the administered
37 fibers, as it is now widely accepted that differences in biological potency among the various amphibole
38 fiber types are due primarily to differences in dimensions, especially in their fiber length distributions.
39 The SAB also recommends that Section 4.6.2.2 be modified to reflect that there are insufficient data to
40 support the claim that the weight of evidence does not support mutagenic mode of action for LA.

41
42 **Inhalation Reference Concentration (RfC)**

43
44 *Estimates of Human Exposure Concentration*

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

8 For modeling of human exposure concentrations, the draft document uses natural-log-transformed
9 exposure data. Log transformation creates its own bias by decreasing the significance of the highest
10 exposures. Since the RfC is based on the transformed data, future use of the RfC at a given site should
11 be based on the natural-log-transformed mean of all exposure measurements from that site. The SAB
12 recommends that the EPA consider sensitivity analyses of additional exposure metrics, such as no
13 exposure since 1980 in any cohort members, and alternative weighting schemes (e.g., residence time
14 weighting).
15

16 *Exposure Response Modeling*

17

18 The SAB recommends that the document provide a clearer description of how the “best” model was
19 chosen. The SAB finds that the draft document does not follow EPA’s *Draft Benchmark Dose Technical*
20 *Guidance* (USEPA, 2001), which states the point of departure (POD) from the model with the smallest
21 AIC should be selected if, among models that adequately fit the data, the lower 95% confidence limit of
22 the benchmark dose (BMDL)s are all within a factor of three. Otherwise, the most conservative BMDL
23 should be used as the POD. If the draft document were to follow EPA’s draft technical guidance, the
24 smallest lower 95% confidence limit of the benchmark concentration (BMCL) should come from the
25 log-probit model with lag 15 exposure. Thus, the document needs a clearer description of why the
26 Michaelis-Menten model was chosen as the “best” model.
27

28 While not recommending a dogmatic following of the EPA’s *Draft Benchmark Dose Technical*
29 *Guidance*, the SAB suggests that a thoughtful approach and discussion of model selection, including
30 consideration of biological/epidemiologic plausibility, combined with careful examination of the data,
31 should play an important role along with the AIC in determining the choice of models. Likewise, the
32 fitted Michaelis-Menten model has an upper plateau of 60% LPT incidence, which is lower than the
33 reported prevalence of 85% reported in a study of highly exposed asbestos insulation workers (Lilis et
34 al. 1991). If the Michaelis-Menten model is to be used, the EPA should consider fixing the plateau level.
35

36 The SAB recommends that model features also should be considered when choosing a model. The SAB
37 suggests examining other exposure metrics besides the simple cumulative exposure, such as time
38 weighting of exposures, in cancer modeling. In addition, the document uses a 10% Extra Risk (ER) as
39 the benchmark response level (BMR) which is in line with EPA’s *Draft Benchmark Dose Technical*
40 *Guidance* for the analysis of quantal datasets from animal studies. However, according to this technical
41 guidance, a BMR of 1% ER is typically used for human quantal response data as epidemiologic data
42 often have greater sensitivities than bioassay data. The authors of the draft document should explain
43 what features of the data set or outcome variable led them to choose a BMR which is considerably
44 greater than the norm for epidemiologic data.
45

46 *Alternative Modeling Approach*

1
2 The SAB recommends performing additional analyses on the full Marysville cohort to increase the
3 number of cases of LPT available for analysis and substantiate that the RfC estimated using the
4 subcohort is scientifically justified. However, the SAB does not find the rationale for the agency's
5 methods to be well justified. The scientific basis for the use of time since first exposure (TSFE) as a
6 covariate is not clear. If it is intended to be a surrogate measure of intensity, the SAB considers date of
7 first exposure to be a better choice. The SAB also finds the method for incorporating TSFE into the
8 analysis is not well justified and recommends that the analysis be revised. In the draft document, the
9 EPA uses TSFE as a predictor for the plateau in the Cumulative Normal Michaelis-Menten model. The
10 plateau provides the maximum proportion of the population that would experience LPT given sufficient
11 exposure and time to develop the disease. No biological justification is given for why this maximum
12 proportion would vary with TSFE. The SAB recommends that the EPA replace the Michaelis-Menten
13 model with a dichotomous Hill model which allows the slope to be estimated. The SAB also
14 recommends fixing the plateau using literature values.

15
16 *Evaluation of Potential Confounders and Covariates*

17
18 The influences of body mass index (BMI), time since first exposure (TSFE), gender, and smoking were
19 described and assessed with respect to inclusion in the overall statistical model for the preferred
20 subcohort. Given that the purpose of the full set of analyses is to estimate the BMC and eventually RfC,
21 the SAB recommends that several of the covariates predictive of the outcome be considered based on
22 whether they impact the BMC estimate rather than merely assessing p-values for how well they improve
23 the predictive quality of the model. In particular, smokers are a sensitive subgroup and should be
24 considered in the RfC estimate. The SAB finds the treatment of BMI as a potential confounder to be
25 appropriate. TSFE is correlated with exposure since subjects with the longest TSFE were exposed in the
26 early years of the cohort when exposures were higher. The preferred subcohort does not have sufficient
27 variation in TSFE to determine definitively whether this is an important covariate in the models.
28 However, there is strong evidence that it is an important factor in the full cohort. The SAB does not
29 agree with the use of the Cumulative Normal Michaelis-Menten model because it makes the biologically
30 implausible assumption that the TSFE only affects the plateau. Instead, the SAB recommends that
31 alternative exposure metrics such as residence-time-weighted exposure be evaluated. The SAB does not
32 consider gender to be a serious concern as it is reasonable to assume that females and males have similar
33 responses to asbestos.

34
35 *Conversion from Cumulative Occupational Exposure to Lifetime Exposure*

36
37 The modeled POD estimate is based on cumulative exposure estimates for the worker cohort examined.
38 The SAB recommends using the full 70 years lifetime when converting cumulative to continuous
39 exposure rather than 60 (70 minus the lag of 10 used for exposure in the POD derivation) ; i.e., do not
40 correct for the lag of 10 for a 10-year lagged exposure. Lagging does not have real meaning in the
41 context of time to event, and that using a divisor of 60 instead of 70 in deriving the RfC is less
42 protective.

43
44 *Selection of Uncertainty Factors*

1 A composite uncertainty factor of 100 (an intraspecies uncertainty factor of 10 to account for human
2 variability and sensitive subpopulations; and a database uncertainty factor of 10 to account for database
3 deficiencies in the available literature for the health effects of Libby Amphibole asbestos) was applied to
4 the POD for derivation of the RfC. The SAB supports the default guideline value of 10 for the
5 intraspecies uncertainty factor. However, the SAB recommends that the EPA consider additional data
6 for the application of a database uncertainty factor (UF_D) of 10. First, additional data have recently been
7 published for the community surrounding a Minnesota expansion plant (Alexander et al., 2012; Adgate
8 et al., 2011). Second, the current view considers Libby Amphiboles as having very similar composition,
9 physical properties, and biological effects as those seen for other amphiboles. This consideration of
10 additional data (Minnesota cohort and data on other amphiboles) might support a lower value, such as 3,
11 for UF_D . On the other hand, it can also be argued that a subchronic-to-chronic uncertainty factor higher
12 than 1 should be used, given that the mean and maximum exposure duration in the study are well below
13 the lifetime exposure of interest. There also is concern that the BMR of 10% for a fairly severe endpoint
14 is not reflected by the choice of a LOAEL- to- NOAEL uncertainty factor (UF_L) of 1. It appears
15 appropriate to consider either a lower BMR or the application of a larger uncertainty factor (UF_L) for
16 this endpoint. Thus, this question deserves additional consideration and more thorough analysis than it
17 receives in the assessment report.

18 19 *Characterization of Uncertainties*

20
21 Overall, the SAB found the discussion on uncertainties in the methodology and approach on the
22 derivation of the RfC to be thorough, detailed, and laid out in a logical and intelligible manner.
23 However, the RfC uncertainty assessment can be strengthened. A key consideration of any such
24 uncertainty assessment is whether the estimated RfC is too high to be adequately protective of public
25 health. The SAB recommends that additional work be done to substantiate the RfC estimate through
26 additional sensitivity analyses and discussion of results and insights from other datasets and studies
27 (e.g., Alexander et al., 2012). In sensitivity analyses, EPA can consider alternative exposure metrics
28 (prioritizing residence time weighted metrics and excluding exposures after 1980), methods to fine tune
29 the RfC estimate from the subcohort (particularly fixing rather than estimating the plateau), and added
30 sensitivity analyses for the full cohort. A new source of uncertainty, the uncertainty in the RfC due to
31 relying on a single study, should be considered.

32
33 With respect to exposure assessment, analytical methods and environmental conditions are substantial
34 contributors to uncertainty because of differences between the 1970s and today. PCM was the only
35 method for measuring airborne fiber concentrations until the 1980's. At the 1970's study site, the vast
36 majority of fibers were almost certainly LAA, so PCM's inability to identify asbestos did not create
37 much uncertainty. Today, even ambient air sampling will yield fiber concentrations that exceed the RfC.
38 Thus, it is important that transmission electron microscopy (TEM) be used to identify and count asbestos
39 fibers in air samples for RfC purposes.

40 41 **Inhalation Unit Risk (IUR)**

42 43 *Exposure-Response Modeling*

44
45 The SAB supports the agency's reliance on the Libby worker subcohort for derivation of IUR because of
46 its focus on good quality exposure data, specific for LAA. However, it is important to acknowledge that

1 this small subcohort may have its own limitations as a basis for modeling exposure-response
2 relationships. A larger population over a lifetime should be considered when selecting the models with
3 which to characterize exposure-response relationships.

4
5 The SAB agrees that the agency clearly described the methods they had selected to conduct the
6 exposure- response modeling for lung cancer and mesothelioma. However, the SAB recommends that
7 the agency provides a broader justification for its choice of statistical models to characterize the
8 exposure response function. First, the SAB recommends that the agency more clearly explains why
9 when considering model selection, it appeared to discount the epidemiological evidence for
10 mesothelioma that suggests the lifetime risk of developing the disease increases the earlier in life that
11 exposure is first received. The SAB recommends that the agency evaluate the time dependence of
12 disease by providing tabulation of mesothelioma mortality rates and lung cancer SMRs by time since
13 first exposure, duration of exposure, and period of first exposure for both the full and sub-cohort.

14
15 A second and related point is that there are several competing models- Weibull and two stage clonal
16 expansion (TSCE) that could have been used instead of or in addition to the Poisson and Cox models,
17 and that these models might have provided very different estimates of risk that are not discussed. Use of
18 the TSCE model, for example, could allow for a more direct evaluation of, and possibly justification for,
19 age-dependency of the IUR.

20
21 Third, the SAB finds that the agency had been overly constrained by reliance on model fit statistics as
22 the primary criterion for model selection. The SAB recommends graphical display of the fit to the data
23 for both the main models and a broader range of models in the draft document to provide a more
24 complete and transparent view of model fit.

25
26 Having made these points, the SAB recognized that the agency did conduct extensive sensitivity
27 analyses of their chosen models in various ways to characterize exposure in the Libby cohort.
28 Consistent with their model and the EPA's Guidelines for Risk Assessment, these sensitivity analyses
29 largely relied on the assumption that the effect of exposure can be modeled as a function of cumulative
30 dose. These analyses, coupled with comparisons of IUR estimates using other published approaches to
31 analysis of the same cohort, provide some reassurance. However, these analyses rely on essentially the
32 same underlying models. They do not address the fundamental question of model uncertainty – that is,
33 whether any one model can or should be assumed to represent the exposure response relationship for
34 Libby amphibole asbestos. This issue is of particular concern for the estimation of risks from partial
35 lifetime exposure where risk is essentially assumed to be independent of when in the course of a lifetime
36 the exposure occurs. Recommendations for addressing model uncertainty are discussed under response
37 to charge question IIIB5.

38 39 *Approach for Quantification of Inhalation Unit Risk*

40
41 In order to derive an IUR which represents the combined risk of mortality from lung cancer or
42 mesothelioma, a cancer-specific unit risk for each tumor type was calculated according to the *Guidelines*
43 *for Carcinogen Risk Assessment* (USEPA, 2005) by linear extrapolation from the corresponding POD.
44 The IUR was then determined as a combined upper bound risk estimate for mortality considering both
45 cancers. The SAB considers the approach is consistent with the agency's own guidance. However, the
46 SAB was divided on whether the independence assumption is fully satisfied. The estimation of the

1 mesothelioma and lung cancer IURs from the same cohort by definition violates the assumption of
2 independence. Violation of the independence assumption could result in either an inflated or deflated
3 upper bound on the combined IUR. The SAB recommends that the EPA perform an analysis evaluating
4 the independence assumption of the risk of mesothelioma and lung cancer mortality. The agency should
5 fit a competing risk model to the data and use this model to calculate the correlation between the two
6 potential event times.

