National Institute for Occupational Safety and Health (NIOSH) Comments on the Interagency Science Discussion Draft IRIS assessment of Libby Amphibole Asbestos (dated August 2014)

Date: September 19, 2014

Informal Comments of the National Institute for Occupational Safety and Health on the August 2014 Agency/Interagency Science Discussion draft
Toxicological Review of Libby Amphibole Asbestos

September 19, 2014

The National Institute for Occupational Safety and Health (NIOSH) thanks the U.S. Environmental Protection Agency (EPA) for opportunity to offer informal comments on the August 2014 Agency/Interagency Science Discussion Draft "***Toxicological Review Of Libby Amphibole Asbestos***" written in support of summary information on the Integrated Risk Information System (IRIS). The general comments below are followed by a specific comment on definitions and criteria, a specific comment about classification of pleural abnormalities, specific comments on reviewed sections, and a set of editorial and clarification comments from one reviewer.

General comments

1. We were allotted a short period of time to review the document, so we were unable to review it in great detail or in its entirety. However, NIOSH supports the EPA assessment of Libby Amphibole Asbestos (LAA) and we offer our comments in the spirit of providing suggestions that EPA can consider to strengthen the document. The EPA has done a good job of being transparent about how it selected localized pleural thickening (LPT) as a critical effect for evaluation of an inhalation reference concentration (RfC) and how it selected the study to use as a source of data for determining the RfC. EPA has gone to great lengths to examine its assumptions and their potential impacts on the RfC and IUR. Finally, EPA was very responsive to the Science Advisory Board (SAB) review. Addressing the SAB recommendations has addressed many of the methodologic concerns highlighted in NIOSH comments on earlier versions of the document. The structured literature review and meta-analysis (Appendix I) were particularly useful to document that pleural plaques were associated with small, but statistically significant decrements in forced vital capacity (FVC) at the population level. As noted in the draft, even though plaques alone are not generally associated with clinically significant decrements in FVC at the individual level, the analysis at the population level still provides an excellent rationale for using LPT (pleural plaques) as a critical effect in the RfC analysis.

2. In general, the draft document now reflects a greater understanding of workplace conditions that may have impacted the occupational data used in this EPA analysis. In some sections, however, edits suggested by the reviewers are not reflected in the text (although they may be reflected in other sections of the document). A review of the entire document by a single scientific editor could eliminate inconsistencies between statements made in different sections of

the document. Clearer language and more detailed explanations of the risk assessment methodology have made the assessment more transparent and the document more accessible.

Recognizing that Libby amphibole asbestos insulation (Zonolite) remains in millions of homes throughout the U.S. and Canada, NIOSH agrees that the potential for ongoing exposure to the Libby amphibole is geographically diverse, i.e., not limited solely to those locations where vermiculite processing plants were once located.

Consistent with the EPA SAB guidance to consider studies of populations exposed to other amphibole fibers, NIOSH suggests that epidemiologic and risk assessment results for the Libby amphibole asbestos might appropriately be considered in future risk assessments of other types of amphibole asbestos.

3. This draft of the EPA document *Toxicological Review of Libby Amphibole Asbestos* provides a good assessment of the potential human health risks including a discussion of data limitations and the uncertainty factors used to derive cancer risk estimates. Given the extensive review of the data and analysis in the text and appendices, EPA may want to consider developing an Executive Summary to highlight the significant data sets and summarize the analysis of risk.

Specific comment about definitions and criteria

The draft document states that the amphiboles contained in the "Libby MT vermiculite" are predominantly tremolite asbestos, richterite, and winchite. EPA has concluded that these three amphiboles were the causative agents for the observed adverse lung effects in exposed workers. Thus, these worker data sets were used in deriving the inhalation unit risk (IUR) estimates for these amphiboles. Since EPA has already derived an IUR of 0.23 (excess cancer risk per 1 fiber/cc) for the "asbestos minerals", a clear statement (possibly in an Executive Summary) should be made about how the IUR for these three amphibole minerals differs from the one derived previously by EPA for asbestos. Tremolite asbestos is generally considered one of the specific "asbestos minerals" regulated by the Federal government; thus, a question exists about what IUR estimate to use for tremolite asbestos given that this is one of the amphiboles in Libby vermiculite.

The draft document acknowledges that the nomenclature (i.e., physical and chemical morphology) used in defining the asbestos minerals and other related minerals (e.g., amphiboles in Libby MT. vermiculite) can often vary among disciplines (e.g., health scientists, geologists). Consideration should be given to providing specific guidance on how to define the physical and chemical properties of "tremolite asbestos, richterite, and winchite" that are deemed appropriate for the IUR estimate. Definitions and criteria on how to identify "tremolite asbestos, richterite, and winchite" will help to achieve consistent application of the IUR estimate.

Specific comment about the change in classification of pleural abnormalities from ILO 1980 to 2000

One concern is how the draft document conceptualizes the change in pleural abnormality classification from the 1980 to the 2000 versions of the International Labour Organization (ILO)

classification system and how this change affects outcomes. Several paragraphs address this concern in a similar manner (e.g., page 4-18, lines 25-38, and page 4-85, line 34 to page 4-86, line 10). Page 4-86, lines 1-4 (and repeated in the 2nd paragraph of Appendix I) state that: "*The 2000 ILO revision defines LPT as the union of what was previously defined as plaques found on the chest wall or in other locations (e.g., diaphragm) in the 1980 guidelines, and what was previously defined as DPT without costophrenic angle obliteration.*" This statement is incorrect—ILO 2000 does not say anything about diffuse pleural thickening (DPT) without costophrenic angle obliteration being counted with LPT.

The presumption that LPT under the ILO 2000 includes not only plaques but also what was previously classified as DPT without costophrenic angle obliteration is not what the pleural abnormality revision in 2000 was about. Rather, ILO 2000 was making it clear that the only DPT that should be recorded under the ILO system is DPT that extends along the lateral chest wall in continuity with an obliterated costophrenic angle. The intent was to improve the specificity of DPT for asbestos-related disease (see below) and not to shift a subset of DPT (i.e., those without costophrenic angle obliteration) to what ILO 2000 calls "Pleural plaques (localized pleural thickening)" on page 6 of the ILO 2000 guidelines booklet and, more simply, "Pleural Plaques" on the ILO Reading Sheet on page 18 of the ILO 2000 guidelines booklet. In comparison, the corresponding category in the 1980 version of the guidelines was labeled "Circumscribed pleural thickening (plaques)." It is clear that in both the 1980 version and the 2000 version, this category refers to plaques.

One pleural classification change in ILO 2000 clearly instructed readers not to record on the ILO classification form what radiologists have called "apical capping"—a common finding in the general population, especially with increasing age, but essentially unrelated to asbestos exposure (See McLoud TC, et al. [1981]. The apical cap. AJR Am J Roentgenol 137(2):299-306.)

Another pleural classification change in ILO 2000 was an explicit criterion for a minimum thickness. This, too, was intended to enhance the specificity of the ILO classification system. Under ILO 1980, the thinnest ("a") width for describing pleural thickening was "maximum width up to about 5 mm" with no minimum. This lack of a minimum thickness left room for a great deal of "noise" in identifying pleural thickening (i.e., some readers may see a very thin thickening that others would consider entirely normal). (See Greene R, et al. [1984]. Asbestos-related pleural thickening: effect of threshold criteria on interpretation. Radiology 152(3):569-573.) ILO 2000 established a minimum criterion of 3 mm, reducing the potential for "noise" in identifying "true" pleural abnormalities. Apparently, the draft IRIS document does not mention this particular revision relating to pleural thickening in the ILO classification system. Portions of the draft that seem presumptive/unwarranted/misleading about the revised criterion for identifying DPT could be omitted (e.g., how some of what was formerly but no longer classified as DPT is now classified as LPT). New content could be added to explain how the ILO 2000 changes (both the new requirement for contiguous costophrenic angle obliteration and the new requirement for a minimum 3 mm thickness) were intended to enhance asbestos-related specificity of pleural abnormalities identified on ILO classification.

These two alternative conceptualizations of the impact of the ILO 2000 changes might be illustrated hypothetically as follows:

Of 100 cases of pleural abnormality identified in a study population under ILO 1980 (70 plaque and 30 DPT), a re-reading under ILO 2000 would result in 100 cases being identified (70+n LPT and 30-n DPT, where n=DPT cases without contiguous costophrenic angle obliteration identified under ILO 1980).

Under the alternative view, which is based on the intent of the ILO revision, a different outcome is more likely. Of 100 cases of pleural abnormality identified in a study population under ILO 1980 (70 plaque and 30 DPT), a re-reading under ILO 2000 would result in 100-(x+y+z) cases being identified (70-x LPT, where x=those plaques that were identified as such under 1980 ILO but are not counted under ILO 2000 because they are <3mm thickness, and 30-(y+z) DPT, where y=cases of DPT identified under ILO 1980 but not counted under ILO 2000 because they are not contiguous with an obliterated costophrenic angle, and where z=other cases of DPT identified under ILO 1980 but not counted under ILO 2000 because they are <3mm thickness.

So, contrary to the draft document, the result is that under ILO 2000 there would be fewer cases counted in both categories—plaque/LPT and DPT. DPT would lose cases that are not contiguous with obliteration of the costophrenic angle (to the extent that some readers may have counted such thickening as DPT under ILO 1980); and both DPT and LPT would lose cases that involve very thin abnormalities (to the extent that some readers may have counted such thickening under ILO 1980). The EPA presumption that LPT would gain the cases that DPT loses, with no net loss, ignores the intent and reality of the ILO revision. ILO 2000 views LPT and "pleural plaques" as fundamentally equivalent terms, as evidenced by the "Pleural plaques (localized pleural thickening)" sub-heading on page 6 of the ILO 2000 guidelines booklet, by the content on pages 5 and 6 under this sub-heading, and by the simple "Pleural Plaques" heading on the ILO Reading Sheet presented on page 18 of the ILO 2000 guidelines.

Specific comments on reviewed sections

Chapter 2. Libby Amphibole Asbestos: Geology and Exposure Potential

1. Section 2-9, lines 26-28: "*The limit of resolution of PCM is usually about 0.25 µm, so fibers thinner than this are usually not observable.*"

Suggested revision: "Depending on the microscope set-up and refractive index of the mounting medium and fibers, the limit of detection of PCM can be up to a fiber width of 0.25 µm. Fibers thinner than the limit of detection are not observable."

2. Section 2-10, lines 22-25: "*Under ISO 10312 counting rules, a fiber is defined as any structure ≥0.5 µm in length that has substantially parallel sides and an aspect ratio ≥5:1. Fibers observed under TEM that meet PCM counting rules are generally referred to as PCMe (PCM-equivalent).*"

Suggested revision: "ISO 10312 defines a fiber as an elongate particle with parallel or stepped sides, an aspect ratio of 5:1 and a minimum length of 0.5 µm, and further defines a PCM equivalent fiber (PCMe) as having an aspect ratio greater than or equal to 3:1, longer than 5 µm

with a diameter between 0.2 µm and 3.0 µm. The counting rules require both types of fiber to be reported."

3. Section 2-11, line 13 of: "-rebeckite" should be "-riebeckite."

Chapter 4 Hazard Identification, pages 4-1 to 4-16

Page 4-2 line 3 and figure 4-1: Components of fertilizer introduce another whole set of potential exposures.

Figure 4-1: Suggest that the following papers be described as Exposure Assessment, rather than Methods: Amandus et al. 1987 (one of them); McDonald et al. 1986 (one of them); Borton et al. 2012. Weill et al. 2011 used the ATSDR screening data and might be called a reanalysis.

Page 4-3, line 10: Rather than "strip-mining", use "mining", or "open-pit mining". Libby was not a strip mine.

On lines 20-21, it might be useful to state where the non-vermiculite fibers went: up the mill stack, into the airstream, over the valley, and probably surrounding valleys. Work by the National Institutes of Health (NIH) estimated the number of tons. Also, tailings piles on the mountain later contaminated the Rainy Creek drainage.

Page 4-4, Section 4.1.1.1.3: The term plant is usually applied to a manufacturing plant. For Libby, it would be better to say mine and mill.

Page 4-6, lines 3-7. Need consistency in capitalization. Line 5, define scrolls.

Page 4-8, Line 5. McDonald et al. 1986 actually identified the mineral as richterite.
The document has benefitted from EPA's response to the SAB review, as well as the interagency comments. The study description in pages 4-1 to 4-16 includes a much more informed presentation and discussion than found in earlier versions.

Table 4-6: The p-value for the trend test for NMRD is missing from the last line on page 4-15, and the p-value for the trend test for asbestosis included in the table differs from that reported in the Sullivan 2007 publication.

The ATSDR exposure estimates, which cover a longer period of exposure, are much lower than the NIOSH and McGill estimates, which seems unlikely if Larson et al. used the Amandus exposure assessment, as indicated in Table 4-1. There were very few new hires after the early 1980s, so the exposure estimates would not be expected to be so much lower. Compare the range of exposure across studies of the same cohort. There is a typo in Table 4-6, middle of page 4-16.

Chapter 4, Pages 4-36 to 4-52

Serious methodologic problems with the Larson et al. 2010 mortality report make citing the results problematic. EPA's IRIS assessment was initially drafted with reference to Sullivan 2007 and, in at least one instance, the Larson et al. paper is incorrectly cited in this document.

Page 4-37, first 3 lines: The meaning of the sentence is not clear. Suggest stating which outcomes comprise the "respectively" for each SMR.

Table 4-15: As this reviewer recalls, the Noonan et al. 2006 cases were all Grace workers (rather than community-exposed). If so, it is worth mentioning here. In the first table in column 3, state the outcome for the risk estimates.

Page 4-40: Typo in SMRs on line 20.

Table 4-16: consider displaying this table on two pages, rather than three. The p-value for the trend test for lung cancer is missing from the last line on page 4-42.

Figure 4-3: Nice comparison. Note the difference in exposure estimates between Larson and the other mortality studies.

Page 4-44: The smoking data used by Amandus et al. 1987 in the radiographic study (N.B., not Amandus and Wheeler) was obtained from several sources. One was a company questionnaire, another was the questionnaire(s) administered at radiographic screening; finally, NIOSH interviewed 16 by telephone to obtain smoking history, if this reviewer remembers correctly. EPA has the records to verify this.

Generalization based on multiple assumptions increases uncertainty. Rather than speculating based on assumptions about similar definitions of smoking status, EPA should directly compare the questions in the National Health Interview surveys with the questions used to collect smoking information from Libby workers; the latter questionnaires are among the Amandus study records that NIOSH provided to EPA to support this IRIS document.

Page 4-45 (four comments):
-lines 8-9 give a reasonable conclusion as phrased.
-lines 20-24: in discussing negative findings from the Dunning et al. results, it might be advisable to comment on sample size. Small numbers are problematic with some outcomes assessed in this paper. Even in the unstratified analysis, high estimators have confidence intervals indicating lack of statistical significance.
-lines 36-37, suggested sentence revision: Only the two deaths occurring 1999-2001 were coded to mesothelioma (C45) under ICD-10.
-lines 37-38: given that comparison rates prior to 1999 do not exist, the fact that Larson et al. 2010 classified all mesothelioma deaths to C45 in an SMR analysis, no matter the year of death, seems to be a methodologic problem. For example, questions to consider are whether cases of peritoneal mesothelioma (C48) were included and what years of death and ICD codes were used for the comparison rates.

Page 4-46, line 1, suggested revision: analysis of deaths occurring through 1998. Line 2: delete the word "only."

In referencing the Larson et al. 2010 study in tables 4-16 and 4-17, use of the term "multiple cause of death data" may be misleading. Multiple cause of death data usually refers to all causes of death listed on the death certificate, including contributing causes, which are sometimes numerous. This is particularly relevant for SMR analysis, as the comparison rates are also based on the usual and more comprehensive definition of multiple cause of death.

Table 4-16: comparing Table 4-16 with Table 5-20 (statistics based on follow-up through 2006) suggests that 5.6% of known deaths in the cohort were not identified by ATSDR—i.e., 1009-952=57/1009=5%.

Table 4-17: the cause of death was apparently unknown for 20% of the deaths identified in the Larson et al. 2010 study. Suggest discussing the effect on validity—i.e., uncertainty around the obtained estimators. Check whether 88/952 is 20% or 9%. In addition, 10% of the ATSDR cohort was lost to follow-up.

Page 4-48: Noted that EPA responded to the NIOSH comment about citing an unsupportable death rate for mesothelioma here, but not in Section 5.

Page 4-50, lines 2-3: Suggest changing the phrasing here, as it could be misleading. The 3rd identified case had not died at the time the manuscript was published in 2012, but may have died since. Deaths in 2012 or later are not included in the denominator for the SMR analysis (deaths 1980 to mid-2011), so the case could not be included in the numerator.
Line 18: Consider including "named after a town in Greece where this abnormality was observed among tremolite-exposed residents" or similar.

Table 4-18: good addition. Clarify the description of pleural plaques in Almopa (i.e., whether 24% of pleural plaques occur in residents over 40, or do 24% of the residents over 40 have pleural plaques.)

Section 5.4, Pages 5-69 to 5-99

Section 5.4.1: Starting this section with the definition of the main measure to be discussed and clearly stated and informative details about how the assessment is done by EPA makes the subsequent material much more comprehensible (transparent), facilitating wider understanding of the document.

Page 5-72 (six comments)
-lines 8-9: While it is true that the NIOSH worker cohort comprises a broad range of exposure experience, generally considered a strength in exposure-response analysis, the sub-cohort analysis presented by EPA severely limits the range of exposure. As the IRIS analysis does not benefit from this strength (#4), it should not be claimed on line 8.

-line 11: Specify that this is an epidemiology study cohort (with data already collected), rather than a worker cohort, as there are undoubtedly others that could be assembled.

-line 24: the Amandus et al. date is incorrect; it should be 1987.

-line 25: This is incorrect. As explained in a previous NIOSH review of this document, Berman and Crump 2008 did not analyze the NIOSH data for this publication. Their conclusions about the Libby cohort were based on a 10-year lagged analysis provided by Sullivan.

-line 27-28: Please rephrase this statement. Again, as stated in the 2011 NIOSH review of this IRIS document, so far as current NIOSH staff are aware, the ATSDR exposure estimates were not obtained from NIOSH. As pointed out earlier in this review, the ATSDR exposure estimates and range of cumulative exposure appear to differ significantly from those used by Amandus and/or Sullivan. Perhaps ATSDR used the published NIOSH Job Exposure Matrix (JEM).

-lines 32-34 are repetitive.

Table 5-20. State that these statistics are based on follow-up through 2006, to avoid questions about why this table differs from the NIOSH publication.

Page 5-74 (four comments)
-line 2: check the punctuation.

-lines 12-13: Do not include reference to ICD-5, ICD-6, and ICD-7 unless deaths during this period were included in your analysis.

-line 15: this is not the usual meaning of imputation in this context. It would be better to use assigned. Note in Sullivan 2007 that other sources of vital status follow-up were used for this cohort, including the SSA, etc.

-line 21: 95%.

Page 5-75: Good comparison of incidence and mortality from SEER data.
-line 5: suggest deleting "data from."
-line 15: suggest deleting "both"
-lines 17 and 19: suggest using "ranged" instead of "ranges" as particular studies are cited, which perhaps do not precisely reflect the whole population experience. Also, note that the sensitivity in the general population in 1981 may differ from the sensitivity of death certificates coded in 2001 or 2006.
-line 24: the phrasing suggests that the underestimation is a function of model choice, but it is largely a function of the outcome.
-line 27: not necessarily. Written notations on some of these death certificates, sometimes on the cause of death lines, clearly indicated that asbestos exposure was causal.

Page 5-76, lines 23-27: Note that the 2011 NIOSH comments on this document point out that the ICD-7 code for cancer of the trachea is 162.0.

Page 5-80, line 2, suggested revision: " …exposure intensity estimates for the 25 locations...".

-line 18: unclear whether this deficit was a choice of the analyst or inspector, or a limitation of the analytic methodology available to Montana at the time. If a limitation, rephrase so the text does not imply omission. If this reviewer recalls correctly, the State of Montana sent a group of dust samples to the ALOSH for an early fiber analysis. Check the NIOSH records provided to EPA to support development of this IRIS document.

-lines 29-30: In developing a job exposure estimate for a given 8-hour workday, the estimated exposure intensity at each location/operation was multiplied by the fraction of the day that someone in that job spent at that location/operation, at that point in time. If a job involved working in more than one location or operation, these estimates were summed over an 8-hour workday.

Page 5-81, lines 31-32: Actually, 66.5 fibers/cc was not high exposure intensity for the time period in question, as Figure 5-5 demonstrates.

-lines 19-35: This text does not accurately describe occupational exposure assessment methods or JEMs. Please refer to the 2011 NIOSH comments on the draft IRIS document, and to Table 4-1 in the current document to develop more precise language. Rather than suggesting that a single exposure value was assigned without any basis to a large number of workers, please convey what was actually done. In addition to using more precise language, include a frequency table of job assignments by time period so that the reader can better assess the potential impact of the exposure estimation and analytic decisions made. After consulting the JEM, for each calendar time period, sort by department and operation, rather than by level of exposure. Those with unknown exposure were coded department 999, operation 999. Those in the labor pool (a known job assignment) are coded department 003, operation 077. Those in the mine with unknown jobs are coded to department 001, operation 999. Those in the mill with unknown job are coded to department 002, operation 999. You will see that the exposure estimates for those with unknown jobs in the mine or mill are substantially different from the estimates for those in the labor pool. Those with unknown department and operation were assumed to have been in the labor pool, under the assumption that the more skilled jobs were union jobs characterized by more control over job assignment and the need to maintain better payroll records.

As in most observational studies (vs. designed laboratory experiments more commonly used in EPA risk assessments), there were several sources of uncertainty in both the available work history records and in data available to support estimation of exposure in specific jobs over time. First, gaps existed in the company records that document the work history—i.e., missing data or unknown jobs. With respect to missing data, the best approach is imputation, and in epidemiology methods is generally considered preferable to discarding existing data. There is a large literature supporting this assertion (Rubin has authored some of the more complete coverage.) Another source of uncertainty is estimation of the actual exposure in some jobs, either because the job tasks vary by day, or because no sampling data are available for the job. For example, the catchall job "laborer," to which many Libby workers were assigned, could mean various tasks on different days. In this case, Amandus assigned the relatively low mill yard exposure (about 2 fibers/cc) to the large number of laborers at the mill, which would have tended

to result in a steeper slope. Similarly, the EPA choice to limit analysis to a subcohort with relatively low exposure might have resulted in a steeper slope.