7
8 *Potential Confounding by Smoking*
9

10 The SAB agrees that the agency's use of the Richardson (2010) method for exploring possible
11 confounding for smoking was appropriate. However, the SAB finds the statement that there is no
12 evidence of confounding by smoking is too strong, and relies more heavily on the p-values which are
13 marginally non-significant than it needs to. More compelling is the argument that could be made about
14 the observation of a negative association with COPD. It is possible that negative confounding is
15 occurring in which case the risk of lung cancer associated with asbestos exposure would be understated.
16

17 *Adjustment for Mesothelioma Mortality Under-ascertainment*
18

19 The number of mesothelioma deaths was adjusted for under-ascertainment stemming from inadequate
20 coding in death certificates. The procedure used is not well described in any detail but can be found in
21 the Kopylev et al.,(2011) reference. A total of 18 mesotheliomas were observed in the Libby cohort
22 from 1980 to 2006. The estimated number of 24 mesotheliomas was obtained after using a Monte Carlo
23 analysis. The ratio of 24 to 18 yields the median of 1.33. The Kopylev manuscript also provides a figure
24 of 1.39 in Table 3, which is the mean later reported in the EPA report. The EPA method appears to be
25 scientifically supported but is not clearly described. The SAB recommends that this section be expanded
26 and more detailed statement of how the numbers were arrived at should be provided.
27

28 *Characterization of Uncertainties*
29

30 The EPA has summarized the many sources of uncertainty and, sometimes quantitatively, the direction
31 and magnitude of the likely impact of each source of uncertainty. However, the sensitivity analyses do
32 not take into account the magnitude and likelihood of multiple sources of uncertainty in the same
33 analysis so the overall distribution of uncertainty in the estimated IURs remains unknown. The SAB
34 notes that an important source of uncertainty that might not be accounted for in the use of the 95%
35 upper confidence limit (UCL) on the IUR and the combined IUR, is that of model uncertainty. The SAB
36 recommends that a more straightforward and transparent treatment of model uncertainty would be to
37 estimate risks using a more complete set of plausible models for the exposure-response relationship,
38 including the Cox and Poisson models. This sensitivity analysis would make explicit the implications of
39 these key model choices.
40

2. INTRODUCTION

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

18
19 The SAB deliberated on the charge questions (see Appendix A) during a February 6-8, 2012 face-to-face
20 meeting. There were two general charge questions on the organization, presentation, and clarity of the
21 draft document, as well as chemical-specific charge questions that focused on: mineralogy and
22 toxicokinetics, hazard assessment of non-cancer and cancer health effects, exposure-response
23 assessment for derivation of an RfC for non-cancer endpoints, cancer weight of evidence classification,
24 mode of action of LAA carcinogenicity, as well as exposure-response assessment for derivation of an
25 IUR for LAA.

26
27 The Executive Summary highlights the SAB's major findings and recommendations. The SAB
28 responses to charge questions are detailed in Section 3. Specific comments on the draft document are
29 listed in Appendix B.
30

3. RESPONSES TO EPA'S CHARGE QUESTIONS

3.1. General Charge Questions:

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 toxicologic review to be well-written, logical, clear and reasonably concise, appropriately presented and referenced relative to the health hazards and exposure response of Libby amphibole asbestos. However, the SAB has identified sections where extraneous, redundant and repetitive materials could be deleted or greatly reduced. Examples where presented materials could be deleted or reduced 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 shorten and simplify the text by limiting 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, clearance and translocation pathways, and risks.
- There are 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)

With respect to the second part of charge question 1 (i.e. clarity and sufficient detail in the presentation and synthesis of the scientific evidence for health hazards from Libby Amphibole asbestos), the SAB finds the scientific evidence for health effects of Libby Amphibole asbestos to be reasonably well presented. However, the SAB has identified areas where the draft document would benefit from greater clarity in writing, 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 a more detailed review of the literature is needed to further support this view.
- Section 4.5 describes the radiologic 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 Libby amphibole as discussed in Broaddus et al., (2011).

1 The intensity of the pleural inflammatory response associated with this exposure appears to be
2 greater than in other asbestos-exposed worker cohorts e.g. Wittenoom, Australia (Reid et al.,
3 2008) and may be linked with associated autoimmune diseases discussed in section 4.5.3.
4

- 5 • The role of smoking in different asbestos-related diseases and other nonmalignant respiratory
6 diseases (e.g. COPD) is of sufficient importance (and misunderstanding) that it should be
7 discussed, especially in relationship to LPT. LPT is not associated with smoking (nor asbestosis
8 to a great degree), but lung function (FEV1) is.
9
- 10 • Although the Marysville subcohort represents the best population upon which to derive the RfC,
11 the SAB recommends that EPA include any X-ray abnormalities as the outcome (localized
12 pleural thickening (LPT) or diffuse pleural thickening (DPT) or asbestosis). The SAB also
13 recommends that EPA validate the results with other cohorts (e.g. Libby Workers cohort, and the
14 Minneapolis exfoliation community cohort).
15
- 16 • The SAB found that the various exposure-response models that were examined were reasonably
17 well described. However, the SAB would like a clearer description how the “best” model was
18 chosen. The SAB suggests a thoughtful approach to model selection. Consideration of
19 biological/epidemiologic plausibility, combined with careful examination of the data, should
20 play an important role along with the AIC in determining the choice between these models.
21

22 *Cancer Effect:*

- 23
- 24 • The SAB agrees the weight of evidence for LAA supports the descriptor *Carcinogenesis to*
25 *Humans by the Inhalation Route*. However, the Agency’s position on the weight of evidence of
26 carcinogenicity via exposure to other routes (oral, dermal) should be more clearly stated.
27
- 28 • The SAB considers that the Agency had been overly constrained by regulatory guidance
29 recommending reliance on model fit as the primary criterion for model selection and would have
30 preferred a broader discussion of biological and epidemiologic criteria as well as statistical
31 criteria. There are many competing models that could have been used instead of the Poisson and
32 Cox models which could have provided very different estimates of risk, but these are not
33 discussed.
34

35 *Relevance of Other Literature Related to Amphiboles*

- 36
- 37 • The toxicological review does not make clear the relevance of the extensive literature on the
38 health effects of other amphibole fibers. Literature on other amphiboles should be included,
39 particularly inhalation studies in rodents. There are numerous publications on the mode of action
40 of other amphiboles, and epidemiological studies of populations exposed to amphiboles
41 environmentally.

42 *Early Lifestage Susceptibility*

43

- There is inconsistency in the tone of the conclusions in Section 4.7.1.1 (Lifestage Susceptibility) and in Section 6.3.3 (Applications to Early Lifetime and Partial Lifetime Environmental Exposure Scenarios for IUR) to support or refute early lifestage susceptibility.

Recommendations

- The review would benefit from greater usage of graphs and figures to highlight conclusions. A figure describing the two major occupational groups studied, including their time-lines of exposure, would be very helpful.
- Add discussion of known amphibole fiber toxicity determinants (dose, durability, dimension, surface chemistry).
- Add some additional causes of death (e.g. COPD) to full- and sub-cohorts (Table 5-6, 5-8).
- The section on susceptible populations could be better organized and more succinctly summarized. The section should especially focus on childhood asbestos exposure, the asbestos susceptibility issue most relevant to this EPA document, and probably the topic where there is at least some (albeit limited) data.
- Encourage the continued monitoring of relevant Libby residents for early onset asbestos associated diseases.
- Re-evaluate other models that might be a better fit for determination of early lifestage susceptibility.
- The draft document could be enhanced with quantitative comparison of the environmental exposures that have taken place in other geographic regions of the world (ie. Anatolia region of Turkey, Greece etc.) with the Libby, Montana community with regard to airborne tremolite. This comparison should include numbers and size of fibers and comparison of health effects.
- The final proposed IUR should be compared with those calculated for other types of asbestos. A table comparing these results with the results from the earlier 1988 EPA report on asbestos would be helpful.

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

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

Adgate, JL; Cho, SJ; Alexander, BH; Ramachandran, G; Raleigh, KK; Johnson, J; Messing, RB; Williams, AL; Kelly, J; Pratt, GC. (2011). Modeling community asbestos exposure near a vermiculite processing facility: Impact of human activities on cumulative exposure. *J Expo Sci Environ Epidemiol* 21: 529-535.

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

5 Antao, V.C. *et al.* Libby vermiculite exposure and risk of developing asbestos-related lung and pleural
6 diseases. *Curr. Opin. Pulmonary Med.* 18:161-167, 2012. PMID: 22139761.
7

8 Cyphert, JM; Padilla-Carlin, DJ; Schladweiler, MC; Shannahan, JH; Nyska, A; Kodavanti, UP; Gavett, SH.
9 (2012). Long-term response of rats to single intratracheal exposure of libby amphibole or amosite. *J Toxicol*
10 *Environ Health A* 75: 183-200. <http://dx.doi.org/10.1080/15287394.2012.641203>.
11

12 Marchand, L.s., St-Hilaire,S., Putnams, E.A., et al.(2012) Mesothelial cell and anti-nuclear
13 autoantibodies associated with pleural abnormalities in an asbestos exposed population of Libby MT.
14 *Toxicology Letters* 208: 168-173.
15

16 Shannahan, JH; Nyska, A; Cesta, M; Schladweiler, MC; Vallant, BD; Ward, WO; Ghio, AJ; Gavett, SH;
17 Kodavanti, UP. (2012a). Subchronic pulmonary pathology, iron overload, and transcriptional activity
18 after libby amphibole exposure in rat models of cardiovascular disease. *Environ Health Perspect* 120:
19 85-91.

20 Shannahan, J.H. *et al.* Transcriptional activation of inflammasome components by Libby amphibole and
21 the role of iron. *Inhalation Toxicology* 24:60-69, 2012. PMID: 22168577
22

23 Webber, J.S., D.J. Blake, T.J. Ward, and J.C. Pfau. 2008. Separation and Characterization of Respirable Amphibole
24 Fibers from Libby, Montana. *Inhal. Toxicol.* 20:8: 733 - 740.
25

26 Zeka A, Gore R, Kriebel D. The two-stage clonal expansion model in occupational cancer
27 epidemiology: results from three cohort studies. *Occupational and Environmental Medicine* 68:618-24.
28
29

30 **3.2. Chemical-Specific Charge Questions:**

31 **3.2.1. Mineralogy and Toxicokinetics**

32 1. In order to inform the hazard identification and dose response of Libby Amphibole asbestos,
33 background material is included in the document briefly describing the mineralogy and toxicokinetics of
34 asbestos and related mineral fibers (Section 2 and 3):
35

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

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

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

13
14 Comments on the subsections follow:

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

- 1 • *Double check that all mineral-species definitions 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 based on the use of mineral species names. The problems
6 in this category are probably most rampant in section 2.2.1.1, which details amphibole
7 mineralogy (central to the report). For example, anthophyllite is not a Li-amphibole.
8
- 9 • The SAB appreciates the discussions that highlighted the complexity and variability of LAA in
10 the context of compositional solid solutions, emphasizing that even the use of mineral-species
11 names for LAA may mislead readers to believe that LAA is represented by a few discrete
12 materials as opposed to a mixture of materials with varying composition. Overall, the mineralogy
13 section could benefit from some technical editing. It presents some irrelevant material (e.g.,
14 section 2.2.1, which is a general description of silicate mineral hierarchy), omits some critical
15 information (e.g., section 2.2.1.1 does not provide the mineralogical definitions of key minerals
16 like winchite or richterite), and presents some erroneous and irrelevant (e.g., some of the
17 vermiculite-mineralogy descriptions in section 2.2.2).
18
- 19 • In the context of the information on the LAA, the report is good. One specific observation that
20 could be added is one reported by Sanchez et al. (2008), namely that they observed no
21 correlation between morphology (fibrous vs. prismatic) and major-/minor-element chemistry.
22 Webber et al. (2008) similarly concluded that there was no correlation between mineral species
23 and fiber width for respirable fibers. In other words, this is consistent with the implication that
24 the large set of compositional data from Meeker et al. (2003) shown in the report reflects the
25 range of compositions associated with inhaled-fiber exposures.
26
- 27 • Discussion on page 2-10 glosses over a serious shortcoming of PCM: it's inability to detect
28 fibers narrower than ~0.25 μm . These thin fibers are the most biologically potent according to
29 the Stanton-Pott hypothesis. The fact that only a third of the Transmission Electron Microscopy
30 (TEM)-visible Libby fibers were PCM-visible is buried in McDonald *et al.* 1986a. Furthermore,
31 Text Box 2-2 does not adequately contrast the capability of EM versus PCM. EM's capability to
32 yield elemental composition via Energy Dispersive Spectroscopy (EDS) and Wavelength Dispersive
33 X-ray Spectroscopy (WDS) provides information to identify different asbestos types. PCM's, in contrast,
34 cannot even determine if the fiber is mineral. Furthermore, the Selected Area Electron Diffraction
35 (SAED) capability of TEM allows determination of crystalline structure, e.g., amphibole versus
36 serpentine. Finally, Box 2-2 incorrectly states that scanning electron microscopy (*SEM*) produces *three-*
37 *dimensional (3-D) images*. Rather, SEM produces 2-D images that reveal surface structure of particles.
38
- 39 • Electron microscopy section on page 2-11 could be clarified. SEM and TEM provide higher
40 magnification to allow better particle morphological analysis. Electron diffraction allows mineralogical
41 assessment. Energy dispersive X-ray analysis allows elemental composition determination, which can
42 corroborate the mineralogical determination. X-ray diffraction (XRD) mentioned in this section is useful
43 for bulk sample mineralogy measurements.
44
- 45 *b. In the absence of toxicokinetic information specific to Libby Amphibole asbestos, the draft*
46 *assessment contains a general summary description of fiber toxicokinetics. Please comment*
47 *on whether this overview of general fiber toxicokinetics is clear, concise and accurate.*

1
2 It is not clear, nor concise, especially since it fails to distinguish between chrysotile and amphibole
3 fibers. Furthermore, it is inaccurate in too many places, as noted below.
4

- 5 1) In view of the fact that the focus of the document is on Libby amphibole fibers, it would be
6 better to shorten and simplify the text by limiting most of the literature reviews and
7 discussions to those dealing with the various kinds of amphibole asbestos fibers. Chrysotile
8 asbestos fibers, which are not a significant complication in exposures to Libby vermiculate,
9 are very different from amphibole fibers in terms of their: a) airborne concentration
10 measurement errors and uncertainties; b) much lower biopersistence; c) clearance and
11 translocation pathways and rates; and d) risks. One rationale for the exclusion of the
12 literature on risks associated with exposures to chrysotile from this document is that most of
13 the risks have been associated with amphibole fibers within the chrysotile ores than to the
14 much more numerous chrysotile fibers that dominate the measured airborne fiber
15 concentrations.
16
- 17 2) There are some notable mis-statements and omissions of knowledge on fiber deposition and
18 dosimetry in the document that, fortunately, are not included in the well-crafted Section 6 on
19 —Major Conclusions in the Characterization of Hazard and Exposure-Response.
20