Industry experience, familiarity with union shop bidding practices, and review of the actual Grace work history records led Sullivan to believe that laborer jobs, often assigned to transient workers in this union shop, were likely to have some of the highest exposures. Working with an industrial hygienist with asbestos mining exposure assessment experience, Sullivan identified (separately for the mine and mill) the unskilled jobs most likely to be assigned to a transient worker. As Table 4-1 reflects, laborers were assigned the weighted-average exposure for all unskilled jobs in the department (if known) during the calendar time period, rather than lower mill yard exposure. The weights are based on the number of workers assigned to unskilled jobs during the same calendar time period. If the job assignment was missing from the Grace records (i.e., unknown job), a similar method of assigning an exposure estimate for that time period was used. The fact that many workers had the same exposure estimate is a function of the fact that many workers were identified as laborers in company records, and may have worked in any one of the three or four unskilled jobs in the department, each of which had a specific (unvarying) exposure estimate assigned to it during that time period. Exposure estimates were assigned in the same way to laborer and unknown jobs for time periods after 1960. Without individual estimates of exposure concentration for each worker, there will be more variability in duration of employment than in concentration of exposure in a given job.

JEMs are developed because sampling data are not available on most workers. Analyzing observational epidemiology data when the exposure assessment is based on a JEM involves recognition that each job task in a given time period will be assigned a uniform exposure based on a relatively few (or no) industrial hygiene samples, input from workers with experience in that workplace or industry at that point in time, and professional experience of the exposure assessment team. In developing the JEM, NIOSH had the benefit of input from workers, for example the Grace worker who stated that when he worked during the 1950s the ground was white for a quarter mile around the complex.

Unless sampling over time is based on selection of a representative sample in each job task, the quantitative data provided by a company is also subject to varying sources of bias that may impact validity. Review of the monthly sampling records provided by Grace (which EPA has access to) documents that in some months company sampling was conducted to confirm suspected high exposures in some operations, in other months to verify the effectiveness of newly installed control measures, at other times sampling locations were chosen based on a corporate directive. If asbestos sampling were systematically done after work areas had been wet down or during specific weather conditions, fiber measurements would document little exposure and be biased downwardGiven all these potential sources of bias, professional judgment based on experience may produce a more reliable estimate of exposure.

Page 5-82, line 3: “28 workers (3%)”
-lines 5-6: again, estimating exposure for these workers was more complex and reasoned than picking a number (66.5 f/cc) and assigning it.

Table 5-22: NIOSH commented previously (2011) on the limitations inherent in basing the IUR on such a small analytic cohort—i.e., analysis based on 28% (n=32) of the lung cancer deaths and 39% (n=7) of the mesothelioma deaths. Limiting the range of the observed exposure data requires extrapolating the model to higher exposures, when basing the modeling on actual observed exposure would be considered preferable by most. There is uncertainty introduced by using a smaller sub-cohort with a limited range of observed exposure.

Figure 5-5: good figure.

Page 5-85, line 1: the individual-level data were developed based on a uniform estimate of exposure in a given job during a given point in time multiplied by individual-level data on duration.
-line 7: add "…exposures, intended to reflect varying hypothesized underlying processes of carcinogenesis—i.e., the fiber acting as a cancer initiator or co-initiator, or acting as a cancer promoter."
The more detailed discussion of the models evaluated considerably improves the document.

Page 5-86, line 10: perhaps the sentence should end with "so we considered several."
-line 33: reverse the order of the descriptors to parallel the order of the named exposure metric.

Page 5-88, line 10: consider deleting "as an expression of a lag time between exposure and mortality," as the phrase obscures the meaning of an otherwise clear sentence.
-lines 19-20: could point out that the fit of the unlagged model may be an indicator of the appropriateness of the exposure metric used in the model, or aid in identifying a pattern with increasing lag time. Otherwise, the unlagged model discussion is not informative.

Line 28. Consider changing "then" to "later."

Page 5-89, line 1: note that the NIOSH Libby worker cohort has more than 50 years of follow-up.
Inclusion of the Peto and Berry models in response to the SAB comments provides a more balanced analysis.

Page 5-90, line 10: rather than citing a 1983 estimate of mesothelioma incidence, use the more precise 2005 CDC estimate of mesothelioma mortality rate cited elsewhere in the document.

Page 5-91, Line 11-12: clarify whether this is a benefit of Win BUGS software, or of the MCMC Bayesian method.

Page 5-92, line 2: explain why longer lags were not considered for mesothelioma, as the latency can be quite long, sometimes 50 years. Perhaps a longer lag was not considered because EPA risk assessment uses a 70 year lifespan, or a small number of deaths was analyzed, or because of the death 15 years after first exposure.
-line 7: as discussed in comments above, the later estimates may not be superior, but they are lower, i.e., closer than population exposures today, thus potentially of more interest to EPA.

Page 5-94, lines 4-5: as explained above and previously, laborer is a job category with a specific exposure concentration assigned; it is not missing data. Indicate whether these estimates reflect this knowledge.

Footnote 26: You can assume that all the female workers were office workers at this point in time—i.e., would have been estimated to have the minimal 0.x f/cc exposure found in the JEM if included in the NIOSH analysis, rather than the 65.5 f/cc concentration estimate for laborers that these EPA generalizations assume.

Page 5-95, line 5: delete "and based on missing job information," a statement that does not reflect the JEM methodology used to estimate exposure or of the work history data being analyzed.

Table 5-29. Explain the difference between SMRs from Montana and US.

Page 5-97, line 10: use the 2005 CDC reference, which is more precise than the 1983 reference.
-line 12: when this analysis was done, we did have estimates of the background risk. Need more qualified language here.

Page 5-98, line 11: clarify "competing risk of death".

Page 5-99, lines 9-12: good discussion, and may be a clearer argument for not controlling for confounding by smoking than all the uncertainty estimation.

-line 24: this reviewer recalls that when time since first exposure is used as the time scale, cumulative exposure shows a better fit.

-line 35: Controlling for potential birth cohort effect is at least partially controlling for changes in smoking prevalence over time.

Page 5-100, line 3: discuss what happens if the time scale is TSFE (time since first exposure). A previous reviewer pointed out that with age as the time scale, the proportional hazards assumption will hold only if age is not an effect modifier.

Chapter 6, pages 1-6

Page 6-1, line 17: perhaps the Marysville studies should be cited here as well.
-line 26: suggest "…vermiculite mined in Libby…"
-line 32: this section does not describe the full range of community exposure. Inadvertent take-home exposures undoubtedly occurred, but there were also exposures that were not inadvertent—e.g., the company gave vermiculite to workers for home use, and gave vermiculite to the town to cover the skating rink and high school track. EPA's estimate (Chris Weiss) of the volume of amphibole asbestos fibers emitted from the mill stack should be included, as well as results of environmental modeling that assessed the potential geographic distribution of these fibers.

Page 6-2, line 11: indicate what/who is VAI. A date appears to be missing. Maximize the impact of the document by making it accessible—e.g., use the brand name "Zonolite."

Page 6-2, lines 28-29: suggest deleting "from the organism".

Page 6-3, lines 33-34: asbestosis is only a small part of nonmalignant respiratory disease, as is evident from comparing risk estimates for NMRD and asbestosis in the Libby cohort. Consider this phrasing "including asbestosis and other nonmalignant respiratory diseases."

Line 35 and page 6-4, line 27, and section 4.1: Sullivan 2007 also reported results for cardiovascular disease, and EPA's repeated reference to this health outcome could be strengthened by including that citation.

Page 6-6, lines 4-7: suggest that these targeted comments are more appropriate to the section of the document where these studies are reviewed, rather than this summary chapter.
-lines 27-28: One of the Amandus et al. 1987 publications addressed exposure assessment rather than health effects and probably should not be included in this list of citations.
-line 36: There is little racial diversity in the worker cohorts studied epidemiologically, perhaps not in all workers exposed, e.g., construction and renovation workers. Suggest different phrasing.

Section 6.1.5 should discuss smoking as a potential modifying effect or confounder, for example on page 6-7, line 1 or in the first paragraph of the section.

Appendix A

Additional exploration of model form and choice of the dichotomous Hill model reflecting the biologic process and data is likely responsive to the NIOSH 2011 question about the meaning of the plateau observed in the data, although the short review period did not allow for review of the new analysis.

The revised document is responsive to NIOSH's concern that 1984 radiographs taken prior to disease progression were used for a significant proportion of the Marysville workers; the final model limits analysis to those workers who had radiography 2002-2005.

Page A-5: when evaluating the effect of TSFE, bear in mind that because exposure ceased at the same point in time for all Marysville workers, and all were alive in 2002, TSFE is a marker for duration of exposure for most of this cohort. As cumulative exposure equals mean exposure concentration*duration, including TSFE and cumulative exposure in the same model may be problematic, leading to the relatively poor fit observed in some cumulative exposure models. EPA may want to reconsider which exposure metric is more predictive of the outcome (cumulative exposure or duration) in light of this observation.

Page A-6: with respect to the discussion about the applicability of the LAA risk assessment to other amphiboles, bear in mind that the EPA SAB recommended that the EPA use data on other amphiboles to re-evaluate the data uncertainty factor.

With respect to the geographic maps showing the extent of potential LAA exposure in the U.S., text attributing some of these exposures to home attic insulation would justify the wide geography included.

Page A-7, lines 1-4: discussion of the role of TSFE would benefit from consideration that it is a marker for duration of exposure in this cohort. This is because all study subjects received radiographs at roughly the same time (2002-2005), and exposure to LAA ceased for all at the same time. So,

TSFE – [radiography date – date LAA last used at Marysville] = duration.

Page A-7, lines 15-17: clarification is needed about whether the pleural and parenchymal risk assessment could be a function of autoimmune disease. If not, should autoimmune effect uncertainty be a consideration in defining the critical level?

Page A-8, line 30: the concern is that risk may have been overestimated, and confidence intervals are wider with a sub-cohort analysis.

Page A-9, line 33: Define the abbreviation "ERD". It is not in the list of abbreviations and acronyms.

EPA's inclusion of graphical model fit display is informative.

Appendix H

Nice mineralogy glossary. A similar glossary for risk assessment terminology is also needed.

<u>Editorial and clarification comments from one reviewer</u>

Pages xviii-ix, List of abbreviations, suggested edits:

-use singular "fluid" (not "fluids") in spelling out "BALF".
-hyphenate "single-breath" in spelling out "DLCO".
-hyphenate "energy-dispersive" in spelling out "EDS" (this would be consistent with hyphenation of "wavelength-dispersive" when WDS is spelled out "WDS" later in this same list.)
-hyphenate "phosphate-buffered" in spelling out "PBS".
-not hyphenate "hypertensive heart" in spelling out "SHHF".
-hyphenate "cross-complementing" in spelling out "XRCC1".

Page 1-1, lines 14-16: Consider deleting apparent redundancy as follows: "In the case of LAA, the RfC is expressed in terms of the lifetime exposure in units of fibers per cubic centimeter of air (fibers/cc) ~~in units of the fibers~~ as measured by phase contrast microscopy (PCM)."

Page 1-1, line 17: Consider hyphenating "extrarespiratory" as "extra-respiratory".

Page 1-1, lines 25-27: Consider deleting apparent over-explication, as follows: "For LAA, the RfC is expressed as a lifetime daily exposure in fibers/cc (~~in units of the fibers~~ as measured by PCM), and the IUR is expressed as cancer risk per fibers/cc (~~in units of the fibers~~ as measured by PCM)."

Page 1-2, lines 24-25: Consider minor edit: "after the external peer review (SAB, ~~(~~2013)**".**

Page 1-3, line 11: Consider minor edit: "The final asbestos IUR is 0.23 excess cancers per 1 fiber/cc continuous**".**

Page 1-3, line 15: For consistency, consider hyphenating both magnesio-riebeckite (magnesioriebeckite) and magnesio-arfvedsonite (magnesio-arfvedsonite). (They are both hyphenated on Page 2-11, line24.)