21 The authors of the earlier sections, in cleaning up the text, should draw on some more
22 authoritative and comprehensive reviews in the literature (e.g., Lippmann 2009; Mossman et
23 al. 2011). One mis-statement in the draft is that impaction is affected by fiber length. Another
24 is that interception is affected by aspect ratio. They should cite the work by Sussman et al.
25 (1991a,b) that demonstrates that interception of amphibole (crocidolite) fibers is only
26 demonstrably in excess when fiber lengths are >10 um. Also, they need to cite the work of
27 Brody and colleagues (Brody et al. 1981, Brody and Roe 1983, and Warheit and Hartsky
28 1990) on chrysotile fiber deposition in the alveolar region in rodents. In terms of deposition
29 sites, there should be no significant difference between chrysotile and amphibole fibers.
30

31 Another mis-statement is that mucociliary clearance is complete within minutes or hours
32 rather than the true time frame of hours to a few days (Albert et al. 1969). The authors also
33 need to acknowledge that particles depositing in the alveolar region can reach the
34 tracheobronchial tree in two ways; 1) on surface fluids drawn onto the mucociliary escalator
35 by surface tension, and 2) by passing through lymphatic channels that empty onto the
36 mucociliary escalator at bronchial bifurcations. They also need to acknowledge that
37 macrophage-related clearance of fibers is only applicable to short fibers that can be fully
38 phagocytosed. They should delete nearly all of the references to chrysotile in the discussion
39 of translocation. The Libby asbestos fibers are essentially all amphibole fibers, and there is
40 very little commonality among serpentine and amphibole fibers in terms of translocation or
41 long-term retention.
42

43 There are also toxicokinetic misstatements in Section 4.2 describing Cancer Bioassays in
44 animals. They should cite the inhalation study of Davis et al. (1985) with fibrous tremolite,
45 which is very similar to Libby amphibole. Also, this section should discuss the tremolite

1 inhalation study of Bernstein et al. (2003,2005) that is cited in Table 4-16, as well as the
2 more recent study by Bernstein et al. (2011) that demonstrated pleural translocation in rats
3 using non-invasive means following airborne amosite asbestos exposure. The study
4 examined animals up to one year following a short 1-week exposure to amphibole and
5 characterized the size of fibers that were present in parietal pleura. Non-cancer inflammatory
6 pleural changes were demonstrated associated with fiber translocation. This paper shows
7 rapid translocation of fibers to the pleura (at least of rodents) and it should be referenced for
8 completeness on toxicokinetic issues. Furthermore, the results of the various studies cited in
9 this section are almost all very difficult to interpret with respect to the toxic effects that were,
10 or were not, reported, since no information was provided on the key dosimetric factor of fiber
11 dimensions.
12

13 **3.2.2. Noncancer Health Effects of Libby Amphibole Asbestos:**

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

20 The rationale for the use of the Marysville OH cohort for development of the RfC was well described
21 and scientifically supported. Although there are clear drawbacks to this cohort due to the lack of
22 sampling prior to 1972 when most of the cohort began work, the use of self-reported work histories, the
23 end of Libby vermiculite use in 1980 and the mixture of vermiculite sources used throughout the life of
24 the plant, these drawbacks are offset by the solely occupational exposure of this cohort, the use of better
25 quality radiographs taken for research purposes and the use of 2000 ILO standards for reading
26 radiographs, and for the EPA preference for a cohort with exposures closer to environmental levels. The
27 selection of the subcohort for the main analysis (118 workers who began work in 1972 or later when
28 exposure data was available and who had X-Rays from the 2002-2005 exam), with the full cohort of 434
29 workers used for confirmatory analysis has a clear and strong rationale.
30

31 Although the SAB believes the Marysville sub cohort represents the best population upon which to base
32 the RfC, there was discussion about the need for additional analyses/cohorts to strengthen and support
33 the RfC given this groundbreaking effort. One suggestion is to use the Marysville cohort but include any
34 X-ray abnormalities as the outcome (localized pleural thickening (LPT) or diffuse pleural thickening
35 (DPT) or asbestosis). In addition, cause of death might be assessed for those who died between the two
36 exams. Another suggestion for providing support and perspective to the Marysville findings is to
37 conduct analogous analyses (to the extent the data permit) of pleural abnormalities among the Libby
38 Workers cohort (Larson et al 2012) and among the Minneapolis exfoliation Exfoliation Community
39 cohort (Adgate et al, 2011 and Alexander et al, 2012). The Libby workers have higher, well
40 characterized occupational exposures, compared to the Marysville cohort, while the Minneapolis cohort
41 of non-workers generally had estimated exposures at the lower end of the Marysville cohort but included
42 women and children, thus providing a cohort more representative of the general population. However,
43 because the Minneapolis cohort had estimated, not measured exposures, it would not be suitable for the
44 primary RfC analysis.
45

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

9 The selection of radiographic evidence of localized pleural thickening (LPT) in humans is the
10 appropriate adverse effect and critical effect for the derivation of the RfC. This is well supported by the
11 lines of evidence presented in section 4.1.1.4.2. The section is scientifically supported and clearly
12 described although, as described below, the SAB believes additional evidence is available and to further
13 support this view and should be reported.
14

15 While other health endpoints might have been considered candidates for the critical effect for deriving
16 the RfC, such as diffuse pleural thickening and small opacity profusion, none is superior to localized
17 pleural thickening. LPT is found at a significantly elevated prevalence in the community of exposed
18 individuals. Localized pleural thickening has the appropriate specificity and is not confounded by
19 cigarette smoking. LPT is physiologically important due to its measurable relationship to altered lung
20 function. LPT is a structural, pathologic alteration of the pleura. The findings reported in this section are
21 compatible with the animal data showing tissue injury and inflammation. Additionally, the presence of
22 LPT itself is predictive of risk for other asbestos-related diseases, including asbestosis, mesothelioma
23 and lung cancer, a point that the EPA should include, as well. The SAB discussed that while it fully
24 agrees with the merits of using LPT detected by chest radiograph and CT scan as the appropriate adverse
25 effect and critical effect for the derivation of the RfC, this approach should not preclude EPA from using
26 more sensitive diagnostic techniques that may identify earlier or more specific pleural changes in the
27 future
28 .

29 Due to the landmark action of developing an RfC for LAA, the SAB discussed the need for the
30 inclusion of a more detailed review of the literature to support the presence of a relationship between
31 localized pleural thickening and both pathologic and physiologic abnormalities. There is additional
32 literature that addresses and demonstrates the relationship between LPT and restrictive lung function
33 that should be included. Published studies suggested by the SAB (Clin et al., 2011; Paris et al., 2009;
34 Lillis et al., 1992) should be considered and include those referenced in the American Thoracic Society
35 (ATS) Statement entitled, *Diagnosis and Initial Management of Nonmalignant Diseases Related to*
36 *Asbestos: Official Statement of the American Thoracic Society*, (ATS,2004) (Miller et al., 1992; Miller,
37 2002; Schwartz et al., 1990; Jarvholm and Sanden, 1986; Hjortsberg et al., 1988; Oliver et al., 1988;
38 Bourbeau et al., 1990; Ohlson et al., 1984; Ohlson et al., 1985; Sichletidis et al., 2006; Van Cleemput et
39 al., 2001; Whitehouse (2004; Wilken et al., 2011). Consistent with that Statement, it is the view of the
40 SAB that large cohort studies have shown a significant reduction in lung function, including diminished
41 diffusing capacity and vital capacity attributable to LPT. The SAB also recommends that the EPA
42 provide a more thorough review of the physiologic relationship between LPT found on chest x-ray and
43 CT scan and lung function, not limiting itself to Libby amphibole asbestos.
44

45 The SAB also suggests that the EPA consider looking at LPT, DPT and small opacity profusion score
46 together as an outcome. There is evidence that LPT is not always the first adverse effect that is detected

1 on chest radiographs, and some individuals with Libby amphibole asbestos exposure can develop either
2 diffuse pleural thickening or increased profusion of small opacities without developing evidence of LPT.
3
4

5 Recommendations:

- 6 • Include a more detailed review of the literature to support the selection of LPT through
7 detailing the studies that show the relationship between localized pleural thickening and both
8 pathologic and physiologic abnormalities.
- 9 • In addition to LPT, include an analysis that uses all radiographic outcomes (LPT, DPT and
10 small opacities).
11
12

13 3. *The database of laboratory animal and mechanistic studies of Libby Amphibole asbestos is*
14 *summarized in the draft assessment (see Section 4.2 and 4.3, details in Appendix D) to inform the*
15 *mechanisms of the biological response to Libby Amphibole asbestos and support the epidemiology*
16 *studies used for derivation of the RfC. Please comment on whether the laboratory animal and*
17 *mechanistic information presented is used appropriately in the draft assessment.*
18

19 The EPA Toxicological Review discusses the different types of minerals present in LA and it is
20 uncertain how the various components relate to adverse health effects, although it is made clear that
21 tremolite is a highly carcinogenic and profibrogenic amphibole. LAA contains ~6% tremolite and
22 there is clear evidence from human and animal studies that tremolite causes adverse health effects in
23 humans and experimental animals. However, since LAA also contains winchite (84%) and richterite
24 (~11%), it would be prudent to determine whether these mineral forms contribute to the adverse
25 health effects of LAA or whether there are interactive effects of winchite or richterite that modify the
26 toxicity of tremolite. The SAB recommended that this issue should be highlighted since it is well-
27 known that tremolite is highly toxic, profibrogenic, and causes malignant mesothelioma (MM).
28 However, the contribution of winchite or richterite to adverse health effects is apparently unknown.
29

30 In general, the laboratory animal studies listed in Tables 4-15, 4-16 and summarized in Appendix D
31 are appropriate and complete. Laboratory animal studies utilizing various stocks and strains of mice
32 and rats as well as hamsters, by a variety of non-inhalation routes of exposure, have been used to
33 ascertain the potential fibrogenic and carcinogenic potential of the LA. While inhalation is regarded
34 as the most physiologically relevant mean of fiber exposure in animals, there is no published study
35 with this route of fiber administration in experimental animals. There have, however, been
36 intratracheal instillation of LAA in short term studies with mice and rats that resulted in airway
37 inflammatory change consistent with earlier changes seen in tremolite-exposed animals. The lack of
38 any inhalation data in rats or mice is an important issue since the deposition of particles and fibers
39 cannot be adequately addressed using intratracheal instillation of a bolus of fibers delivered in
40 aqueous suspension. For example, the development of pleural lesions may be quite different when
41 comparing fibrogenic or carcinogenic fibers or particles by inhalation versus instillation. While
42 inhalation studies have been conducted with tremolite (e.g., Bernstein et al 2005), the relative potency
43 of inhaled LAA should be compared to that of tremolite. This could add new information for
44 refining the RfC for LAA.
45

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 interaction, the ability of LAA
4 to induce reactive radical species, inflammatory gene expression, and micronuclei, a marker of
5 genomic instability. Unfortunately, with the exception of the later, 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 specific
8 to the effects of LAA or other types of asbestos, but rather generalized mediators of non-allergic or
9 allergic inflammatory responses. Likewise, pro-inflammatory cytokines (e.g., interleukin-8),
10 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 EPA review, the inhalation reference concentration
19 (RfC) is intended to define an exposure level at or below which there is unlikely to have any adverse
20 health effects. Given the complexities and limited data base available in the literature on both animal
21 and mechanistic studies of LAA, the SAB agrees that a more conservative approach in deriving the
22 RfC is therefore appropriate as a policy choice.
23

24 **3.2.3. Carcinogenicity of Libby Amphibole Asbestos:**

25 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. In the Libby Amphibole report, the SAB
32 agreed with the EPA's position that, while concrete laboratory studies in unequivocal support of the
33 carcinogenicity of the fiber mix are lacking, there is strong epidemiological data that supports the
34 notion that Libby Amphibole fiber (LA) is closely linked to cancer incidence in humans under
35 occupational settings. The occupational studies appeared most persuasive at showing dose-related
36 increased risks of lung cancer and mesothelioma among workers exposed by inhalation. However,
37 the numbers of cases are small, particularly in the sub-cohort used from the Marysville, Ohio plant
38 that had lower estimated levels of exposure. The case series in the community, while supportive, do
39 not provide the same level of evidence for an association, or for the strength of the association.
40 Nonetheless, the epidemiologic evidence from the occupational studies does support the choice of
41 descriptor "carcinogenic to humans by the inhalation route" for LAA under the conditions of
42 exposure in those studies.
43

44 On the other hand, the only solid evidence that the LAA is carcinogenic to animals is in hamsters
45 injected intraperitoneally with a single, 25 mg dose of the fiber mix, which is not a physiologically
46 relevant route of exposure in humans. Although inflammation of the lung has been demonstrated

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

10
11
12 2. *Due to the limitations of the data available, the draft assessment concludes that there is insufficient*
13 *information to identify the mode of carcinogenic action of Libby Amphibole asbestos. Please comment*
14 *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*
17 *of 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 LA is fully justified. In view of these complexities and uncertainties, the default linear
37 extrapolation at low doses is therefore appropriate as a policy choice. This choice receives at least
38 limited support from data on carcinogenesis by other amphiboles.

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

1 The selection of the Libby cohort is scientifically supported and clearly described. It appears to be the
2 best cohort available for cancer outcomes. This cohort has been thoroughly studied previously, has
3 detailed work histories with a job exposure matrix available, had elevated asbestos exposure, had a wide
4 range of measurements of asbestos exposure (covering a two order range of magnitude), was large, and
5 had cancer mortality data available. Limitations of this cohort include limited smoking information.
6 Also, outcomes are based on death certificates, which could undercount cancer endpoints, especially
7 mesothelioma.

8
9 Libby amphibole asbestos is the only possible source of the asbestos measured in the air samples (i.e. no
10 other sources of asbestos at the mine and associated facilities).

11 It should be noted, however, that this study population may not be representative of the larger population
12 since most of its members are white males, exposed as adults, and contains more cigarette smokers than
13 the larger population. If a residential study is ever completed that includes a larger proportion of women,
14 other races, and those exposed as children, the derivation of the IUR should be revisited. Additionally, it
15 is noted that the endpoints are based on cancer mortality on death certificates. While this might seem to
16 lead to an undercounting of actual cases of lung cancer, it seems unlikely that lung cancer in a heavily
17 asbestos exposed population in a remote part of the United States, would either be missed on a death
18 certificate or would significantly undercount incidence (i.e., most cases would not be curable)..
19 Mesothelioma cases, in contrast, might not be fully accounted for using death certificates. The section is
20 clearly written.

21
22 Use of the sub-cohort post 1959 seems reasonable due to the lack of exposure information for many of
23 the earlier workers. 706 out of 991 workers hired before 1960 had all department and job assignments
24 listed as unknown. Thus, it would seem highly problematic to include these workers in the model.
25 However, that leaves 285 workers with at least some information. Possibly some additional analysis
26 could be done on that group. However, of the 991 workers, 811 had at least one job with an unknown
27 job assignment.

28
29 It would be informative to calculate an overall Standardized Mortality Ratio (SMR) for the two cohorts
30 for lung cancer. Comparison should be made with both Montana and U.S. data. The later cohort also had
31 lower levels of exposure to asbestos, which would be closer to the lower levels found in the
32 environment.

33
34
35 *4. Mortality from lung tumors and mesothelioma in the Libby worker cohort was selected to serve as the*
36 *basis for the derivation of the IUR. Please comment on whether this selection is scientifically supported*
37 *and clearly described. If a different health endpoint is recommended for deriving the IUR, please*
38 *identify this endpoint and provide scientific support for this choice.*

39
40 Use of the endpoints lung cancer and mesothelioma are entirely appropriate for derivation of the IUR.
41 They are scientifically supported and clearly described. Mesothelioma is specific to asbestos,
42 eliminating the potential for confounding. While it is possible to consider an alternative model focused
43 on mesothelioma alone to derive the IUR, the number of deaths from mesotheliomas is small and this
44 would likely understate the overall cancer risk. The issue of smoking should be summarized with greater
45 clarity.

1 Since determining the cancer outcome from mortality rather than incidence data may have resulted in an
2 undercount of both cancer outcomes, the discussion would benefit from more detail on how the use of
3 incidence data could impact the derived IUR. In addition, the mesothelioma outcome may be
4 underrepresented because the cohort has been followed for 25-46 years and lag times from exposure to
5 detectable disease onset range from 15 to > 60 year. Mesothelioma also may have been underreported on
6 death certificates. Under-represented outcomes could lead to an underestimated IUR. While there is
7 sufficient information for derivation of the IUR, revisiting derivation of the IUR after additional follow
8 up is warranted.” It was recommended at the meeting that additional follow-up of both the
9 occupationally and environmentally exposed populations would be helpful.

10
11 It would also have been useful to know the other major categories of mortality in this cohort. This could
12 include the numbers of COPD, cardiovascular, colorectal cancer, and other cancer deaths. The report
13 mentions laryngeal (n = 2) and ovarian (n = 0) cancer deaths in the text. Tables 5-6 and 5-8 are mistitled
14 since the titles do not reflect the fact that the number of deaths from mesothelioma and lung cancer are
15 included in the tables. The titles should either be changed and additional causes of death included in the
16 tables or new tables should be created that focus on the causes of death.

17
18 It would be helpful to have a clearer comparison of the Libby asbestos risk assessment with other
19 asbestos cancer risk assessments / reviews, including the earlier EPA assessment in 1986. Have non-US
20 agencies /groups attempted similar quantitative risk assessments? This should be summarized more
21 clearly.

22
23 An overall summary set of tables or figures describing the major cohorts (Libby workers, community,
24 Marysville plant), and the studies / exposure information associated with each would be helpful for the
25 review process.

26
27 *5. The database of laboratory animal and mechanistic studies of Libby Amphibole asbestos is*
28 *summarized in this draft assessment (see Section 4.2 and 4.3, details in Appendix D) to inform the*
29 *mechanisms of the biological response to Libby Amphibole asbestos and support the epidemiology*
30 *studies used for derivation of the IUR. Please comment on the use of laboratory animal and mechanistic*
31 *information in the draft assessment.*

32
33 The SAB agreed, with minor exceptions, that the database of laboratory animal and mechanistic
34 studies pertaining to LA is appropriately presented for support of the analysis of the human effects
35 observed. These studies are informative in identifying similar mechanism and progression of
36 pathological changes in animals as are seen in humans, and help in establishing that similar
37 pathological endpoints are seen with other amphibole fibers. Although as noted earlier, the
38 mechanistic studies fall short of delineating a complete mechanism of action, yet they are useful in
39 identifying some common themes and potential key mechanism in asbestos toxicity, and will
40 undoubtedly be valuable in directing future research on this topic.

41
42 It is now widely accepted that the toxicity and carcinogenicity of mineral and synthetic vitreous
43 fibers is governed fiber dimensions, *in vivo* durability, and dose, and that all long amphibole fibers
44 are very durable *in vivo*. Thus, the differences in biological potency among the various amphibole
45 fiber types are due primarily to their differences in dimensions, especially in their fiber length

1 distributions. The SAB noted that the text in Sections 4.2 and 4.3, and the Tables cited therein, are
2 deficient in not citing all that is known about the dimensions of the administered fibers.

3
4 **Recommendations:**

- 5
- 6 • Section 4.2 should start with a discussion of the relevance of routes of exposure, and then
7 should proceed to discuss inhalation data, followed by a discussion of data from other, less
8 relevant routes of exposure.
 - 9
 - 10 • Areas of needed improvement in the report include: 1) a discussion on known determinants
11 of fiber toxicity; and 2) the differences between LA and other known amphiboles in fiber size
12 distributions.
 - 13
 - 14 • Section 4.6.2.2. should be modified to reflect that there are insufficient data to support the
15 claim that weight of evidence does not support mutagenic mode of action for LA.
 - 16
 - 17

18 **3.2.4. Inhalation Reference Concentration (RfC):**

19 *1. Exposures to Libby Amphibole asbestos for workers in the Marysville, OH facility were reconstructed*
20 *based on industrial hygiene data collected in the facility from 1972 to 1994. Exposures from 1957 to*
21 *1971 were estimated based on extrapolation from the available industrial hygiene data. The*
22 *information used for the exposure reconstruction was based on employee interviews, court and company*
23 *records, and the expert judgment of the researchers. Is the methodology used for the exposure*
24 *reconstruction reported in Appendix F and the subsequent development of exposure estimates used in*
25 *the analyses scientifically supported and clearly described?*
26

27 The approach described in the Appendix F is detailed and specific. The strengths and weaknesses of the
28 approach are clearly laid out. Enormous uncertainties are associated with the *unmeasured* pre-1972
29 exposures: subjectivity of workers' estimating relative concentrations, and unsupported weighting of
30 Libby/South Carolina fiber concentrations. Hence the report appropriately eliminates this set of
31 estimates and adheres to only measured exposures for its derivation of RfC. Alternatively, the EPA
32 might search for PCM measurements from WR Grace exfoliation plants during the 1960s and use these
33 for pre-1972 exposures.
34

35 For modeling purposes, the authors of the report used natural-log-transformed exposure data. Log
36 transformation, of course, creates its own bias by decreasing the significance of the highest exposures.
37 For example, the 1973 log-transformed mean concentration of 1.2 fibers/cc is more than six times lower
38 than the arithmetic mean of 7.4 fibers/cc. Since the RfC is based on the transformed data, future use of
39 the RfC at a given site should be based on the natural-log-transformed mean of all exposure
40 measurements from that site.
41

42 In the text, there should be a table summarizing the changes in proportion of each type of vermiculite
43 used (S. Carolina, Libby and African) at the Marysville plant throughout time frame represented by the
44 cohort. It should be explicitly discussed in this section that Libby vermiculite usage ended in 1980 and
45 that the fiber counts used in the cumulative exposure calculation for the production workers, though

1 small are generally 1.5-6.3 times higher than background. These fibers are presumably from
2 combinations of African/Virginia/South Carolina vermiculite that were used from 1980-2000. Likewise,
3 the description of the calculation of the CHEEC in section 5.2.3.1 would benefit by addition of a version
4 of the material on pg F-19 to clarify the correction factors, and breathing rate adjustments made due to
5 extended work hours during some seasons. The approach used has the typical drawbacks of
6 oversimplification of breathing rate (one size fits all) but is consistent with previous EPA approaches.
7

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

15
16 *2. Exposure-response modeling was conducted using the incidence of localized pleural thickening in*
17 *workers and cumulative exposure to estimate the point of departure (POD) for derivation of the RfC.*
18 *EPA's estimate of the POD is based upon a Michaelis-Menten model applied to the subcohort of*
19 *workers examined in 2002-2005 and first exposed to Libby Amphibole asbestos in 1972 (when*
20 *measurements of fiber levels in the workplace began) or later with cumulative exposure as the*
21 *explanatory variable. Is the selection of the model scientifically justified and clearly described? Has the*
22 *modeling and the choice of a benchmark response (BMR) for the POD of 10% extra risk of localized*
23 *pleural thickening been clearly described and appropriately conducted according to EPA's Draft*
24 *Benchmark Dose Technical Guidance (U.S. EPA, 2000b)?*
25

26 The SAB found that the various exposure-response models that were examined were reasonably well
27 described. However, the SAB recommends a clearer description of how the “best” model was chosen. It
28 appears that EPA fits a series of quantal response models, retained models with adequate fit according to the
29 Hosmer Lemeshow test (presumably based on $p > 0.1$, but this should be stated). Then, among the retained
30 models, they selected the model with the lowest AIC. From a statistical standpoint, this methodology is
31 scientifically justified. It does, however, deviate slightly from the decision tree for selection of the POD in
32 the EPA's Draft Benchmark Dose Technical Guidance (p. 36-37); the decision tree states that the POD from
33 the model with the smallest AIC should be selected if, among models that adequately fit the data, the
34 BMDLs are all within a factor of three. However, the BMCLs from the candidate models are not within a
35 factor of three. Thus if the authors of the draft document were to strictly follow the draft technical guidelines,
36 the most conservative (smallest) BMCL should be used as the POD which comes from the log-probit model
37 with lag 15 exposure. Thus the authors need a clearer description of why the Michaelis-Menten model was
38 chosen as the “best” model.
39

40 Having said that, the SAB does not mean to recommend a dogmatic following of the EPA's Draft Benchmark
41 Dose Technical Guidance Document. Rather, the SAB recommends that a thoughtful approach to model
42 selection including consideration of biological/epidemiologic plausibility, combined with careful examination of
43 the data, should play an important role along with the AIC in determining the choice between these models. For
44 example, model fit (visual comparison of model predictions to data and/or local smoother estimates from data) in
45 the region of BMR should play an important role in model selection. Likewise, the fitted Michaelis-Menten
46 model has an upper plateau of 60% LPT incidence, while a study of highly exposed asbestos insulation

1 workers reported a prevalence of 85% (Lilis et al., 1991). EPA should consider fixing the plateau at a
2 level justified by the literature.

3
4 The SAB recommends that model features should also be considered in choosing a model. For example, the
5 Dichotomous-Hill model is attractive because it allows estimate of an exposure slope parameter, allowing the
6 exposure effect to scale as covariates are added, the exposure metric changed, or the plateau fixed. The
7 SAB also recommends examining other exposure metrics besides the simple cumulative exposure, such as
8 time weighting of exposures as in cancer modeling. The authors explain that their choice of a 10% Extra
9 Risk (ER) as the benchmark response rate (BMR) is in line with the EPA's *Draft Benchmark Dose Technical*
10 *Guidance*. However, that rate is generally considered to apply specifically to the analysis of quantal datasets
11 from animals studies (which is the context in which it was developed). In the EPA's *Draft Benchmark Dose*
12 *Technical Guidance*, it is mentioned that a BMR of 1% ER is typically used for human quantal response data
13 as epidemiologic data often have greater sensitivities than bioassay data. The authors should explain what
14 features of the data set or outcome variable led them to choose a BMR which is considerably greater than the
15 norm for epidemiologic data.

16
17 Recommendations:

- 18 • Consider model features and balance plausibility, localized fit, and technical guidance when
19 choosing the best model and explain decisions in more detail.
- 20 • Evaluate impact of different time weightings of the exposure metric.
- 21 • Either lower the BMR to be more consistent with common practice for epidemiologic data or
22 provide more justification for the 10% BMR used to calculate the POD.

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 from
26 1957 and later and a Cumulative Normal Michaelis-Menten model that incorporates both cumulative
27 exposure and time from first exposure as explanatory variables. Please comment on whether EPA's
28 rationale for presenting these alternative approaches is scientifically justified and clearly described.
29 Please identify and provide the rationale if a different approach for identifying the most appropriate
30 population within the cohort of Marysville workers is recommended as the basis for estimating a POD.