Page 2-5, lines 13-15: Having already mentioned amosite and crocidolite, it would be appropriate and informative to insert parenthetical content as follows: "Sodic amphiboles (riebeckite [also known as "crocidolite"], arfvedsonite)" and "Iron-magnesium-manganese-lithium amphiboles (anthophyllite, cummingtonite-grunerite [also known as "amosite"])"

Page 2-7, Text Box 2-1: Consider revising the definition provided for "Fiber (regulatory)." The current definition lacks any length criteria. It also appears to ignore OSHA (and MSHA)'s regulation of asbestos fibers with aspect ratio of greater than *or equal to* 3:1 (not just greater than 3:1) [see https://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9996].

Page 2-7, Text Box 2-1: Consider revising the awkwardly worded and confusing definition provided for "Fibril."

Page 2-8, lines 4-7: The following statement is confusing and consideration should be given to splitting it into three separate sentences for clarity: "Typically, a fiber is defined as a highly elongated crystal with parallel sides, where acicular crystals are "needlelike" in appearance, and prismatic crystals may have several parallel faces with a low aspect ratio (ratio of length to width, <3:1)."

Page 2-9, footnote: This footnote seems a bit misleading. The footnote ("*Most techniques for analyzing air samples distinguish individual fibers from more complex structures composed of two or more fibers, including bundles, clusters and matrix particles. …*") does not seem consistent with the OSHA mandatory counting rule: "Count bundles of fibers as one fiber unless individual fibers can be clearly identified and each individual fiber is clearly not connected to another counted fiber". Perhaps the footnote should say: "Most techniques for analyzing air samples do not distinguish individual fibers from more complex structures composed of two or more fibers, including bundles, clusters and matrix particles. …"

Page 2-9, line 24: Suggest upper case "M" in referring specifically to NIOSH Method 7400.

Page 2-10, line 2: Suggest hyphenating “high-energy”.

Page 2-10, line 7: Suggest hyphenating “energy-dispersive” because “wavelength-dispersive” is hyphenated in the third bullet on this page.

Page 2-10, line 8: Consider edit: “This makes it ~~easy~~ possible to distinguish ...”

Page 2-11, line 21: Consider edit for clarity: “individual fiber structures…”

Page 2-11, line 30: Consider edit: “….within the length of ~~the~~ a single fiber”.

Page 2-11, line 32: Correct misspellings: “…for tremolite-richterite-magnesio-~~riebecktite~~riebeckite. ~~Magneiso~~Magnesio-riebeckite …”.

Page 2-16, lines 6-7: Consider edit: “…straight with uniform diameter, ~~a l~~ath- or needle-shaped, or curved.

Page 2-16, line 16: Consider edit: “…95% of the structures ~~ranked as~~ were considered possible asbestos.”

Page 2-18, lines 1-2: Suggest edit: “…using ~~the optical system of an~~ electron ~~microprobe~~ microscopy and EPMA…”.

Page 2-18, line 8: Consider edit: “most fibers identified as LAA have ~~thicknesses~~ widths”.

Page 2-18, lines 10-11: Consider edit: “from <1 μm to ≥100 μm. Aspect ratios also range widely, from 3:1 to ~~greater than~~ ≥100:1”.

Page 2-18, line 2: Consider edit: “as a soil amendment in ~~homes~~ home gardens…”.

Page 2-18, lines 11-12: Consider edit: “playing in ~~the~~ vermiculite piles”.

Page 2-22, lines 1-2: Consider edit: “were exposed to LAA ~~that was~~ released during ~~the~~ processing operations”.

Page 2-22, line 3: Consider edit: “on ~~the~~ 28 Libby vermiculite expansion and processing facilities”.

Page 3-1, lines: Consider edit: “and samples of particles ~~rat~~ respirable ~~samples~~ by rats (<2.5 μm)”.

Page 3-1, line 18: Consider hyphenating “rat-respirable” in this context.

Page 3-1, footnote 6: Consider edit: “Respirable fibers are those that can ~~penetrate into~~ reach the alveolar regions when inhaled … ” (“Penetrate” is technical jargon that may be confusing to

some readers, particularly since asbestiform fibers are also known to penetrate (in a very different sense) into/through tissue.)

Page 3-3, Figure 3-1: Suggest correcting diagram so that the arrow pointing to "sputum" originates from the "mucus/phlegm" box and not from the "gastrointestinal tract" box.

Page 3-4, line 3: Consider edit: "…but no experimental data exist to verify ~~its presence~~ this …"

Page 3-4, lines 4-5: Consider edit: "…depends on ~~the~~ fiber ~~dimensions~~ dimension and density ..."

Page 3-6, lines 10-11: Consider edit: "…are ~~captured~~ characterized by ~~characterizing~~ the particle's…"

Page 3-6, lines 16-18: Should revise the following statement because of grammatical problems and apparent circular logic: "However, characterizing a fiber by its aerodynamic diameter is dubious because as a fiber's aerodynamic properties depend, in addition to density, on both its length and width, as well as its orientation with respect to the convective airflow (Asgharian and Anjilvel, 1998; Cheng, 1986)."

Page 3-6, line 25: Should hyphenate "mechanism-specific".

Page 3-6, lines 37-38: Consider edit: "at the surface of ~~embedded~~ objects entrained in that airflow".

Page 3-7, line 3: Consider edit: "Deposition in the nasal and oral passages is mainly by impaction ~~and diffusion~~."

Page 3-7, lines 8-11: Consider edit: "can bypass the filtering of the upper respiratory tract and ~~are~~ be inhaled directly into the larynx/trachea, especially during exertion (e.g., exercise or work), thereby altering deposition ~~as a result of the increased turbulence~~." Two variables—exertion, which increases air flow rates, and mouth breathing—are invoked in this statement. Lower airway turbulence is increased during exertion as a result of increased flow rates in the larynx and below, but inhalation through the mouth avoids the normally turbulent nasopharyngeal region. Might be best to leave this simply as altering deposition without asserting the increased turbulence via mouth breathing.

Page 3-7, lines 14-15: Consider revision: "The relative contribution of each mechanism depends on the fiber characteristics, region-specific airway anatomy, and respiratory flow rates (air velocities)." Later in this paragraph, there is mention of velocity as a factor for sedimentation, but the influence of air velocity could be invoked in describing other mechanisms of deposition, as well.

Page 3-7, lines 26-27: Consider clarifying: "The aerodynamic diameter of fibers that can deposit in the tracheobronchial region is in the range of 1−5 μm. Fibers with an aerodynamic diameter of <1 μm deposit in the bronchioles and the alveoli (ICRP, 1994)." Fibers that are

aerodynamically larger and smaller than 1-5 μm also can deposit in the tracheobronchial region, and fibers with an aerodynamic diameter < 1 um deposit not only in the bronchioles and the alveoli but also elsewhere in the respiratory tract. It is a matter of how likely they are to deposit in the various regions.

Page 3-7, lines 28-34: This section of the draft document is on "Deposition of Fibers in the Respiratory Tract," so everything from "However" on line 28 to the end of this paragraph would be better moved elsewhere. This particular content involves issues of fiber retention and handling of deposited fiber by the body.

Page 3-7, lines 35-36: Suggest edit for clarity: "Fibers with aerodynamic characteristics conducive to ~~penetrating the peribronchiolar space and~~ depositing in the respiratory bronchioles and alveoli may cause pulmonary fibrosis and other associated diseases." Alternatively and more simply, "Fibers with aerodynamic characteristics conducive to ~~penetrating the peribronchiolar space and~~ depositing in the ~~alveoli~~ alveolar region of the lungs may cause pulmonary fibrosis and other associated diseases."

Page 3-8, line 7: Suggest edit: "~~Alveoli~~ Alveolar deposition is limited".

Page 3-9, lines 5-6: Consider edit: "~~Different m~~Mechanisms of physical and physicochemical clearance of fibers ~~depends~~ depend on the fiber size, physicochemical characteristics, and site of deposition (IOM, 2006)."

Page 3-9, line 23: Consider edit: "remove ~~inhaled~~ deposited fibers"

Page 3-9, lines 24-25: Consider edit: "the sticky mucus lining much of the respiratory tract".

Page 3-9, line 35: Consider edit: "due to ~~subsequent~~ swallowing".

Page 3-10, line 1: Consider edit: "to examine ~~the~~ gastrointestinal tissue response".

Page 3-10, line 12: Consider edit: "Some fibers are not cleared via the mucociliary escalator from the respiratory tract, leading to".

Page 3-10 line 34: Consider edit: "~~Durable fiber i~~Impaction of durable fibers".

Page 3-10, lines 2-3: Consider edit: "migrate ~~to the bronchoalveolar junctions~~ along epithelial surfaces to ciliated bronchioles, where they are removed".

Page 3-10, lines 7-9: Suggest edit: "such as the overwhelming of phagocytosis and the mucociliary escalator by an excessive number of particles ~~from a decrease in the rate of mucociliary clearance~~ (often termed "overload")".

Page 3-10, lines 12-14: Consider edit: "Limited inhalational laboratory animal studies exist at concentrations of fibers ~~below overload occurred~~ insufficient to induce overload; therefore

information is insufficient to determine mechanisms of inflammation at lower doses ~~as reviewed in~~ (Mossman et al., ~~(~~2011)."

Page 3-10, line 25: Consider edit: "Fibers that are too ~~large~~ long to be easily engulfed"

Page 3-10, lines 24-27: Consider edit: "Once fully coated, ~~these~~ fibers within asbestos bodies may or may not participate directly in asbestos disease~~ once the fiber is fully coated~~. ~~For instance, t~~The presence of iron in the coating could provide a source for catalysis of reactive oxygen species (ROS)~~ similar to that observed with fibers~~."

Page 3-11, line 30: Consider edit: "fibers deposited on ~~Type~~type I alveolar" (NOTE: Upper case is not used near the top of page 3-12 when "type I alveolar epithelial cells" are mentioned.)

Page 3-11, lines 32-33: Consider edit: "Fiber length ~~would~~ may play a key role in this aspect of clearance~~, much as described above for phagocytosis by alveolar macrophages~~."

Page 3-11, line 36: Consider edit: "the alveolar epithelial surface".

Page 3-12, line 4: Consider edit: "and the tissue ~~of deposition~~upon which the fibers deposit".

Page 3-12, lines 4-5: Consider edit: "on the ~~fibers'~~ physicochemical characteristics of the deposited fibers".
Page 3-12, line 7: Consider edit: "increase in permeability, but could be hindered by fibrosis".

Page 3-12, line 8: Consider edit: "~~was~~ has been reported".

Page 2-12, line 10: Consider edit: "Fibers ~~were~~ have been identified".

Page 3-12, line 17: Suggest hyphenating "two-fold".

Page 3-12, line 17: Consider edit: "thickening of the ~~pleural wall~~pleura".

Page 3-12, line 19: Consider edit: "the thoracic lymph nodes".

Page 3-12, line 32: Consider edit: "from another inhalational rat study".

Page 3-12, line 33: Consider edit: "that ~~the~~ longer amphibole fibers".

Page 3-12, lines 26-27: Consider edit: "that the ~~average-length fiber~~ average length of fibers found in the lung (regardless of type) was longer than ~~those~~ that of fibers found in the lymph nodes or plaques".

Page 3-12, line 37: Consider edit: "crocidolite fibers ~~(Union for International Cancer Control [UICC])~~ through"

Page 3-12, line 38: Consider edit: "These transplacental migration studies".

Page 3-13, line 8: Consider edit: "in ~~the lung's~~ extracellular lung fluids".

Page 3-13, line 12: Consider edit: "physically ~~diminished~~ degraded through splitting".