31
32 The SAB agrees that the rationale for performing additional analyses of the full Marysville cohort is
33 scientifically justified; the analysis of the entire cohort increases the number of cases of localized
34 pleural thickening (LPT) available for analysis and substantiates the RfC estimated using the subcohort.
35 However, the SAB did not find the rationale for their methods to be well justified. First, there was
36 general confusion among the SAB members about the scientific basis of using time since first exposure
37 (TSFE) as a covariate. In particular, what is TSFE supposed to be measuring? Is it supposed to be
38 another measure of exposure? There is some suggestion in the IRIS document that it is a surrogate
39 measure of intensity since people with larger TSFEs would be more likely to have been exposed to
40 higher levels of Libby amphibole asbestos present during the early time periods. If TSFE is a surrogate
41 of intensity, why did the EPA choose to use it rather than date of first exposure?

42
43 The SAB also finds that the method for incorporating TSFE into the analysis is not well justified and the
44 analysis should be revised. Currently, the EPA uses TSFE as a predictor for the plateau in the
45 Cumulative Normal Michaelis-Menten model. The plateau provides the maximum proportion of the
46 population that would experience LPT given sufficient exposure and time to develop the disease. No

1 biological justification is given for why this maximum proportion would vary with TSFE. The SAB
2 concludes that a more natural way to incorporate TSFE into the model would be to allow it to affect the
3 rate of change in the probability of LPT; i.e., include it in the linear predictor portion of the model
4 alongside cumulative exposure. The functional form of TSFE could then be selected using standard
5 approaches (e.g., comparing AICs). Since adding TSFE to the model should affect the coefficient of
6 cumulative exposure, EPA should replace the Michaelis-Menten model with a dichotomous Hill model
7 which allows the slope to be estimated. Finally, the SAB recommends fixing the plateau using literature
8 values as recommended in the response to charge question 2 in Section 3.2.4 of this report.
9

10 **Recommendations:**

- 11 • Improve the scientific justification for using TSFE in the analysis which includes a clear
12 explanation of its meaning.
- 13 • Revise the full cohort analysis using a) the dichotomous Hill model, b) TSFE in the linear
14 predictor alongside cumulative exposure, and c) a fixed plateau. This analysis should include a
15 rigorous selection of the functional form of TSFE.
16
17

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

28 **Potential confounders and covariates**

29
30 The influences of age, body mass index (BMI), time since first exposure (TSFE), gender, background
31 rate of LPT, model function, and smoking were described and assessed with respect to inclusion in the
32 overall statistical model for the preferred subcohort. Due to the smaller sample size and to the more
33 restricted range of TSFE in the subcohort, the conclusions regarding the importance of this variable are
34 different in the full Marysville cohort and the preferred subcohort. Given that the purpose of the full set
35 of analyses is to estimate a BMC and eventually RfC, inclusion of several of the covariates predictive of
36 the outcome should be considered based on whether they impact the BMC estimate rather than merely
37 assessing p-values for how well they improve the predictive quality of the model. In particular, smokers
38 are a sensitive subgroup and thus should be considered in the RfC estimate.
39

40 **Age**

41
42 Age at X-ray was included in the model while age at first exposure was not. However, there would
43 obviously be some correlation between age at first exposure and time since first exposure. The age
44 variable was not statistically significant and was therefore dropped from the final model (Appendix E).
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BMI

In section 5.2.3.3.1., it would be helpful if the justification for considering BMI as a covariate were briefly explained. It is included elsewhere, but readers may have missed it. Otherwise, the treatment of BMI as a potential confounder appears appropriate.

TSFE

TSFE is correlated with exposure since subjects with the longest TSFE were exposed in the early years of the cohort when exposures were higher. However, the preferred subcohort does not have sufficient variation in TSFE to determine definitively whether this is an important covariate in the models. There is strong evidence that it is an important factor in the full cohort. The SAB does not agree with the use of the Cumulative Normal Michaelis –Menten model because it makes the biologically implausible assumption that the TSFE only affects the plateau. Instead, the SAB recommends that alternative exposure metrics such as residence-time-weighted exposure, be evaluated that more directly account for TSFE.

Smoking

Smoking is included in the follow-up by Rohs et al. However, the ever/never categorization of smoking is much less informative than the pack-year analysis of smoking used in the earlier study by Lockey et al.

There is an important discussion of the evidence linking pleural changes and smoking in footnote 34 on page 5-46. We suggest that this information be moved into the body of the report, and amplified somewhat. A table summarizing the relevant studies (irrespective of type of asbestos) summarizing the evidence regarding the role of smoking would be useful. A distinction should be made regarding evidence for possible confounding between smoking and pleural effects and the role of smoking on the risk of pleural thickening. If smoking affects the risk of pleural thickening, regardless of whether it is also associated with asbestos exposure (i.e. as a confounder), it will decrease the estimated BMC. Smokers may therefore be a sensitive subgroup and this should be addressed in consideration of the RfC. The sensitivity analysis for smoking shown in Appendix E does suggest that smokers will have a higher risk for LPT and a concomitantly lower BMCL.

Gender

There is little discussion of gender, except in places where the number of females is listed as too few to analyze in any detail. The SAB did not regard that this as a serious concern as it is reasonable to assume that females and males have similar responses to asbestos.

Overall comments with respect to confounders and covariates

The SAB recommends that a table be included summarizing the results of the various sensitivity analyses and how they change the POD.

1 **Exposure-dependent censoring**

2
3 The exposure-dependent censoring discussion is based on results from Rohs et al that inappropriately
4 separated deceased non-participants from the remaining non-participants. Once all non-participants are
5 combined there is no evidence of exposure-dependent censoring.

6
7 **Recommendations:**

- 8
9 • Revise consideration of the additional covariates to include their impact on the BMCL,
10 particularly smoking as smokers are a sensitive subgroup.
11 • Discard the analyses based on the Cumulative Normal Michaelis-Menten model.
12 • Remove the discussion of exposure-dependent censoring and revise the summary of Rohs et al to
13 combine all non-participants into a single group.
14

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

21 The SAB agrees that the conversion is clearly explained and follows standard practice. However, the
22 SAB recommends a revision: we recommend using the full 70 year lifetime in the conversion rather than
23 60 (70 minus the lag of 10 used for exposure in the POD derivation) given that the exposure metric is
24 arbitrarily related to the prevalence data so lagging does not have real meaning in the context of time to
25 event and that using a divisor of 60 instead of 70 in deriving the RfC is less protective.
26

27 **Recommendation:**

- 28
29 • Use the full 70 year lifetime when converting cumulative to continuous exposure; i.e., do not
30 correct for the lag of 10 for a 10-year lagged exposure.

31
32 *6. Please comment on the rationale for the selection of the uncertainty factors (UFs) applied to the*
33 *POD for the derivation of the RfC. Are the UFs appropriate based on A Review of the Reference Dose*
34 *and Reference Concentration Processes (U.S. EPA, 2002; Section 4.4.5) and clearly described? If*
35 *changes to the selected UFs are proposed, please identify and provide scientific support. Specifically,*
36 *please comment on the rationale for the selection of the database uncertainty factor (UF_D) of 10 applied*
37 *in the derivation of the RfC. The database uncertainty factor accounts for the lack of data on effects*
38 *other than in the respiratory system, including other effects observed in community and laboratory*
39 *animal studies (cardiovascular disease and autoimmune effects) that have not been well-studied (See*
40 *Section 5.2.3 of the Toxicological Review); and lack of health data assessed at later time points. Is the*
41 *rationale for the UF_D appropriate and clearly described? Please provide the rationale if a change in*
42 *the UF_D is proposed.*
43

44 Uncertainty factors were selected in accordance with the usual procedures laid out in EPA risk
45 assessment guidelines. A value of 10 was selected for UF_H (human inter-individual diversity) and UF_D

1 (database uncertainty) with a value of 1 for all others. This results in a relatively low value for the
2 resulting RfC (comparable to the 10^{-5} lifetime risk level predicted by the cancer unit risk), which is the
3 consequence of a relatively severe and sensitive critical endpoint, with remaining uncertainty which is
4 substantial (but not unusual, in comparison with other RfC derivations).
5

6 In considering the use of these uncertainty factors, it is important to note first that these are defined, and
7 their values in various specific situations specified, in the RfC risk assessment guidelines (U.S. EPA
8 2002 and others), and are used to ensure that the RfC meets its definition as a level at which there is
9 reasonable confidence that no adverse health effects will occur. In other words, it is not a minimal effect
10 level, and there is no explicit prediction of a dose response relationship at specific levels above the RfC.
11 Risk managers are tasked with evaluating the significance of exposures above the RfC based on other
12 criteria, including characterization of severity, dose-response, and uncertainty provided in the
13 Toxicological Review. It has also been pointed out that wherever possible the uncertainty factors should
14 be replaced by data-based calculations (for example, toxicokinetic or toxicodynamic models and
15 distributions of population characteristics). While this is sound advice in principle, there do not appear
16 to be any obvious opportunities to apply this approach in the current case.
17

18 Use of a UF_H of at least 10 is standard in considering health protective levels based on effects in the
19 workforce, who are generally healthier and less diverse than the general population. In fact, arguments
20 have been made that this is an insufficiently large factor to cover all sensitive sub-populations,
21 especially children. Some treatment of the question of inter-individual variability is offered in the later
22 summary of conclusions (Section 6). There is no specific evidence on the relative sensitivity of children
23 to the non-cancer effects of Libby asbestos, although some indications with other amphiboles suggest
24 the possibility of enhanced effects following exposure at younger ages. Overall, it seems unlikely that a
25 departure from the default guideline value of $Uf_H = 10$ could be justified.
26

27 Selection of a UF_D of 10 is explained and justified based on the limited number of studies of exposure to
28 Libby asbestos (Libby workers, ATSDR community study and Marysville workers) and the lack of
29 evaluation of potentially more sensitive alternative endpoints. This seems reasonable and consistent
30 with the guidelines. In particular, this uncertainty factor would not be reduced even if improved
31 exposure estimates allowed consideration of the full cohorts (or a larger fraction thereof). However,
32 some additional data have recently been published (for the community surrounding a Minnesota
33 expansion plant^{1,2}).
34

35 Although there appears to be a rationale for at least an initial consideration of LAA as a unique material
36 (to provide an unbiased comparison with other amphiboles), the current review has identified very
37 substantial grounds for considering this material as having very similar composition, physical properties,
38 and biological effects to those seen for other amphiboles. The most relevant comparison would be to
39 tremolite, since Libby Amphibole is ~6% tremolite, an amphibole that is known to cause cancer and
40 non-cancer effects in human populations. However, it is uncertain how other components of Libby

¹ Alexander, BH; Raleigh, KK; Johnson, J; Mandel, JH; Adgate, JL; Ramachandran, G; Messing, RB; Eshenaur, T; Williams, A. (2012). Radiographic evidence of nonoccupational asbestos exposure from processing Libby vermiculite in Minneapolis, Minnesota. *Environ Health Perspect* 120: 44-49

² Adgate, JL; Cho, SJ; Alexander, BH; Ramachandran, G; Raleigh, KK; Johnson, J; Messing, RB; Williams, AL; Kelly, J; Pratt, GC. (2011). Modeling community asbestos exposure near a vermiculite processing facility: Impact of human activities on cumulative exposure. *J Expo Sci Environ Epidemiol* 21: 529-535.

1 Amphibole (richerite and winchite) interact as a mixture with tremolite to modify toxicity. This
2 consideration of data on other amphiboles is particularly pertinent to discussions of the mode of action,
3 as well as the exposure/response relationships, for Libby amphibole. In the light of this similarity it
4 appears reasonable, and indeed necessary, to at least debate the question of whether the available data on
5 non-cancer health effects of amphiboles are sufficient to mitigate the acknowledged data shortage for
6 Libby amphibole itself. This consideration of additional data (Minnesota cohort and data on other
7 amphiboles) might support a lower value, such as 3, for UF_D . On the other hand, there are substantial
8 remaining uncertainties which are not addressed by these additional data, including those raised by
9 consideration of the severity of the endpoint and the selection of the BMR (see below). It can also be
10 argued that a subchronic-to-chronic uncertainty factor (UF_C) higher than 1 should be used, given the
11 mean and maximum exposure duration in this study are both well below the lifetime exposure of
12 interest. Thus, the eventual selection of a value of 10 for UF_D , or similar uncertainty spread across
13 several factors, may well be appropriate, but this needs to be evaluated explicitly once all the additional
14 information has been incorporated in the discussion.

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

22
23 ***Recommendations:***

- 24
- 25 • Review additional data identified since the draft report was prepared, and in particular the
26 exposure/response relationship for non-cancer endpoints in the Minneapolis community cohort.
 - 27 • Determine whether this new analysis is supportive of the existing analysis based on the
28 Marysville data, and if so whether this warrants reduction of the value of UF_D since the limited
29 data basis for the original analysis has been expanded.
 - 30 • Reassess the selection of the BMR, to reflect the severity of the chosen endpoint in the
31 Marysville cohort and the precision available in the data. Whether or not the chosen BMR is
32 changed, present this analysis in the document rather than simply asserting that a “default” value
33 was chosen. Similar consideration should be applied to the Minneapolis cohort to provide a
34 valid comparison.
 - 35 • Review additional sources of uncertainty, i.e. timescale of cohort coverage, additional
36 uncertainty resulting from target population diversity, and endpoint severity. Consider adjusting
37 UF_D , UF_C or UF_L if necessary to accurately reflect the overall uncertainties in these categories:
38 provide specific justification for the choices made rather than claiming unsupported use of
39 default values.

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

43
44 In the report there are two sections on uncertainty for the RfC: an application of uncertainty factors
45 following standard EPA practice (section 5.2.4), and a discussion of the uncertainties in the overall

1 methodology and approach (Section 5.3). This response focuses on the latter. Overall the SAB found
2 the discussion to be thorough, detailed, and laid out in a logical and intelligible manner. The document
3 can be improved by harmonizing the full set of uncertainty discussions, including both the discussion of
4 RfC uncertainty and the related discussion of the IUR uncertainty. In addition, the RfC uncertainty
5 assessment can be strengthened. A key consideration of any such uncertainty assessment is whether the
6 quantity of interest (here the estimated RfC) is too high to be adequately protective of public health. The
7 SAB recommends that additional work be done to substantiate the RfC estimate through additional
8 sensitivity analyses and discussion of results and insights from other datasets (e.g. cause of death for the
9 deceased non-participants in Rohs et al.) and Alexander et al. studies. In considering other studies, the
10 appropriate assumption is that Libby amphibole asbestos fibers have the same mechanisms of toxicity
11 and quantitative risk relations as for other asbestos fibers. In sensitivity analyses, consider alternative
12 exposure metrics (prioritizing residence time weighted metrics and excluding exposures after 1980),
13 methods to fine tune the RfC estimate from the subcohort (particularly fixing rather than estimating the
14 plateau, allow the slope parameter to be estimated, use a lifetime of 70 regardless of the exposure
15 metric), and added sensitivity analyses in the full cohort using suggestions from the SAB subgroup
16 charged with discussing the RfC estimate. Finally, a new uncertainty topic should be added: the
17 uncertainty in the RfC due to relying on a single study.

18
19 With respect to exposure assessment, analytical methods and environmental conditions are substantial
20 contributors to uncertainty because of differences between the 1970s and today. As discussed throughout
21 the Report, PCM was the only method for measuring airborne fiber concentrations until the 1980's.
22 PCM's limitations are well-detailed in the report: an inability to detect fibers smaller than 0.25 μm , an
23 inability to differentiate asbestos fibers from other fibers, and a limitation to counting only fibers longer
24 than 5 μm . Today, TEM can easily detect and positively identify airborne asbestos of all sizes. But,
25 because the RfC is based on 1970's PCM analyses, the RfC must be implemented in a way that most
26 closely replicates analysis in the 1970's. At the 1970's study site, the vast majority of fibers were almost
27 certainly Libby amphibole asbestos, so PCM's inability to identify asbestos did not create much
28 uncertainty. Today, even ambient air will yield fiber concentrations that exceed the RfC. The culprit
29 fibers will likely be cellulose fibers from cotton, wood, paper or synthetic fibers, rather than asbestos.
30 Hence, today's PCM counts will be from fibers that are unrelated to the RfC. Thus it is important that
31 TEM be used to identify and count asbestos fibers in air samples for RfC purposes. Finally, Page 5-118,
32 Lines 22-33 of the report discuss the two-fold under-reporting of fibers because of PCM's poorer
33 resolution in the 1970's, 0.44 μm versus 0.25 μm today. Because today's PCM analysts have no
34 capability for discriminating fibers > 0.44 μm , the need for TEM analysis of samples collected for RfC
35 purposes is even more important. A TEM protocol for PCME fibers wider than 0.44 μm could be easily
36 developed.

37 38 **Recommendations:**

- 39 • Harmonize the uncertainty discussions across the document
- 40 • Add a new uncertainty topic: Uncertainty due to reliance on a single study
- 41 • Substantiate the RfC estimate through
 - 42 ○ Additional sensitivity analyses of the subcohort
 - 43 ○ Discussion of results from other studies
 - 44 ○ Additional sensitivity analysis of the full cohort
- 45 • Use TEM to identify and count asbestos fibers in air samples for RfC purposes

1 **3.2.5. Inhalation Unit Risk (IUR):**

2
3 1. *Exposure-response modeling was conducted separately for lung cancer and mesothelioma mortality. The POD estimates for these endpoints are based upon analysis of the subcohort of workers first exposed after 1959 when the exposure data were judged to be better characterized. The exposure-response modeling included consideration of a variety of exposure metrics that varied with time and incorporated different lag and decay parameters. Based on the results of the exposure-response modeling, a lifetable analysis was used to determine the PODs for each type of cancer for the various exposure metrics. Have the exposure-response modeling and determination of the PODs from lifetable analysis been appropriately conducted and clearly described? If a different approach to exposure-response analysis is recommended as the basis for the estimating the IUR, please identify the recommended methods and provide a rationale for this choice.*

13
14 In general, the SAB agreed that the Agency clearly described the methods they had selected to conduct the exposure response modeling for lung cancer and mesothelioma. The risk calculations in the life tables appeared correct but would benefit from clearer explanations. Some suggestions for clarifications are noted below.

18
19 However, the SAB concluded that the Agency had been overly constrained by reliance on model fit as the primary criterion for model selection and recommends a broader discussion of biological and epidemiologic criteria as well. For the mesothelioma data, for example, the Peto model was disregarded due to a poorer fit than the Poisson model. The results for this analysis are not shown, and given the particular interest in this model, should have been. A parametric survival model (e.g., Weibull) could have also been used to obtain estimates of absolute risk. It would also be appropriate to compare the results of the final model against those from fitting a two stage clonal expansion (TSCE) model. Use of (TSCE) model would allow for a more direct evaluation of, and possibly justification for, age-dependency of the IUR. The Richardson (2008) paper provides a publicly available and transparent approach to application of the TSCE. Ultimately, there are many competing models that could have been used instead of the Poisson and Cox models which could have provided very different estimates of risk (e.g., parametric survival models, accelerated failure time models, additive models), but that are not discussed.

32
33 As discussed in more detail in individual comments, there exists a base of epidemiologic evidence for mesothelioma that suggests that the lifetime risk of developing the disease increases the earlier in life that exposure is first received. The Peto model (Peto, 1979; Peto et al., 1982) was developed to explain these observations in the empirical data. While the Peto model has been more widely used for risk assessment, most notably in the previous IRIS summary for asbestos, it has also only been formally fitted to data in a limited number of cohorts (HEI-AR, 1991). Ongoing analysis of incidence of mesothelioma appears to be consistent with the exposure response relationship described in the Peto model. This draft Toxicological Review needs to do a more complete job of justifying why this and other epidemiologic evidence should be excluded as a basis for selection of a plausible model for predicting mesothelioma risk. Chapters 2 and 3, for example, consider toxicological and other evidence developed with exposures to asbestos that are not strictly LAA. Is there reason to believe that the cohorts used in the development of the Nicholson/Peto model, and the exposures they experienced were so unrepresentative of the LAA exposures that they should be assumed to provide no information about the time course of the development of disease?

1
2 The SAB recognizes that the agency’s effort to focus on good quality exposures specific to LAA has led
3 to reliance solely on the Libby worker subcohort. This rationale is understandable but at the same time,
4 it is important to acknowledge that this small subcohort may have its own limitations as a basis for
5 modeling exposure-response relationships for a larger population over a lifetime.
6

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

21 This issue is of particular concern for the estimation of mesothelioma risks from partial lifetime
22 exposures where risk is essentially assumed to be independent of when in the course of a lifetime
23 exposure occurs. For example, one year of exposure to a given concentration in childhood yields the
24 same lifetime average daily dose as one year of the same exposure in adulthood. Is this assumption
25 consistent with the relevant body of evidence on the development of asbestos related disease? If not,
26 there is some probability – not well characterized -- that this approach underestimates the relative effect
27 of early exposure, but exaggerates the effect of exposure later in life.
28

29 **Recommendations:**

- 30 • Expand discussion of model selection to explain the reliance on model fit criteria for model
31 selection. In particular, why should the broader epidemiologic evidence on the time course of
32 disease not argue at least for the presentation of more than one statistical model?
 - 33 ○ Provide in an appendix the details of the Nicholson/Peto model fit for which the text
34 currently states “data not shown.”
- 35 • Present the fit to data graphically for both the main models and for a broader range of models.
36 This step would provide a more thorough and transparent view of fit, particularly in the region of
37 the BMR, than is allowed by examining summary statistical values alone.
- 38 • Allow evaluation of the time dependence of disease by providing tabulations of mesothelioma
39 mortality rates and lung cancer SMRs by time since first exposure, duration of exposure and
40 period of first exposure (for both the full and sub- Libby workers cohorts).
41

42 **Clarifications requested:**

- 43 • Poisson regression analyses: the mathematical form of the regression function should be given, and
44 discussion of whether the potential for over-dispersion was assessed.
- 45 • Cox proportional hazards modeling: the reasons for not conducting a Bayesian analysis as was
46 done for the Poisson regression model for mesothelioma should be given.

- Life-table analysis: the method used to estimate the hazard function for the exposed population should be clearly spelled out in the text. Was it based on a nonparametric estimate of the baseline hazard from the sub-cohort? Given that the SEER data were used to calculate the background incidence of lung cancer, it would seem more appropriate to use those data to estimate the baseline hazard and then use the regression coefficient obtained from the Cox model applied to the sub-cohort data to obtain the hazard of the exposed group. Thus, the reasons for not using the SEER data to estimate the baseline hazard should be explained.

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

The SAB recognized the challenges in controlling for smoking given the lack of data on smoking histories for the cohort. The agency had taken reasonable steps to identify the potential for confounding using independent approaches. However, the SAB regarded the statements (on p 5-96 and again on p 5-127) to the effect that --- because the proportional hazards assumption is satisfied in the subcohort, there is no evidence of confounding by smoking ---as too strong. This conclusion requires some strong assumptions including one that the decline in smoking prevalence observed in the general U.S. population also occurred in the Libby cohort.

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

Recommendations:

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

1 *Guidelines for Carcinogen Risk Assessment (U.S., EPA, 2005; Sections 3.2 and 3.3) by linear*
2 *extrapolation from the corresponding POD (i.e., the lower 95% confidence limit on the exposure*
3 *associated with 1% extra risk of lung cancer or 1% absolute risk of mesothelioma mortality). The IUR*
4 *was then determined as a combined upper bound risk estimate for mortality considering both cancers.*
5 *Has this approach been appropriately conducted and clearly described?*
6

7 The SAB concluded that the description of the procedure used was clear and sufficient to determine that
8 the analysis was correctly conducted. It was consistent with the agency's own guidance; however, the
9 SAB was divided on whether the independence assumption should be assumed to be fully satisfied.

10
11 A justification for independence assumption is the observation that both mesothelioma and lung cancer
12 contribute substantially to the overall cancer-related mortality in the study cohort; the endpoints affect
13 different sites in the body and could occur independently with no interference one from the other. In
14 this case, the calculation of the two risk estimates separately and then addition of the two estimate
15 distributions to obtain MLE and 95% upper confidence limit estimates for the joint distribution is
16 correct. The relatively straightforward approach to calculating the confidence limits on the combined
17 estimate works in this case because both the Poisson and Cox proportional models result in a normal
18 density function for the likelihood estimate. It should be noted that this condition is not necessarily
19 fulfilled when some other models (including multistage polynomials) are used to fit tumor incidence
20 data.

21
22 However, the estimation of the mesothelioma and lung cancer IURs from the same cohort by definition
23 violates the assumption of independence. Violation of the independence assumption could result in
24 either an inflated or deflated upper bound on the combined IUR depending on the sign of the correlation
25 between the two cancer-specific IURs. A better approach would be to jointly model the two outcomes
26 using a Bayesian approach in which dependency could be introduced through a shared random effect in
27 the regression models or a correlated prior for the exposure effects in each model. At the very least, this
28 very restrictive assumption must be mentioned and the potential consequences of a violation of this
29 assumption must be discussed.

30
31 Recommendation:

- 32
33 • The EPA should perform an analysis evaluating the independence assumption of the risk of
34 mesothelioma and lung cancer mortality. More specifically, they should fit a competing risk
35 model to the data and use this model to calculate the correlation between the two potential event
36 times (see Section 2.7 of Klein and Moeschberger, 2003).

37
38 4. *Please comment on the adjustment for mesothelioma mortality underascertainment. Is this*
39 *adjustment scientifically supported and clearly described? If another adjustment approach is*
40 *recommended as the basis for the IUR, please identify that approach and provide the scientific*
41 *rationale.*

42
43 The number of mesothelioma deaths was adjusted for under-ascertainment stemming from inadequate
44 coding used in death certificates. The procedure used is not well described in any detail but can be found
45 in the Kopylev et al. (2011) reference. A total of 18 mesotheliomas were observed in the Libby cohort
46 from 1980 to 2006. The estimated number of 24 mesotheliomas was obtained after using a Monte Carlo

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

5
6 No additional adjustment approach is described in the EPA report. They should provide an additional
7 estimate using the 37% figure mentioned on page 46 of the Kopylev et al. (2011) reference. This is the
8 percentage of mesothelioma cases that would be missed using previous histopathological analyses of
9 cancer registry data. Using 37% would yield an estimate of about 29 mesothelioma cases instead of 24.
10 The median ratio would then be 1.61 instead of 1.33. This number, and its related mean, should be
11 utilized to provide a separate analysis of unit risk for comparison purposes.

12
13
14 *5. Please comment on whether the document adequately describes the uncertainties and limitations in*
15 *the methodology used to derive the IUR and whether this information is presented in a transparent*
16 *manner.*

17
18 In Section 5.4.6.1 of the draft document, the EPA should be commended for summarizing the many
19 sources of uncertainty considered in the course of this document and evaluating at least qualitatively,
20 and sometimes quantitatively, the direction and magnitude of the likely impact of each source of
21 uncertainty. This is a welcome advance in the discussion of uncertainties for IRIS toxicity reviews.