Page 3-13, line 17: Consider edit: "dimension (length, ~~diameter~~width, aspect".

Page 3-13, line 17: Consider edit: "toxicity, as the initial deposition sites in the respiratory tract ~~tissues~~ determine".

Page 3-13, line 27: Consider edit: "biopersistence of deposited fibers ~~once deposited~~".

Page 3-13, line 29: Consider edit: "To the extent that a fiber ~~and its composition are~~ is resistant".

Page 3-13, line 31: Consider edit: "~~The degree of f~~Fiber durability ~~determines the~~ is a determinant of retained dose at the site of deposition".

Page 3-14, line 12: Consider edit: "While informative, ~~this~~ analysis of tissue fiber burden has some limitations".

Page 3-14, lines 22-23: Consider edit: "The relative contribution of fiber dimensions and ~~chemistry~~ composition that drive the toxicity of ~~the~~ fibers remains poorly understood".

Page 3-16, lines 1-2: Consider deleting the entire first sentence of this paragraph: "~~Studies have also associated exposure to fibers to other biological activities, including 1 autoimmune effects and pulmonary function impacts~~."

Page 3-37, line 27: Consider edit: "(e.g., ~~reactive oxygen species~~ ROS production)."

Page 3-17, line 11: Does "outer pleural" in "the implant was made to the outer pleural tissue" refer to "parietal pleural"? If so, consider edit: "the implant was made directly to the parietal pleural tissue."

Page 3-17, lines 11-12: Consider edit: "it is unknown how the dissolution ~~and clearance~~ of fibers in the agar…"

Page 3-17, line 16: Consider edit: "is ~~an overinterpretation of the data~~ clearly limited"

Page 3-17, line 20: Suggest edit: "et al. (1987; 1974) ~~and~~ who showed that shorter fibers".

Page 3-17, line 22: Consider edit: "physiological ~~clearance and~~ deposition and clearance mechanisms".

Page 3-18, line 26: Consider edit: "through ~~direct pathological evidence from~~ fiber burden analysis of human mesothelioma tissue".

Page 3-18, line 30: Consider edit: "width, which, ~~is~~ on initial consideration might seem contrary to the "Stanton Hypothesis.""

Page 3-18, lines 31-33: Consider edit: "as ~~the digestion and ashing process may lead to shorter fibers, or any~~ longer fibers that had been translocated to the mesothelial tissue may have broken down by dissolution or fiber breakage during life, or the digestion and ashing process may itself have degraded longer fibers to shorter fibers."

Page 3-18, lines 36-38: Consider edit: "asbestosis was associated with shorter (>2 μm), thicker (>0.15 μm~~,~~) fibers; mesothelioma with longer (>5 μm), thinner ~~fibers,~~ (<0.1 μm) fibers; and lung cancer with longer(>10 μm), thicker (>0.15 μm) fibers."

Page 3-18, lines 10-11: Consider edit: "concluded that ~~all sized~~ fibers of all sizes are associated with increased mesothelioma risk."

Page 3-20, line 6: Consider edit: "The health effects from asbestiform tremolite exposure". Tremolite can be either asbestiform or non-asbestiform.

Page 4-2, lines 10-11: Consider edits: "studies of environmental or residential exposure to asbestiform tremolite or asbestiform tremolite-chrysotile mixtures and to crocidolite ~~amphibole~~ is presented". Tremolite can be either asbestiform or non-asbestiform; crocidolite is always an asbestiform amphibole, so "crocidolite amphibole" is redundant.

Page 4-3, lines 11-12: Consider edit: "the mining operations ~~had~~ were associated with lower intensity exposures compared to the milling operations".

Page 4-6, Table 4-2: This table and the source of its data (Amandus et al. 1987a) both attribute 48 fiber measurements collected in 1967-1968 to NIOSH. This seems an error, as NIOSH did not exist until after passage of the OSHA Act in 1970. Please check the years of the measurements.

Page 4-7, line 6: Consider edit (but see comment re Page 4-6, Table 4-2): "Because measures from sample filters were not available before ~~1968~~ 1967,…".

Page 4-7, lines 21-22: Consider edit: "PCM analysis does not distinguish ~~between~~ fiber mineralogy or detailed morphology,".

Page 4-8, lines 4-5: Suggest hyphenating: "sodium-rich".

Page 4-8, line 17: Consider edit: "These data are limited in one sense by the minimum ~~diameter~~ width and…".

Page 4-8, line 21: Suggest hyphenating "PCM-visible".

Page 4-10, table footnote: Suggest hyphenating "single-breath".

Page 4-16: Suggest deleting redundant column, as follows:
Community-based studies in Libby, MT

Comparison area (Montana reference rates):			Comparison area (U.S. reference rates):		
Libby city limits	40.8	(13.2, 95.3)	~~Libby city limits~~	63.5	(20.5, 148)
Extended Libby boundary	47.3	(18.9, 97.5)	~~Extended Libby boundary~~	74.9	(30.0, 154)
Air modeling	44.3	(19.1, 87.2)	~~Air modeling~~	71.0	(30.6, 140)
Medical screening	40.6	(18.5, 77.1)	~~Medical screening~~	66.1	(30.2, 125)
Libby valley	38.7	(19.3, 69.2)	~~Libby valley~~	63.7	(31.7, 114)
Central Lincoln County	36.3	(18.1, 64.9)	~~Central Lincoln County~~	59.8	(29.8, 107)

Page 4-17, lines 1 and 4: Suggested edit for sections heading and sub-heading: "***~~Pathological Alterations~~ Radiographic Abnormalities of the Lung Parenchyma…"***.

Page 4-17, Text Box 4-1: Consider edits:

Title: "**~~Pathological Alterations~~ Radiographic Abnormalities of the Lung Parenchyma and Pleura**"

"…as well as the affected zone(s) of the lung."

"The costophrenic angle is ~~measured as~~ the angle between the ribcage and the diaphragm on a standard posterior-anterior~~-viewed~~ radiograph". It is not how the radiograph is "viewed" but how it is taken (i.e., how the x-rays pass through the body from the back to the front before they hit the x-ray film. Jargon sometimes is used to refer to this as a P-A "view."

Page 4-17, Text Box 4-1: The source cited for the contents of this text box is the ILO 2002 revision. But some of the studies relating to Libby LAA were based on earlier versions of the ILO classification system, which differ from the 2000 version. In particular, the explicit quote that "DPT of the chest wall … is recorded on the lateral chest wall 'only in the presence of and in continuity with, an obliterated costophrenic angle'" is from the 2000 version, but that guidance was not explicit in the earlier versions. Insertion of a note to that effect at the bottom of this text box could be informative to readers.

Page 4-17, lines 12-13: The statement that "The criteria provide for the exclusion of anomalies potentially due to nonasbestos-related causes (e.g., trauma, tuberculosis)" is true, particularly with the ILO 2000 revisions relating to pleural abnormalities. However, it depends on the "study" protocol used in any particular situation. Specifically, as pointed out in the ILO 2000 guidelines: "In epidemiological studies, therefore, the study protocol will usually require that all appearances described in these Guidelines and seen on the standard radiograph are to be classified. … When the Classification is used for some clinical purposes, the protocol may require that medical readers classify only those appearances which the reader believes or

suspects to be pneumoconiotic in origin." Earlier versions of the ILO system differed with respect to such guidance (e.g., see page 3 of the ILO 1080 guidance booklet.)

Page 4-18, line: Consider edit: "(0 = absence of ~~opacity~~ small opacities or the presence of small opacities less profuse than Category 1, 3 = highest level of ~~opacity~~profusion). Category 0 clearly does not necessarily mean that there are no small opacities present. See ILO guidelines.

Page 4-18, line 19: Consider edit: "with the second number ~~indicating a grade~~ allowing an indication of an alternative category that was seriously considered as an alternative". Sometimes there is no serious consideration of an alternative category—e.g., 0/0/, 1/1, 2/2, and 3/3—so the second number does not always indicate an alternative.

Page 4-18, lines 20-21: Consider edit: "Large opacities are scored based on their (aggregate) dimension(s) ~~within the lung zone(s) they occupy~~." The "within the lung zone(s) they occupy" is confusing in the context of classifying large opacities. See ILO guidance.

Page 4-8, lines 22-23: Consider edit: "including obstructive pulmonary deficits from narrowing and/or distortion of airways, restrictive pulmonary deficits from the decreased elasticity of the lung or displacement of lung tissue by mass lesions, …"

Page 4-18, lines 25-38: Consider edit for clarification: "~~According to the 2000~~ ILO guidelines (ILO, 2002, 1980, 1971)~~,~~ have all classified pleural abnormalities as some form of either (a) localized pleural thickening (LPT) or (b) diffuse pleural thickening (DPT).~~, defined as pleural thickening that is present~~ Beginning with the ILO 2000 guidelines, DPT was to be identified "only in the presence of and in continuity with an obliterated costophrenic angle (CPA)." Previous ILO guidelines (ILO, 1980, 1971) defined DPT without the requirement for CPA obliteration~~;~~. ~~t~~Thus, ~~under the 2000 ILO guidelines, the LPT category includes not only what previous ILO guidelines defined as "plaques," but also what was previously defined may have been identified as DPT without an a contiguous obliterated costophrenic angle. The 2000 ILO category of LPT also includes what previous ILO guidelines defined as "plaques. Different researchers implementing the earlier ILO guidelines variously used terms such as "discrete" or "circumscribed" or "pleural" to describe these plaques.~~ In published reports, researchers who have analyzed the results of ILO-classified chest x-rays have adopted various terms used in different versions of the ILO guidelines that correspond to what ILO 2000 refers to as "pleural plaque" and "localized pleural thickening." These terms include "pleural plaque(s)," "discrete pleural thickening," "circumscribed pleural thickening," and "localized pleural thickening (LPT)." For example, the 1980 ILO guidelines referred to "circumscribed [*pleural thickening*] (plaques)" and the 2000 ILO guidelines refer to "pleural plaques (localized pleural thickening)." As a result, more recent studies sometimes use the term "LPT" to refer to findings that correspond to what past studies would have labelled "pleural plaques.""

It is incorrect that "under the 2000 ILO guidelines, the LPT category includes what was previously defined as DPT without an obliterated costophrenic angle." (See above "Specific Comment on Change in Classification of Pleural Abnormalities from ILO 1980 to 2000.") What seems insufficiently covered in this and similar passages in the draft document is the distinction that can be made between the classification and how researchers have taken classification results

and reduced them for specific studies/analyses. There is an important distinction between the classification system (i.e., how individual chest x-rays are classified) and the categorization of outcomes in any particular study. For example, many studies have simply combined both local and diffuse pleural thickening into a single (combined) "pleural abnormality" outcome. For another example, some studies may ignore the presence of LPT in an individual study subject when DPT is also present in that individual. (See comment below regarding page 4-24, lines 1-11.)

Page 4-18, lines 36-37: There is an apparent misunderstanding expressed in "Examples of pleural plaques (a subset of LPT) as visualized…." Pleural plaques are not a subset of LPT. Rather, in the ILO system, "pleural plaques" and "LPT" are interchangeable terms. (See ILO 2000 guidance, pages 6 and 19.) Thus, suggest the following edit: "Examples of pleural plaques (~~a subset of~~ i.e., LPT) as visualized…."

Page 4, line 37: Suggested edit: "…in Figures 4-2A and 4-2B~~ from Official Journal of the ATS (2004)~~." Leave the citation of the source to the figures themselves. Problems with "Official Journal of" include the odd use of upper case and the fact that the ATS publishes more than one journal.

Page 4-19, line 5: Suggested edit: "Circumscribed pleural thickening (i.e., pleural plaque) was seen in" NOTE: Though the authors of the cited paper used the redundant term "circumscribed plural plaque," there is no need for the draft IRIS document to confuse readers by using that redundancy.

Page 4-20, line 4: Consider edit: "and ~~of~~ air flow".

Page 4-20, line 5: Consider edit: "amount of air that can be exhaled forcefully after a full inspiration." Both the forceful expiration and the maximum prior inspiration are key factors in the measurement of FVC.

Page 4-20, line 6: Similarly, consider edit: "amount of air exhaled forcefully after a full inspiration in a given time period".

Page 4-20, line 8: Consider edit: "and ~~multiple~~ measurements of multiple forced expirations (≥3) are typically needed". Multiple measurements are made from each expiration, but a key is assessing their repeatability on multiple expiratory maneuvers.

Page 4-20, line 13: Consider edit: "the reduction in FVC would typically be greater than that for FEV1".

Page 4-20, lines 14-15: Consider edit: "from ~~inflammation or scarring of the parenchyma,~~ interstitial lung disease~~, fibrosis,~~ (including inflammatory and/or fibrotic diseases) or other conditions that restrict the ability of the lungs to expand." The suggested edit avoids apparent redundancy in the original wording.

Page 4-20, lines 16-18: Consider edit: "Obstructive lung function (or obstructive ventilatory defect) refers to reduced airflow, and is most commonly characterized by ~~inflammation or obstruction~~ narrowing of the airways. It is indicated by a reduction in FEV1 without ~~an accompanying change~~ a proportionate reduction in FVC…". Deleting "inflammation or obstruction" in this sentence avoids circularity of "obstruction" characterizing "obstruction" and also rids the sentence of a sole specifying pathological description (inflammation) when other pathological descriptions (e.g., airways scarring, etc.) underlie obstructive airflow. Airways obstruction can also result from distortion of airways by processes extrinsic to the airways. The key with respect to reductions in FEV and FVC is not that FVC cannot be reduced in obstructive lung function—indeed FVC is often reduced in obstructive impairment—but rather that any reduction seen in FVC is not proportionate to larger reductions in FEV.

Page 4-20, lines 19-20: Consider edit: "Both restrictive and obstructive conditions can result in dyspnea (shortness of breath).~~,~~ Many of the various underlying diseases that are associated with restrictive and obstructive lung function cause cough~~,~~ and chest pain." NOTE: it is reasonable to relate dyspnea to ventilatory impairments in a very direct sense. But the relationship of cough and chest pain to impairment cannot be done so directly. Some diseases that cause substantial ventilatory impairment do not themselves cause cough or chest pain.

Page 4-20, line 22: Suggested edit of section heading: ***"Results: ~~pathological alterations~~ Radiographic abnormalities of lung parenchyma and pleura …"***
Page 4-20, line 28: Consider edit: "For the analysis, ~~the~~ classification indicating pleural abnormalities".

Page 4-20, lines 32-38: Consider deleting the last sentence in this paragraph: "~~This classification would be equivalent to the LPT 35 classification used in the revised ILO guidelines (ILO, 2002); however, the results reported in the 36 paper are for thickening on the chest wall only (rather than including other sites) are not 37 equivalent to the 2000 ILO LPT classification.~~"

First, it is incorrect that "*the results reported in the paper are for thickening on the chest wall only.*" In fact, Amandus et al. (1987a) separately reported results for "any pleural change," "pleural calcification," and "pleural thickening on the wall" (see Amandus et al. and see IRIS document Table 4-7). Second, it is incorrect that Amandus's category of "pleural plaque, diffuse pleural thickening of the chest wall, diaphragm or other site, but excluded costophrenic angle obliteration" would be equivalent to the LPT classification used in the revised ILO guidelines (ILO, 2002)." LPT in the ILO 2000 version (published in 2002) does not include diffuse pleural thickening. LPT is localized (i.e., not diffuse) pleural thickening.

Page 4-22, lines 1-2: Consider edit to correct apparent errors: "Amandus et al. (1987a) reported pleural thickening of the chest wall in 13% and small opacities (≥1/0) in ~~9.1%~~ 9.8% of ~~current~~ employees." A total of 18 of 184 were determined to have small opacities (profusion ≥1/0); and the study was of workers employed anytime between 1975 and 1982 who had accumulated 5 years of tenure at the Libby vermiculite operation.

Page 4-22, lines 2-4: Given the inclusion of former workers by Amandus et al., the comparisons in following statement can be questioned: "Similar data were reported by McDonald et al.

(1986b), with 15.9 and 10% with pleural thickening of the chest wall and small opacities, respectively."
If all (former as well as current) workers studied by McDonald et al. are considered (see preceding comment on Page 4-22, lines 1-2 that the Amandus et al. results were not restricted to current workers), the appropriate comparison figures would be 18.4% (45 of 244)—rather than 15.9%—with small opacities (≥ 1/0) and 27.9% (68 of 244) —rather than 10%—with pleural thickening. (See the remainder of this same paragraph, lines 7 to 11.) In addition, a minor point….There seems to be no rationale for expressing the McDonald et al. result for pleural thickening rounded off to the nearest percent when the other results summarized in this statement were expressed to the nearest tenth of a percent.

Page 4-22, lines 23-25: Consider edit for clarity: "The lack of statistical significance in these models may reflect a nonlinearity ~~resulting from~~ reflected in the ~~lower~~ observation of the lowest prevalence ~~in the second expose Category 2 compared to exposure Category 1~~ not in the lowest exposure category, but rather in the second of four exposure categories."

Page 4-22, lines 31-33: Consider edit: "Diffuse pleural thickening (in the presence of ~~costrophenic~~ costophrenic angle obliteration) and parenchymal ~~lesions~~ small opacities (profusion ≥1/0) were each detected in 5% of the workers."

Page 4-22, lines 36-37: Consider edit: "For a diagnosis of restrictive spirometry (excluding mixed restrictive and obstructive spirometry) (prevalence = 16%), …"

Page 4-24, lines 3 and others: "localized pleural thickening is spelled out here without using the abbreviation "LPT" (which has been established). Likewise for DPT. Suggest electronic search of the document for these two terms and careful consideration of where "LPT" or "DPT" abbreviations would suffice in place of the spelled out terms.

Page 4-24, lines 1-11: This paragraph description of how radiographic abnormalities were assessed by Rohs et al. (2008) is problematic. One problem is that the description mixes Rohs' description of criteria for a final determination of LPT with the ILO's description of when to classify DPT on the lateral chest wall; and it confuses ILO classification of a chest X-ray (CXR) by an individual B Reader with how Rohs et al. used multiple ILO classifications to make a final determination for each CXR. In addition, the draft document inappropriately invokes the notion that this is all consistent with the ILO 2000 system. The Rohs et al.'s pertinent description of methodology relating to the CXRs is not well presented, but it seems clear that the approach described by Rohs et al. would—for example—take a film classified by each of the three B Readers as having LPT plus costophrenic angle obliteration plus DPT (all according to the ILO classification system) and categorize it (for purposes of analysis in this study) as having DPT but not LPT. In other words, for the Rohs et al. radiographic determinations and subsequent analyses, DPT trumped LPT. There is nothing clearly wrong with that approach, but it is inappropriate to assert that this is consistent with the ILO system, which has nothing to say about it. A suggested simplified replacement paragraph intended to "say it like it was" without invoking any "consistency with ILO 2000" other than to indicate that the readers classified the CXRs using that system: "Three board-certified radiologists, blinded to all identifiers, independently classified the radiographs using the 2000 ILO classification system (ILO, 2002).

Rohs et al. (2008) determined that localized pleural thickening was present when at least two of the three readers recorded pleural thickening without costophrenic angle blunting, that diffuse pleural thickening was present when at least two of the three readers recorded pleural thickening with blunting of the costophrenic angle, and that interstitial abnormalities indicative of asbestosis were present if at least two of the three readers identified small irregular opacities of profusion 1/0 or greater. Radiographs classified as unreadable (*n* not reported) were not used in the analysis."

Page 4-24, line 14: Suggested edit: "The 80 workers with pleural thickening ~~include~~ included 68 with LPT (85%) and".

Page 4-25, Table 4-9 title: Suggested edit: "**Prevalence of pleural ~~pathological alterations~~ abnormalities according to…**"

Page 4-25, lines 6-7: Suggested edit: "BMI is a potentially important confounder because fat pads can ~~sometime~~ sometimes be misclassified on chest x-rays as localized pleural thickening."

Page 4-26, lines 5-7: It is asserted here that: "In addition, none of these other chemicals is volatile. Thus, it is unlikely that workers would be co-exposed by inhalation to these other chemicals." Just because the chemicals were not volatile does not mean that they were not aerosolized (in wet or dry form).

Page 4-26, line 14: Suggested edit: "The prevalence of pleural ~~pathological alterations~~ abnormalities was 28.7% in 2004" "Pleural abnormalities" is the ILO term.

Page 4-26, line 15: Suggested edit: "compared to a 2% prevalence observed in 1984 (10/501). *[Insert here a sentence that parallels the preceding sentence on pleural abnormalities but summarizes small opacities findings from the 1984 to the 2008 studies.]* ~~This increase~~ These increases in prevalence ~~is~~ are most…"

Page 4-27, line 30: Suggested edit: "However, if participation was ~~related~~ differentially ~~based on~~ related to exposure and".

Page 4-28, line 15: Suggested edit of section heading: "**Results: ~~pathological alterations~~ Radiographic abnormalities of ~~parenchema~~ lung parenchyma and pleura**". The studies relating to Libby were of chest x-rays, etc., not of tissue specimens. Spell parenchyma with a "y". And specify that it was lung parenchyma and not some other parenchyma that was assessed radiographically.

Page 4-28, lines 27-28: Suggested edit: "after excluding ~~former workers from~~ those who had formerly worked at the vermiculite mining and milling operations". This suggested edit avoids ambiguous wording implying that these former workers were excluded from the vermiculite operations.

Page 4-28, line 28 and 31: Suggested edit: "pleural ~~anomalies~~ abnormalities". ILO system refers to them as "abnormalities, not "anomalies."

Page 4-29, line 20: Suggest deleting comma: "the plant)~~,~~ based on".

Page 4-29, line 22: Suggested edit: "..with a worker employed at the plant), measures…".

Page 4-30 and 4-31, Table 4-11title: Suggested edit: "~~Pathological alterations~~ **Radiographic abnormalities** of ~~parenchema~~ **lung parenchyma** and pleural in …".

Page 4-30, Table 4-11: Suggested edit of Peipins et al. results: "Moderate-to-severe ~~FVC$_1$~~ restriction". If this "FVC" is retained, at least delete the subscripted "1" associated with it.

Page 4-30, Table 4-11: Suggested edit of Weill et al. study details: "Outcomes: (1) Small lung opacities ~~Profusion ≥1/0:~~ defined as "any two readers reporting any profusion ≥1/0," (2) Plaque~~:~~ defined as "any two readers reporting any diaphragm or wall, or other site plaques, even if the readers did not agree on specifics~~.~~," (3) DPT or CAO~~:~~ defined as "any two readers reporting any DPT or CAO, even if the readers did not agree on specifics."

Page 4-30 and 4-31, Table 4-11: Suggested edit of Weill et al. results: "Profusion" bears no relation to "Plaque" or to "DPT/COA," so Profusion should be deleted entirely or perhaps moved to the "≥1/0" cell. Alternatively, the Weill et al. design and results descriptions could very reasonably employ the abbreviation "SO" (for "small opacities" as an outcome in place of the current "≥1/0" label for this outcome.