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

30
31 The sensitivity analyses in the document are well described, appear well-done and provide reassurance
32 that, under the assumptions of the basic models and approaches chosen to estimate the IUR that the
33 particular exposure metric and lag, for example, do not appear to make a big difference in the value of
34 the IUR. However, they do not take into account the magnitude and likelihood of multiple sources of
35 uncertainty in the same analysis so the overall distribution of uncertainty in the IURs estimated remains
36 unknown. Consequently, the SAB did not think that the following statement had been fully justified:
37 *“the selected combined IUR from of mesothelioma and lung-cancer mortality accounts for (emphasis*
38 *added) both the demonstrated cross- metric uncertainty as well as several additional uncertainties,*
39 *which could have resulted in underestimates of the mesothelioma and lung-cancer mortality risks” (p 5-*
40 *105, lines 1-5).*

41
42 The SAB identified that an important source of uncertainty that might well not be accounted for by
43 using the 95% UCL on the IUR and the combined IUR -- or at least that had not been represented by the
44 sensitivity analyses provided -- was model uncertainty, the issue raised in the response to question 1 in
45 Section 3.2.5 above.

1 Recommendations:

- 2 • The SAB recommends that a more straightforward and transparent treatment of model uncertainty
3 would be to estimate risks using a more complete set of plausible models for the exposure-
4 response relationship (discussed in response to question 1 in Section 3.2.5), including the Cox
5 and Poisson models. This sensitivity analysis, while not a full uncertainty analysis, would make
6 the implications of these key model choices explicit.
- 7 • The SAB recommends that the agency conduct a full uncertainty analysis by modeling the joint
8 distributions of the major sources of uncertainty it has identified in its evaluation. However, the
9 SAB recognizes the challenge of conducting such an analysis.
- 10 • There is uncertainty associated with a composite IUR for mesothelioma and lung cancer, because
11 it relies on an assumption of independence of the endpoints. Other methods that do not require
12 this assumption should be explored (See response to question 1 in Section 3.2.5.)

13 Clarifications requested:

- 14 • The description of independent censoring is incorrect; the Cox model assumes that the event and
15 censoring processes are independent conditional upon the covariates in the model; i.e.,
16 conditional upon exposure. Thus, if the only link between the two processes is the exposure
17 variable, which is unlikely, the assumption is valid.
- 18 • The statement on p. 5-127, lines 4-5 that since the proportional hazards assumption is satisfied in
19 the sub-cohort, “there is no evidence of confounding by smoking...” is too strong. It is based on
20 some strong assumptions including the assumption that the decline in smoking prevalence
21 observed in the general U.S. population also occurred in the Libby cohort. This statement should
22 be deleted.
- 23

24

4.0. 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.

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2 **APPENDIX A: EPA’S CHARGE QUESTIONS**

3
4 **EPA Charge to the SAB for the IRIS Toxicological Review**
5 **of Libby Amphibole Asbestos**

6
7 **August 2011**
8

9 **Introduction**

10 The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the
11 scientific basis supporting the draft Toxicological Review of Libby Amphibole asbestos that will appear
12 on the Agency’s online database, the Integrated Risk Information System (IRIS). IRIS is prepared and
13 maintained by the EPA’s National Center for Environmental Assessment (NCEA) within the Office of
14 Research and Development (ORD). An existing IRIS assessment for asbestos which includes a
15 carcinogenicity assessment was posted on IRIS in 1988. The draft on which EPA is now seeking review
16 is the first IRIS assessment specific to Libby Amphibole asbestos³.

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

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

30 The external review draft Toxicological Review of Libby Amphibole asbestos is based on a
31 comprehensive review of the available scientific literature on the health effects of Libby Amphibole
32 asbestos and was developed in adherence with general guidelines for risk assessment set forth by the

³ 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, MT.

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

1 National Research Council in 1983 (NRC, 1983)⁴ and numerous guidelines and technical reports
2 published by EPA (see Section 1 of the assessment)⁵. Specifically, this draft IRIS assessment provides
3 an overview of sources of exposure to Libby Amphibole asbestos, characterizes the hazard posed by
4 exposure to Libby Amphibole asbestos for carcinogenicity and noncancer health effects based on the
5 available scientific evidence, and presents a qualitative and quantitative health assessment, including the
6 derivations of a chronic inhalation reference concentration (RfC) and an inhalation unit risk (IUR) that
7 can be combined with exposure information in a risk assessment to estimate noncancer hazard and
8 carcinogenic risk, respectively, in humans. The assessment does not address oral exposure to Libby
9 Amphibole asbestos.

11 Charge Questions

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

21 General Charge Questions:

- 23 1. Is the Toxicological Review logical, clear, and concise? Has EPA clearly, and in sufficient detail,
24 presented and synthesized the scientific evidence for health hazards from Libby Amphibole asbestos?
25
- 26 2. Please identify any additional peer-reviewed studies from the primary literature that should be
27 considered in the assessment of noncancer and cancer health effects of Libby Amphibole asbestos.
28

⁴ NRC (1983). *Risk Assessment in the federal government: managing the process*. Washington DC: National Academy Press.

⁵ <http://www.epa.gov/iris/backgrd.html>

1 **Chemical-Specific Charge Questions:**

2

3 **I. Background**

4 **A. Mineralogy and Toxicokinetics**

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

8

9 a. Please comment on whether the presentation of the available data on the mineralogy of Libby
10 Amphibole asbestos is clear, concise and accurate.

11

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

15

16 **II. Hazard Identification of Libby Amphibole Asbestos**

17 **A. Noncancer Health Effects:**

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

23

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

31

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

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B. Carcinogenicity:

1. Under EPA’s *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005; www.epa.gov/iris/backgrd.html), the draft IRIS assessment characterizes Libby Amphibole asbestos as “carcinogenic to humans” by the inhalation route of exposure. Please comment on whether the cancer weight of evidence characterization is scientifically supported and clearly described.
2. Due to the limitations of the data available, the draft assessment concludes that there is insufficient information to identify the mode of carcinogenic action of Libby Amphibole asbestos. Please comment on whether this determination is appropriate and clearly described. Note that in the absence of information to establish a mode of action, a linear low dose extrapolation is recommended by the *Guidelines for Carcinogen Risk Assessment* (U.S., EPA, 2005; Section 3.3). If it is judged that a mode of action can be established for Libby Amphibole asbestos, please identify the mode of action and its scientific support (i.e., studies that support the key events, and specific data available to inform the shape of the exposure-response curve at low doses).
3. An occupational cohort of workers from Libby, MT exposed to Libby Amphibole asbestos (i.e., the Libby worker cohort) was selected as the basis for the derivation of the inhalation unit risk (IUR). 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 IUR, please identify this study and provide scientific support for this choice.
4. Mortality from lung tumors and mesothelioma in the Libby worker cohort was selected to serve as the basis for the derivation of the IUR. Please comment on whether this selection is scientifically supported and clearly described. If a different health endpoint is recommended for deriving the IUR, please identify this endpoint and provide scientific support for this choice.
5. The database of laboratory animal and mechanistic studies of Libby Amphibole asbestos is summarized in this draft assessment (see Section 4.2 and 4.3, details in Appendix D) to inform the mechanisms of the biological response to Libby Amphibole asbestos and support the epidemiology studies used for derivation of the IUR. Please comment on the use of laboratory animal and mechanistic information in the draft assessment.

III. Exposure-Response Assessment

A. Inhalation Reference Concentration (RfC):

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

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

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

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

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

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.

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

B. Inhalation Unit Risk (IUR):

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

2. Smoking is a strong independent risk factor for lung cancer and may be an important confounder of the lung cancer mortality analysis. Data on individual smoking habits and history were largely missing

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1 and could not be used to control for potential confounding in regression analyses. However, EPA used
2 three approaches to evaluate the confounding issue, including restriction of the cohort and two analytic
3 evaluations of the potential for confounding by smoking (see Section 5.4.3.6.5). Please comment on
4 whether the methods and analyses are clearly presented and scientifically justified. If additional
5 analyses are recommended, please identify the methods and scientific rationale.
6

7 3. In order to derive an IUR which represents the combined risk of mortality from lung cancer or
8 mesothelioma, a cancer-specific unit risk for each tumor type was calculated according to the *Guidelines*
9 *for Carcinogen Risk Assessment* (U.S., EPA, 2005; Sections 3.2 and 3.3) by linear extrapolation from
10 the corresponding POD (i.e., the lower 95% confidence limit on the exposure associated with 1% extra
11 risk of lung cancer or 1% absolute risk of mesothelioma mortality). The IUR was then determined as a
12 combined upper bound risk estimate for mortality considering both cancers. Has this approach been
13 appropriately conducted and clearly described?
14

15 4. Please comment on the adjustment for mesothelioma mortality underascertainment. Is this adjustment
16 scientifically supported and clearly described? If another adjustment approach is recommended as the
17 basis for the IUR, please identify that approach and provide the scientific rationale.
18

19 5. Please comment on whether the document adequately describes the uncertainties and limitations in
20 the methodology used to derive the IUR and whether this information is presented in a transparent
21 manner.
22
23
24

APPENDIX B: SPECIFIC COMMENTS

Section 1:

Page 1-2: Lines 3-4: The RfC is described in the preceding paragraph and does not need to be listed here.

Page 1-3: Line 1, 2. IRIS IUR – It is important to emphasize that excess cases are based on central tendency – not upper bound estimates.

Page 1-3 line 2: Stomach cancer is listed as associated with asbestos exposure; this statement is incorrect. The IARC Monograph vol. 100C states: “Asbestos causes mesothelioma and cancer of the lung, larynx, and ovary.” Positive associations were noted for gastrointestinal cancer and asbestos exposure; however, the Working Group was divided on the evidence supporting a causal association with colon cancer. The meta-analysis conducted by the IOM in 2006 showed a suggestive relationship between asbestos exposure and cancers of the pharynx, stomach, and colorectum.

Page 1-4 lines 15-17: Although workers exposed to vermiculite with no significant amphibole contamination do not show adverse health effects, it is not clear whether the mixture of vermiculite plus Libby amphibole fibers are related to the health effects observed in Libby, MT.

Page 1-5: Lines 3-8: It is confusing to include the discussion for general asbestos here. Suggest moving up to Section 1.1.1.

Section 2:

Page 2-2 line 7 and p. 2-12 line 26: It is stated that vermiculite ore is expanded at 150°C; however, Bandli and Gunter, 2006 state that expansion occurs at 1100°C.

Page 2-6 Figure 2-4d. Chrysotile is listed as an example of a sheet silicate; however, it also occurs in fibrous form.

Top of page 2-7, the identification of the amphibole groups presented here is a bit different from the scheme in Leake et al (1997). Generally, the groupings are based on B site composition.

Page 2-12: A section regarding durability of vermiculite should be added or included in Table 2-1.

Page 2-20: Line 12 through 24: Need to clarify that the amphibole fibers identified in Marysville have the same characterization as those in Libby. How much of the asbestos in Marysville was from other places, such as South Carolina. How significant is the lack of information on the South Carolina ore?

Page 2-21 line 24: A map and total population of the Libby community should be included.

Page 2-22 and 2-23: The text switches from s/cc and f/cc and this is confusing. These data should be presented as a table with the units clearly defined. Nonoccupational exposure levels are commonly

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1 expressed as f/1; for example, in Goldberg and Luce, 2009. This may be less confusing than 5.1×10^{-4}
2 s/cc, for example, on line 11, p. 2-23. On lines 29-30, exposure pathways for residents living near other
3 expansion plants were mentioned; are there any air sampling data available in these communities?
4

5 Figure 2-12 shows morphology data (CDFs) for particles as reported by U.S. EPA (2010). It might be
6 useful to compare these with other morphology data that are cited in report (e.g., Amandus et al. (1987)),
7 which show a different distribution. Have exposures evolved with respect to particle morphology?
8

9 The text box on comparison of PCM and TEM needs expansion as background. The SAB recognizes,
10 however, that most of the evaluation will be based on data derived from PCM, due to the nature of the
11 published work.
12

13 PCM section on page 2-10 is a bit unclear regarding identification of particle morphology. PCM can
14 differentiate fiber from non-fiber (which to me is morphology) but can't identify composition (elemental
15 or mineralogical).
16

17 Electron microscopy section on page 2-11 could be clarified. SEM and TEM provide higher
18 magnification to allow better particle morphological analysis. Electron diffraction allows mineralogical
19 assessment. Energy dispersive X-ray analysis allows elemental composition determination, which can
20 corroborate the mineralogical determination. X-ray diffraction (XRD) mentioned in this section is useful
21 for bulk sample mineralogy measurements.
22

23 Page 2-12. Composition of vermiculite should be as above.
24

25 Table 2-1. Composition of vermiculite should be as above. Mohs hardness is about 2 (looks like a typo
26 in the table).
27

28 Page 2-18. Seems the particle size distribution of the ore samples will depend in part on how energetic
29 the sample prep was. Might be good to point that out here, and emphasize in Appendix C.
30

31 Appendix C could provide more detail on how the work was done.
32

33 Figure 2-4 (d) caption—Chrysotile formula should be $Mg_3Si_2O_5(OH)_4$; vermiculite formula should be
34 $(Mg,Fe,Al)_3(Al,Si)_4O_{10}(OH)_2 \cdot 4H_2O$. The vermiculite structure should also indicate the presence of
35 interlayer cations, not currently represented in the formula above.
36

37 Discussion on page 2-10 glosses over a serious shortcoming of PCM: it's inability to detect fibers
38 narrower than $\sim 0.25 \mu m$. These thin fibers are the most biologically potent according to the Stanton-Pott
39 hypothesis. The fact that only a third of the TEM-visible Libby fibers were PCM-visible is buried in
40 McDonald *et al.* 1986a. Furthermore, Text Box 2-2 does not adequately contrast the capability of EM
41 versus PCM. EM's capability to yield elemental composition via EDS provides information to identify
42 different asbestos types. PCM's, in contrast, can't even determine if the fiber is mineral. Furthermore,
43 the SAED capability of TEM allows determination of crystalline structure, e.g., amphibole versus
44 serpentine. Finally, Box 2-2 incorrectly states that *SEM produces three-dimensional (3-D) images*.
45 Rather, SEM produces 2-D images that reveal surface structure of particles.
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Section 3:

Page 3-5: Line 19, 32. impaction is not materially affected by fiber length.