Page 4-31, Table 4-11: Suggested edit to Alexander et al. design: "Clinical examination, chest x-rays read by 2000 ILO classification guidelines ~~(posterior-anterior)~~."

Page 4-32, line 12: Suggested edit: "for two ~~other~~ symptoms,".

Page 4-32, Table 4-12 title: Suggested edit: "**Pulmonary function and respiratory ~~system changes~~ symptoms/conditions …".**

Page 4-32, Table 4-12: Suggested edit of table showing Vinikoor et al. results: "OR (95% CI)[a] by Exposure Category". Suggested edit intended to clarify what the exposure column headings are.

Page 4-33, line 1: Suggested edit of section heading: "~~*Pathological alterations*~~ *Radiographic abnormalities of lung ~~parenchema~~ parenchyma and pleura in relation to pulmonary function*".

Page 4-33, lines 5-10: There is more to be summarized about Weill et al. Suggested edit: "…reported an association between the presence of pleural plaques and a reduced mean ~~decrement~~ (approximately 5% below predicted) in FVC ~~measures~~ (Weill et al., 2011), and of an increased risk of restrictive pulmonary function (Larson et al., 2012b). The authors of the first study (Weill et al., 2011) concluded that the ~~change~~ mean reduction in FVC associated with pleural plaques (in the absence of other pleural abnormality or small opacities in the lung parenchyma) was "probably clinically insignificant.," though a modest mean effect can indicate clinically significant plaque-associated lung function effects on a subset of individuals included

in that mean. The authors did not offer an assessment of "clinically insignificant" for their finding of the more substantial mean reduction of FVC (>20%) associated with diffuse pleural thickening (in the absence of small opacities in the lung parenchyma)." A relevant paragraph from the Weill et al. paper (with italicized/bracketed annotations inserted): "Our review of the ATSDR data does not support the conclusion that pleural changes are associated with clinically significant reduced lung function. According to PEIPINS [6], 1,183 participants >25 yrs of age were categorised as having any pleural abnormality. However, in a more focused analysis *[Note that this "more focused analysis was restricted to plaques/LPT.]*, our review of the lung function in the group (n=482) that had pleural plaques but no other radiographic abnormalities *[i.e., not DPT or small opacities]* indicated that mean FVC was 95.63% pred." *[Note that the same Table 4 from which this 95.63% figure is taken also shows that the group (n=33) who had DPT/CAO (but no other radiographic abnormalities), had a mean FVC that was only 78.76 % predicted. Moreover, note that these values are presented in terms of percent of predicted values (i.e., relative to a norm of 100%) based on general healthy/non-smoking population norms. But that same Table 4 shows that with a mean FVC of 103.15% predicted, Libby subjects with no radiographic abnormalities actually exceeded 100% of predicted by several percent—making those lower than normal mean FVC values for those with plaques and those with DPT that much more substantial. All these results are sown in Table 4-13.*]

Page 4-33, line 10: Suggested edit: "….rather than on a difference in ~~the~~ population means ~~of the distribution~~".

Page 4-33, lines 12-14: Suggested edit: "…~~increasing~~ risk of restrictive lung function ~~was seen~~ increased with increasing index score based on plaque width and extent ~~size~~. ~~and across categories of~~ Among those with restrictive impairment, risk of functionally significant pulmonary impairment was associated with the presence of plaques with a high index score (OR 1.7, 2.1, and 2.3, respectively, for outcomes of mild, moderate, and severe levels of impairment)."

Page 4-33, lines 14-17: Suggested edit: "These two analyses, using essentially the same data set, illustrate that ~~the clinical perspective of an~~ what ~~appears~~ may appear on first thought to be an "insignificant" ~~decrement in~~ impact on lung function (i.e., a relatively small mean ~~difference~~ decrement in lung function among an affected population) is entirely compatible with ~~a population perspective of an increased risk of an adverse outcome~~ the presence of clinically important individual lung function decrements for some individuals within that population."

Page 4-33, lines 20-27: Suggested edit: "Whitehouse (2004) examined changes in pulmonary function measures in 123 LAA-exposed patients (86 former employees of the vermiculite operations, 27 family members of employees, 10 Libby residents with only environmental exposures) seen in a pulmonary disease practice serving the Libby, MT area. The mean age of ~~study participants~~ these patients was 66 years~~, and the mean follow-up time was 35 months~~. ~~Chest x-rays or high-resolution computed tomography scans revealed no evidence of interstitial changes in 67 (55%) of the 123 patients, and~~ Of these 123 patients, 56 ~~patients~~ (45%) were ~~found~~ felt to have radiographic evidence of interstitial changes at profusion ~~C~~category 0/1 or 1/0 evident on their initial chest x-ray. No evidence of interstitial changes were found in the other 67 (55%), but all 67 had evidence of pleural disease (either pleural plaques or diffuse pleural

thickening). For the entire group of 123, the average yearly loss of pulmonary function over a mean follow-up time was 35 months was 2.2% for FVC, 2.3% for total lung capacity, and 3.0% for DLCO. For the subset of 67 patients with pleural disease (in the absence of interstitial abnormality), the corresponding mean declines were 2.2%, 2.3%, and 2.9%, respectively. " The suggested edit is intended to organize the information, and add information about the lung function changes among those with pleural disease only. However, this sort of clinical study still does not provide anything useful vis a vis EPA's IRIS effort. A clinical paper with more relevance to EPA's IRIS effort is a new study by Black et al. (2014) (see http://onlinelibrary.wiley.com/doi/10.1002/ajim.22330/pdf). They reported on a small case series of patients with progressive pleural thickening associated with progressive decline in lung function. A quote from the paper: "The form of pleural thickening described in the five cases does not conform to "typical" patterns of pleural disease described in asbestos disease. The International Classification of Radiographs of Pneumoconioses [International Labour Office, 2011] provides definitions and standards for classifying two basic types of pleural thickening in asbestos disease: pleural plaques and diffuse pleural thickening. … The cases presented here do not fit either of these two "traditional" definitions for pleural thickening. They demonstrate a lamellar thickening of the pleural surface that progressively extends vertically and along the inner border of the chest wall and the surface of the lungs. It progressively increases in thickness although persisting as an overall generally thin lamellar pleural thickening that is usually missed in regular chest X-rays, even when interpreted by experienced B-readers. This radiographic change, though typically subtle, is accompanied by decrements in pulmonary function, limitations of physical activity and/or significant chest pain that is usually very difficult to treat." (Perhaps this report could be mentioned in the last paragraph of this section of the report, where the reports by Wright and Srebo & Roggli are briefly covered.

Page 4-35, lines 4-7: The paragraph on the Winters et al. study ends with a long sentence describing limitations of this study. This is in contrast to the preceding description of the Whitehouse study. Suggest that the descriptions be consistent and either include or not include limitations for both studies.

Page 4-35, Table 4-14: There is no indication of the units in which the lung function results are presented. Suggested edit of table heading: "Mean % predicted (SD)~~, by group~~" [No need for the "by group", as that is obvious.]. Additional suggested edits of table sub-headings: "Pleural, only" and "Interstitial, only"

Page 4-36, lines 6-8: Consider edit: "and various ~~forms of~~ adverse respiratory effects, with effects seen in both occupationally exposed worker populations and in community populations with ~~residential (~~nonoccupational~~) routes of~~ exposure."

Page 4-36, lines 24-27: unclear why there is not more about lung function impacts associated with DPT. The focus seems to be weighted towards lung function impacts of plaque/LPT, mentioning Weill's finding of a small mean effect of plaque, but not mentioning Weill's finding of a much more substantial lung function deficit among those with DPT.

Page 4-36, lines 5 and 13: Consider edit: "category of cardiovascular~~ related~~ mortality"

Page 4-84, line1: Consider edit: "Although the adverse effects of asbestiform tremolite are reported" [Tremolite can be either asbestiform or non-asbestiform.]

Page 4-84, line 14-16: Suggested edit: "~~Radiographic evidence of small opacities in the lung is direct evidence of scarring of the lung tissue and is the~~ In clinical practice, fibrotic scarring of lung tissue consistent with mineral dust and mineral fiber toxicity is most commonly identified as small opacities in the lung on radiographic examinations." ["Direct evidence" would take the form of examination of lung tissue obtained via biopsy, surgical excision, or post-mortem. Also small opacities are not necessarily evidence of scarring, though in asbestosis, they typically are.]

Page 4-84, lines 17-20: Consider edit: "scarring of the parenchymal tissue of the lung contributes to ~~measured~~ changes in pulmonary function, including ~~obstructive pulmonary deficits from narrowing airways,~~ restrictive pulmonary deficits ~~from impacting the~~ due to increased stiffness (reduced elasticity) of the lung, ~~as well as decrements in~~ impaired gas exchange due, in part, to alveolar wall thickening, and sometimes mild obstructive deficits due to asbestos-induced airways disease." [Such scarring contributes to reduced lung function, whether or not it is measured. Main effects are restriction and impaired gas exchange, so mention them first. Give lesser importance to obstructive effects, as these are not so obvious and not so well understood. See ATS (2004).]

Page 4-84, line 23: Suggested edit: "processed, have ~~an~~ been found to have increased prevalence" [Use of present tense seems odd in the context of some studies that are now decades old.]

Page 4-85, line 3: Suggested edit: "(~~grade~~category 1/0 or greater)" [ILO terminology]

Page 4-85, line 4: Suggest inserting comma: "respectively, of the expected value"

Page 4-85, lines 25-27: Consider edit: "These ~~diseases~~ outcomes and the finding of a positive exposure-response relationship for mortality from all nonmalignant respiratory diseases are not inconsistent with asbestos toxicity among Libby workers~~, and the evidence of a positive exposure-response relationship for mortality from all nonmalignant respiratory diseases, supports this association~~." [The original wording seemed to imply much more about these findings than is reasonably supportable.]

Page 4-85, line 30: Consider edit: "Pleural thickening caused by mineral fiber exposure mainly includes two distinct biological" [The two discrete types of lesions mentioned in this sentence are a conceptual construct. Real pathology is much more complicated.]

Page 4-85, line 32-34: Consider edit: "Both of these forms of pleural thickening can be ~~viewed~~ identified on standard radiographs, however smaller/thinner plaques and thinner diffuse thickening ~~lesions~~ may not be detected, particularly if they are not calcified or are obscured by other normal chest structures. (~~h~~High-resolution computed tomography is a radiographic method that ~~can~~ is more sensitive and specific ~~detect smaller lesions~~ than ~~are visible on~~ standard chest x-rays (i.e., it can detect pleural abnormalities that are not evident on standard chest x-rays and it can more reliably exclude fat tissue that sometimes masquerades as pleural thickening on

standard chest x-rays)." It is not just that "smaller" pleural lesions can't be detected. And it is not just that HRCT is more sensitive; it is also more specific.

Page 4-85, line 34 to Page 4-86, line 10: Consider edit: "~~Current~~ ILO guidelines (2002) state that pleural thickening on x-ray can be ~~Localized (LPT) or~~ ~~Diffuse~~ diffuse (DPT) or localized (LPT) or. The term "LPT" was not ~~defined~~ explicitly used as such ~~by the ILO~~ until the 2000 guidelines, which used the term "pleural plaques (localized pleural thickening)"~~were published~~ (ILO, 2002). Previously, the 1980 ILO guidelines ~~defined only circumscribed pleural thickening (plaques) and~~ two main categories—diffuse pleural thickening (DPT), with or without costophrenic angle obliteration, and what was then referred to as "circumscribed pleural thickening (plaques)." ~~The 2000 ILO revision defines LPT as the union of what was previously defined as plaques found on the chest wall or in other locations (e.g., diaphragm) in the 1980 guidelines, and what was previously defined as DPT without costophrenic angle obliteration.~~ Neither classification for pleural thickening (LPT or DPT) in the 2000 ILO guidelines corresponds exactly with the pleural thickened categories defined in the previous versions of the ILO classification ~~systems~~ (1980, 1971).~~for pleural thickening; LPT is defined more broadly than the previous category of pleural plaques, while~~ DPT is defined more narrowly due to the requirement for contiguous costophrenic angle obliteration newly established in the 2000 ILO guidelines, and there is now an explicit 3-mm minimum thickness criterion that was not included in the earlier versions. Both changes were intended to make the ILO system for classifying pleural abnormalities more specific for asbestos-related effects. ~~Different researchers have used different terminology for circumscribed pleural thickening or plaques when implementing the 1980 ILO guidelines, most often using the terms "pleural plaques."~~ In published reports, researchers who have analyzed the results of ILO-classified chest x-rays have adopted various terms used in different versions of the ILO guidelines that correspond to what ILO 2000 refers to as "pleural plaque" and "localized pleural thickening." These terms include "pleural plaque(s)," "discrete pleural thickening," "circumscribed pleural thickening," and "localized pleural thickening (LPT)." See above Specific Comment on Change in Classification of Pleural Abnormalities from ILO 1980 to 2000. Also, be careful about calling the ILO 2000 guideline "current." ILO now has a more recent version of the guidelines (see http://www.ilo.org/safework/info/WCMS_108548/lang--en/index.htm) that include provisions relating to digital radiography, though the ILO 2000 versions remain applicable for conventional "film-screen" radiography.

Page 4-86, line 9: Consider edit of heading: "**~~Libby Amphibole Asbestos~~ Summary of Noncancer Health Effects of Exposure to Libby Amphibole Asbestos**"

Page 4-86, line 10: Consider edit: "The studies ~~in~~ of humans summarized"

Page 4-86, line 15: Consider edit: "that ~~used~~ processed LAA-containing vermiculite ore ~~contaminated with LAA~~"

Page 4-86, line 22: Consider edit: "similar pleural abnormalities and pulmonary function deficits consistent with ~~parenchymal~~ effects of tissue damage caused by LAA" [Not sure why parenchymal effects" is invoked here. Pleural abnormalities are themselves associated with lung function deficits.]

Page 4-86, lines 23-24 : Consider edits: "~~Although limited, a~~Animal studies also support the toxicity of LAA to pleural and pulmonary tissues." [Why emphasize "limited" here? Better to do that where it's more appropriate.]

Page 4-88, lines 12-13: Consider edit: "The etiology pathogenic mechanism(s) of parietal plaques is largely unknown with respect to mineral fiber exposure."

Page 5-13: Figure 5-3: Please check this figure. Several of the numbers in the Venn diagrams appear to be wrong. For example, the upper right diagram shows some individuals had both LPT and DPT, but that does not seem possible based on numbers presented by Rohs et al. in their 2008 paper. According to that paper, a total of 80 had pleural abnormalities: 64 had LPT only, 10 had DPT only, 4 had LPT with small opacities, and 2 had DPT with small opacities. That totals 80, with no individuals having both LPT and DPT. Even a "between-the-lines" reading of their description of how they categorized pleural thickening outcomes suggests that LPT and DPT were mutually exclusive, so they both couldn't be present in the same individual.
Page 5-14, Line 34-35: Reconsider wording: "whether pleural plaques (a subset of LPT) impact lung function." [Without further specification, the implication that "pleural plaques are a subset of LPT" reflects a lack of conceptual rigor. It might be said that pleural plaques as classified under the ILO 2000 guidelines encompass more abnormalities than pleural plaques classified under ILO 1980 guidelines.]

Page 5-15, line 29: Consider edit: "interstitial opacity profusion ~~scores~~ of 1/0 or greater".

Page 5-15, line 32: Suggest inserting comma: "(median of 317.8 fibers/cc-yr), and highest for".

Page 5-15, lines 33-34: No need for upper case "C" in the three occurrences of "category.

Page 5-16, lines 1-2: Consider edit: "The clinical perspective suggests that pleural plaques do not clinically ~~impede~~ impair lung function for most people who have asbestos-related plaques."

Page 5-16, line 9: Consider edit: "statistically significant decreases in mean".

Page 5-16, lines 14-15: Consider revising "between those with no radiographic abnormalities and those with LPT or pleural plaques" to clarify whether or not the latter group(s) were free of any evidence of parenchymal small opacities.

Page 5-16, lines 16-23: Consider edit: "As stated by ATS (2004), the majority of individuals with pleural plaques ~~(subset of LPT)~~ alone may have well-preserved lung function. However, ~~this may not be the case~~ for individuals who are already at the lower end of the "normal" range of function, already have compromised function, or have increased vulnerability or susceptibility due to other factors (such as chronic disease, other environmental exposures, smoking, etc.)~~. For any of these individuals~~, even a relatively small decrease in lung function ~~may~~ can be important~~, but once averaged into the whole study population (i.e., looking at only average changes in the whole group) the sensitive individuals' contribution to the population-wide change in mean pulmonary function measures is muted~~."

Page 5-16, lines 24-29: Consider edits: "Accordingly, ~~there is a difference in considering~~ what ~~is~~ may be significant from a clinical perspective (i.e., an individual effect, sometimes impacting particularly vulnerable individuals, that impairs health) ~~compared to an epidemiological perspective~~ is not readily evident to those who consider only mean effects on populations. ~~The clinician's focus is the individual patient, and decisions made in that context (i.e., benefits/risks of medical treatments or tests). In contrast, the population-level (risk assessment) perspective considers any changes in the population distribution of pulmonary function and the potentially increased risks of adversity to subpopulations of the general population~~. [Population-level perspective can take the form of relative frequency of categorically defined impaired lung function, though such studies are much less frequent that those based on comparing mean effect in exposure-defined subpopulations.]

Page 5-17, line 18: Correct spelling of "decrements".

Page 5-18, lines 3-4: Recheck: "Among the 66 individuals with LPT, 10 also had DPT or interstitial opacities,…" [Rohs et al. (20008) clearly state: "Of the participants with pleural changes, 64 had localized pleural thickening only, 10 had diffuse pleural thickening only, and 6 had both pleural thickening (4 localized and 2 diffuse) with interstitial changes. Of the 80 participants with pleural changes, …" This would indicate that there were 68 (64+4) and not 66 with LPT. Rohs et al.'s numbers (presented in their paper) means that there were no individuals with both LPT and DPT. A total of 80 had pleural abnormalities: 64 had LPT only,10 had DPT only, 4 had LPT with small opacities, and 2 had DPT with small opacities. See above related comment on Figure 5-3.]

Page 6-2, line 13: Consider edit: "wallboard. ~~Other r~~Residents living".

Page 6-3, line 16: Consider edit: "following exposure to ~~Libby Amphibole~~LAA".

Page 6-3, lines: Consider edits: "Although the adverse effects of asbestiform tremolite are reported in 19 the literature, the contribution of asbestiform winchite and asbestiform richterite to the aggregate effects ...," [all three of these minerals can be in non-asbestiform, but especially in this Summary, it might be good to clarify the asbestiform nature of these minerals in LAA.]

Page 6-3, lines 27-28: Consider edit: "Radiographic assessments of study participants in both cohorts ~~indicate radiographic~~ identified abnormalities consistent with".

Page 6-3, lines 7-8: Consider edit: "Decreased pulmonary function (as percentage of the predicted forced vital capacity) ~~is~~ was reported for participants with radiographic abnormalities (Weill et al., 2011)."

Page 6-5, lines 4-5: Consider edit: "~~However, l~~Limitations in the number, scope, and design of these studies make it difficult to reach conclusions ~~as to~~ about the role of asbestos exposure in either cardiovascular disease or autoimmune disease."

Page 6-6, lines 20-21: Consider edit: "~~Certain populations could be more susceptible than the general population to adverse health effects from exposure to LAA.~~" Alternatively: "Certain segments of the general population~~s~~ could be more susceptible ~~than the general population~~ to adverse health effects from exposure to LAA."

Page 6-11, lines 31-32: Suggested edit (including hyphenation of "asbestos-related": "HRCT can identify asbestos-related lesions in the respiratory tract~~, which~~ that cannot be identified by standard radiographs"

Page 6-12, Lines 34-40: Consider edit: "Conventional radiographs—rather than ~~the~~ more sensitive and specific high-resolution computed tomography—were used to determine the health outcome. Localized pleural thickening may be difficult to detect on these radiographs, leading to the potential for outcome misclassification. However, uncertainty in the detection of LPT in each individual is considered minimal ~~due to the use of a team of highly~~ because determinations of pleural outcomes were based on agreement among independent classifications of each radiograph done by multiple qualified chest radiologists ~~evaluating the radiographic films and the use of consensus diagnosis~~." [Not a "team," in that they classified independently. Not a "consensus," in the sense of a consensus reading of each film done jointly by multiple readers. Not a "diagnosis" in the clinical sense.]

Appendix I: [Time limitations did not permit this reviewer to suggest specific edits for this Appendix.]

Page I-1, lines 13-35: Suggested edit: "The term "LPT" ~~LPT~~ was not ~~defined by the ILO~~ explicitly used as such by the ILO until the 2000 guidelines ~~were published~~ used the term "pleural plaques (localized pleural thickening)" (ILO, 2002)."

See comment above on Change in Classification of Pleural Abnormalities from ILO 1980 to 2000, as well as editorial comments suggesting edits intended to correct views in the draft IRIS document of the ILO 2000 changes relating to classification of pleural abnormalities. The draft document seems to make too much of the changes made, and this aspect of the draft prevents a more direct and unencumbered presentation as it relates to LPT terminology and impacts of ILO 2000 on same.

Page I-28, lines 18-21: Reconsider: "First, LPT comprises both pleural plaques as defined in 1980 ILO in addition to plaques in other locations and what was formerly defined as DPT without costophrenic angle obliteration."
See: Specific Comment on Change in Classification of Pleural Abnormalities from ILO 1980 to 2000, as well as other editorial comments.

Page I-29, lines 18-21: Reconsider: "While no medical society has expressed a consensus statement on the individual-level effects of the pulmonary deficits associated with LPT as defined by the ILO 2000 guidelines, there have been such statements regarding the impact of deficits associated with plaques as defined by the ILO 1980 guidelines." This statement reflects an unwarranted view of what the ILO 2000 changes involved. See: Specific Comment on

Change in Classification of Pleural Abnormalities from ILO 1980 to 2000, and other related comments made concerning LPT terminology.

Page 1-30, lines 29-31: Consider edit: "exposure and indicate that pleural plaques (~~and~~ LPT) are associated with declines in pulmonary function. Although the decrements in mean pulmonary function measures associated with the presence of pleural plaques ~~or~~ (LPT) may not be generally considered clinically significant". See above Specific Comment on Change in Classification of Pleural Abnormalities from ILO 1980 to 2000, and other related comments made concerning LPT terminology. Use these terms as does ILO 2000, on which basis there is no reasonable justification for thinking in terms of "pleural plaques **and** LPT" or "pleural plaques **or** LPT." ILO 2000 views these as essentially equivalent terms, as evidenced by the "Pleural plaques (localized pleural thickening)" sub-heading on page 6 of the ILO 2000 guidelines booklet, by the content on pages 5 and 6 under this sub-heading, and by the simple "Pleural Plaques" heading on the ILO Reading Sheet presented on page 18 of the ILO 2000 guidelines.