Page 3-6. Line 1. Replace “sedimentation and impaction” with “interception”. Cite work by Sussman et al. (1991a,b) that demonstrates that interception of fibers is demonstrably in excess when fiber lengths are >10 μm .

Page 3-6: Line 24-36. There is a need to cite the work of Brody and colleagues (Brody et al. 1981, Brody and Roe 1983, and Warheit and Hartsky 1990) on fiber deposition in the alveolar region.

Page 3-7 and p. 3-8: There are several references to fiber burdens in the lungs and pleura; however, there are many technical limitations and caveats in interpretation of these data as discussed in detail in Broaddus et al. (2011) and in Roggli, 1990, 1992; Roggli and Sharma, 2004; Dodson and Atkinson, 2006. The statement regarding systemic translocation of asbestos fibers on p. 3-8 lines 12-18 is very definitive, but it should be qualified by the technical limitations involved in quantitation of tissue fiber burdens. On Page 3-7, lines 12-13, there are additional measurements of pleural fiber burdens that should be included (see review by Broaddus et al., 2011).

Page 3-8. Line 20. Change: “minutes or hours” to “hours or a few days”.

Page 3-8: Line 22. Particles depositing in the alveolar region can reach the tracheobronchial tree in 2 ways; 1) on surface fluids drawn onto the mucociliary escalator by surface tension, and 2) by passing through lymphatic channels which empty onto the escalator at bronchial bifurcations.

Page 3-9. Line 18. Insert “short” before “fibers”.

Page 3-10, Section 3.2.1.1.5 Remove nearly all of the discussion of chrysotile in the discussion of translocation. 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.

Page. 3-10, lines 28-31: The term “overload” should be described more precisely.

Page 3-11, lines 1-2: The role of inflammasome activation following “frustrated phagocytosis” should be included. Inflammasome activation also occurs in response to other crystalline materials, including quartz. Is quartz present in vermiculite mined in Libby, MT?

Page.3-11, line 3: It is unclear whether all inhalation studies in rodents have been conducted under overload conditions.

Page 3-11, line 6: “Encapsulation” is misleading; the title of this paragraph should be “Formation of asbestos bodies”. It is incorrect that most are formed on amosite fibers; other minerals including silicates can also form ferruginous bodies (Churg and Green, Pathology of Occupational Lung Disease).

Page 3-11, line 28: It is not clear that fiber translocation is hindered by fibrosis; no reference is given.

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Page 3-12: See comments above regarding difficulties in tissue fiber burden analysis. The studies on transplacental transfer of asbestos fibers are not widely accepted due to technical concerns.

3.3 Summary

Page 3-15, lines 8 and 9: This sentence on location of deposition and clearance is confusing.

Section 4:

page 4-2: This paragraph describing health impacts of nonoccupational exposure to asbestos fibers is very important; however, it is incomplete. A recent review of this topic was published by Goldberg and Luce, 2009. A table should be included in this section summarizing the magnitudes and health risks associated with these exposures. The region of Casale Monferrato in Italy is most relevant to the exposure in Libby, MT and the epidemiology studies describing occupational, household, and environmental exposures related to this asbestos-cement plant should be described.

Page 4-56, line 28: Tremolite is one of the asbestos fibers in Libby amphibole, but this statement is confusing.

Page 4-4, Line 3-4: What were the years of operation for each of the 2 processing plants?

Page 4-6, Line 5: What was the time-interval for collection of samples after 1974 – 8 hours?

Page 4-6, Lines 10-12: Suggest clarifying the year when further standardization of the PCM method began. When did 25 µm width become the limit of resolution?

Table 4-2: a footnote needs to be added to explain the units of measurement of the MESA/MSHA and company records.

Page 4-9: Lines 9 through 16: What samples were the TEM and EDS performed on? What percentage of samples was this done on, how many samples? Were the samples collected from various operations?

Page 4-9: Line 23: Need to specify asbestos fiber.

Page 4-10: Line 10 through 12. These two sentences need to be rewritten. They do not make sense.

Table 4-3: Table should specify the years samples were collected and method used to characterize dimensions. The percents in the fiber length column add up to 101%.

Table 4-4: It is called out that the Amandus and Wheeler study did not include women, even though the description specifies “men”. For the McDonald studies there is no mention of whether women were included and the description specifies “men”.

Figure 4-1: Cannot see the Phase 1 Sites on this Figure. Suggest redoing figure so it is legible on Black and White copy.

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1 Page. 4-20, section 4.1.1.3.4. Evidence of carcinogenicity from other studies of amphibole asbestos
2 should be cited here. Similarly in section 4.1.1.4. Noncancer Effects, the literature from other studies of
3 workers exposed to amphiboles should be included.
4

5 Page. 4-27, line 20. The sentence is not clear: “Because Larson et al. (2010b) analyzed multiple causes
6 of death, the observed association between exposure and cardiovascular disease-related mortality may
7 reflect, at least in part, a consequence of an underlying respiratory disease.”
8

9 Section 4.1.1.3.4, pg 4-20: In the summary of cancer mortality risk in the Libby vermiculite mining
10 operation workers it is stated that studies provide evidence of an increase risk of lung cancer mortality
11 and of mesothelioma mortality among the workers in the Libby vermiculite mining and processing
12 operations, but it would be helpful to be more specific. What was the increased risk among these
13 workers? A numeric (i.e., quantitative) range of the relative risk based on the epidemiologic studies cited
14 would be more informative.
15

16 Section 4.1.1.4.3., pg 4-27, Cardiovascular-related mortality: This section states that the combined
17 category of cardiovascular-related mortality resulted in modestly increased risks, but it would be helpful
18 to clarify whether this was specifically related to occupational exposures. The last sentence of this
19 section should also clarify that “...the observed association between exposure and cardiovascular
20 disease-related mortality...” should specify what type of exposure; i.e., “...occupational Libby
21 amphibole exposure...?”
22

23 Page 4-42: A paragraph is included describing other exposures at the Marysville, Ohio plant; however,
24 no other exposures in Libby, MT were discussed. Saffiotti has reviewed all chemicals associated with
25 development of malignant mesothelioma in rodent studies (chapter 4 in Pass et al., Malignant
26 Mesothelioma); are related chemicals present in the Libby Community?
27

28 Page 4-49: Line 10. Instead of starting this discussion with “No inhalation...”, start with the inhalation
29 study of Davis et al. (1985) with fibrous tremolite, which is very similar to “Libby amphibole”, as
30 opposed to the Gouveneur tremolite cited on line 23 as not being fibrous. Also, what about the tremolite
31 inhalation study of Bernstein et al. (2003,2005) that is cited in Table 4-16 on page 4-53?
32

33 Page 4-54, lines 30-31: The specific markers used to evaluate changes in homeostasis, etc. should be
34 included.
35

36 Page. 4-71, line 25. In section 4.5.1.1. Pulmonary Fibrosis (Asbestosis), evidence from other studies of
37 amphiboles should have been included.
38

39 Page 4-80, 4.6.2. Mode-of-Action Information. A great deal is known about the mode of action of
40 asbestos fibers generally and amphiboles specifically, which should be assumed to be relevant to Libby
41 asbestos. The mathematical modeling of mesothelioma and lung cancer patterns that has been done for
42 other asbestos exposures shows clearly that cumulative exposure is not the best exposure metric. The
43 duration of exposure is a stronger predictor than the intensity. This is reasonable for an early stage
44 carcinogen, which asbestos appears to be. See work from the 1980s of Peto, Moolgavkar and others.
45 Also the recent Zeka paper I cited on the first page.

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Section 4.2 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 factors of fiber dimensions.

Page 4-69: Line 23. What does “there are limited data” mean? Is this a positive or negative statement?

Page 4-70: Line 19. What is being said here?

Page 4-76, lines 22 and 26: The Pietruska et al., (2010) paper described genotoxicity of Libby amphibole, not oxidative stress, surface iron, or inflammatory markers.

Page 4-77, lines 15-16: The link between fibrosis and proliferation is not clear. Line 17: The association between cytotoxicity and cell proliferation in noncancer health effects is not clear. The cited papers do suggest a link between inflammation and pulmonary fibrosis.

Page 4-78. Line 4,5. The statement that: “the mode of action of Libby amphibole asbestos cannot be established” is too easy a cop-out. The weight of the evidence cited in this document supports the toxic equivalence of Libby amphibole fibers with tremolite fibers in particular, and with all amphibole fibers more generally, and this should be stated here!

Page 4-78: Line 26. Change “cannot be established” to “will not, for some unstated reason, be established here”.

Page 4-79: Line 15. Change “from” to “related to”.

Page 4-83, lines 9-11: The cited studies do not provide any evidence for effects of transplacental transfer of asbestos fibers on fetal development.

Page 4-88: Line 28. Is it 2008, or 2007 as in the reference list?

Page 4-87, lines 13-25: A recent review of molecular alternations in malignant mesothelioma and genetic susceptibility was published in an IARC Monograph, vol. 100C. This paragraph is incomplete and confusing because it cites experimental data but omits molecular alterations in human malignant mesotheliomas. This document should make the distinction between acquired molecular alterations in malignant mesothelioma and inherited, germ-line mutations that may increase susceptibility to the development of malignant mesothelioma.

Table 4-1 lists two epidemiologic papers that are not discussed in the text that is titled Description of cohorts: Moolgavkar et al , 2010 using the NIOSH Amandus/Sullivan cohort (also not included in Table 4-4) and Rohs et al, 2008 using the Lockey Marysville cohort.

Section 5:

Page 5-13: If the reference group is exposed, this is more likely to bias the results rather than be a source of uncertainty.

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Page 5-31, section 5.2.3.3.1. Statistical model evaluation and selection. Explain here why BMI considered a relevant covariate. Line 20. “initial modeling was done using a standard logistic regression model, as is commonly applied in 20 analysis of epidemiological data.” This is a poor justification. In fact, modern methods for analysis of cross-sectional data avoid the logistic model because the odds ratio over-estimates the prevalence ratio, which is the correct measure of association. See Spiegelman 2005 and Barros 2003 papers referenced below.

Page 5-35, section 5.2.4 Application of Uncertainty Factors. This section might be integrated with section 5.3 on Sources of Uncertainty. The latter, which are thoughtfully described and fairly comprehensive, should be linked to the decisions about specific uncertainty factors being applied in section 5.2.4. As it is now, the justifications for the 100-fold UF are cryptic and pro forma and not very convincing. The two 10-fold factors, intraspecies and database, should be justified including the specific issues laid out in section 5.3. Also please explain briefly how these 2 factors are described in the EPA standard methods so that the non-expert can understand them.

Page 5-53. Section 5.4.2. Choice of Study/Data—with Rationale and Justification. This makes clear that the analysis applies only to Libby asbestos. But it provides no justification for this choice.

Page 5-69, line 19. “The RTW exposure metric in this current assessment is sometimes called the cumulative burden, or the area under the curve”. This is confusing. The area under the curve (AUC) is often used to refer to the simple cumulative exposure. Here it is the AUC for the “cumulative cumulative exposure” or something like that. I would not describe the RTW as an AUC.

Page 5-72, line 22. Rothman’s discussion of comparing latencies is out of date. Time windows rather than lagging is a more widely accepted approach now. See page 321 in Checkoway’s occupational epidemiology textbook, 2nd edition, 2004.

Page 5-49, sections 5.3.7 and 5.3.8. I recommend that a table be included summarizing the results of the various sensitivity analyses and how they change the POD.

Section 6:

Page 6-8 Lines 29 through 31 and Page 6-9 Lines 1-13: It follows from the first two sentences that asbestos should be considered as carcinogenic by other routes until there is adequate testing showing otherwise. This is because there is inadequate testing for the oral and dermal routes and mesothelioma is not considered a port-of-entry cancer. However, the conclusion of the paragraph concludes Libby asbestos is considered carcinogenic to humans by the inhalation route. It should also be stated that Libby asbestos is considered carcinogenic to humans by other routes.

Page 6-10: Lines 1-9: Is LPT considered to be a LOAEL? If so, need to state.

Page 6-14: Lines 29 through 31 and Page 6-15 Lines 1-15: Would these effects have a lower LOAEL than LPT?

Page 6-26: Line 25: There may not be adequate years of follow-up for mesothelioma in this cohort.

Appendix E:

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Page E-7: Clarify whether the models below Table E-4 are written correctly. (Are the added terms for smoking outside of the exponential function? If so, what constrains the probabilities to between 0 and 1?)

Page E-10: I think the figures E-2 are overinterpreted somewhat (lines 21-22). The degree of flattening depends on exposure. Also the exposure distribution exacerbates the graphical sense of flattening given the large difference in the exposure mean for the fourth vs. all the other quartiles. It would help to add 95% CIs for each of the proportions displayed in Figures E-2.

Table E-6: Are there typographical errors for the BMC in the >1972 cohort and exposure lags of 10-20? They don't vary with T. Why are some BMCL estimates not provided?

Appendix F:

Page F-5, line 20: *plotted..and found to be visually similar* Were these viewed as raw data or as log plots. If they were log plots, as shown in Figure F-1, the data would look similar even if they weren't. That's what log plots do.

Table F-1: Where did *COMBINED* come from? There is no discussion of it in the text.

Page F-12, line 8: *...mean values of years having at least 40 exposures measurements (1973, 1976, and 1978).*

Table F-2 shows 1977 with 68 *Trionize* samples. Was 1977 included in drawing the line?

Page F-21, line 34: *Tables 5-7 provide a list of all 280 subjects participating in the 2004 Marysville health update* (Rohs et al., 2008). The Rohs article available from HERO only goes up to Table 4. Tables 5-7 could not be located.