DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR SILICA

March 2017

Peer reviewers for the third pre-public comment draft of the Toxicological Profile for Silica were:

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All typographical errors were corrected.

Comments provided by Reviewer #1:

COMMENT 1: Page 2, lines 32-34: Redundant.

RESPONSE: *Lines indicated were deleted.*

COMMENT 2: Page 4, line 7: Typically 10 or more years, not several.

RESPONSE: *Change made as indicated.*

COMMENT 3: Page 4, line 14: See Hessel, 2000 cited herein and Erren 2009a herein.

RESPONSE: *Regarding the statement that "silicosis and lung cancer pose the greatest risks to human health," no change has been made. A large body of literature supports that silicosis poses a significant risk to human health. For lung cancer, the International Agency for Research on Cancer (IARC 2012), National Institute for Occupational Safety and Health (NIOSH 2002) and the National Toxicology Program (NTP) 13th Report on Carcinogens (NTP 2014) have concluded that respirable c-silica is carcinogenic to humans.*

COMMENT 4: Page 4, line 31-32: Needs to be more nuanced and acknowledge the controversy

RESPONSE: *Text was revised to be consisted with text noted in Comment 6.*

COMMENT 5: Page 17, line 8: I question the failure to develop any MRLs for silica. ATSDR has developed MRLs for other substances that have variable toxicity depending on form/particle size/ionic compound/surface characteristics.

RESPONSE: *The Agency elected not to develop MRLs for c-silica because silicosis, the most sensitive effect, is a serious adverse effect, and a no-observed-adverse-effect level (NOAEL) value for silicosis has not been identified. Per ATSDR guidance, MRLs are not to be derived based on a LOAEL value for a serious adverse effect. The Agency elected not to develop MRLs for a-silica as available toxicity data for various types of a-silica show a wide range of potencies, and there are limited data for each type of a-silica.*

COMMENT 6: Page 19, lines 4-15: Much better phrasing that page 4.

RESPONSE: *No change needed.*

COMMENT 7: Page 22, lines 22-24: Not true. PFT findings are variable depending on co-exposures (i.e., smoking) and stage of disease but they are still useful in diagnosis/monitoring silicosis.

RESPONSE: *Text was revised: "Pulmonary function tests can be used to evaluate pulmonary function and are useful in monitoring silicosis."*

COMMENT 8: Page 22, lines 29-34: Contradicts earlier paragraph that states no PFTs are useful.

RESPONSE: *Text in the earlier paragraph was revised to resolve the contradiction as noted (see Comment/Response 7).*

COMMENT 9: Page 23, line 12-13: Also pulmonary hypertension, right heart strain and COR pulmonale.

RESPONSE: *Text revised to include effects noted above.*

COMMENT 10: Page 25, line 3-4: Related more to number of workers with c-silica exposure and regulatory environment than level of development.

RESPONSE: *The sentence noted above was deleted.*

COMMENT 11: Page 41, lines 14-15: Equally likely to overestimate. More accurate to say quantitative risk estimates should be interpreted with caution.

RESPONSE: *Change made as indicated above.*

COMMENT 12: Page 41, line 29: Where does this number come? I don't see it in the cited articles a 17%. Rate of systemic sclerosis is difficult to believe.

RESPONSE: *The incidence range was removed from this sentence.*

COMMENT 13: Page 43, line 9: Swollen glands is the colloquial term; use "lymphadenopathy" instead.

RESPONSE: *Change made as indicated above.*

COMMENT 14: Page 45, lines 7-8: Rephrase.

RESPONSE: *Sentence revised to: "However, these studies did not provide quantitative estimates of exposure."*

COMMENT 15: Page 52, lines 6: Replace "smokers and nonsmokers" with "smoking and nonsmoking"

RESPONSE: *The paragraph with the statement indicated above was deleted as part of the revision of the* "Crystalline Silica, Smoking and Lung Cancer" *section based on Comments 28 and 29 from Reviewer #2).*

COMMENT 16: Page 80, lines 1-3: This doesn't imply dermal absorption. It may represent deposition of inhaled or ingested silica in the skin.

RESPONSE: *The following sentence was added: "This finding could indicate dermal absorption or dermal deposition of inhaled or ingested silica."*

COMMENT 17: Page 85, lines 1-8: Redundant from 3.4.2 Distribution.

RESPONSE: *Sentence has been revised to: "Based on observations made in rodents of silica particles in mediastinal lymph nodes following inhalation, lymph may provide a mechanism for system distribution of silica particles (Absher et al. 1992; Vacek et al. 1991)."*

COMMENT 18: Page 86, lines 29-30: Clarify.

RESPONSE: *Sentence has been revised to: "Injury to other pulmonary cells (e.g., epithelial cells and fibroblasts) resulting from interactions with c-silica particles may also contribute to alveolitis."*

COMMENT 19: Page 89, lines 15-17: Clarify.

RESPONSE: *Sentence has been revised to: "As discussed above, silicosis is associated with chronic inflammation, which triggers activation of tissue repair, proliferation, and hyperplasia of mesenchymal cells and alveolar epithelial cells."*

COMMENT 20: Page 100, line 13: Workers at high altitude are at risk for more rapid progression/development of silicosis. See Clin Tox 2011 49: 629-640.

RESPONSE: *The following was added to the text: "In a recent review, Vearrier and Greenberg (2011) concluded that workers at high altitude are at risk for more rapid development and progression of silicosis."*

COMMENT 21: Page 104, line 10: Add "acute"

RESPONSE: *Revised as suggested.*

COMMENT 22: Page 112, lines 10-11: Incomplete sentence.

RESPONSE: *Edited as follows: "No associations were observed between oral exposure in humans to c-silica and cognitive impairment or increased risk of Alzheimer's disease."*

COMMENT 23: Page 112, lines 13: Add “exposure.”

RESPONSE: *Revised as suggested.*

COMMENT 24: Page 135, lines 26: Add “Stone.”

RESPONSE: *Revised as suggested.*

COMMENT 25: Page 145, lines 6-7: Homeopathic remedies do not contain an active ingredient.

RESPONSE: *No change. The profile does not state or imply that the homeopathic product discussed (silicea) contains an active ingredient.*

COMMENT 26: Page 152, line 1: Units.

RESPONSE: *Added* mg/m^3.

Comments provided by Reviewer 2:

GENERAL COMMENTS

See two attached documents, with annotations, the text and the tables. In general I think it is fine but is confused about the issues of lung cancer among non-silicotics, and on the difference between interaction and confounding with regard to smoking. There is also some mixing up of mortality and incidence data with regard to kidney disease.

ADDITIONAL COMMENTS

COMMENT 1: Page 11, line 11: These would appear to be risks during a specific follow up period – not 'incidences.'

RESPONSE: *Change made as suggested.*

COMMENT 2: Page 11, line 21: Need to define the 'low end' of exposure. In the Figure 3.2 below the low end looks fairly well defined, and there is a lot of data in Table 3.2 in what looks like the low end, for both morbidity and mortality. So I am not sure this statement is well supported.

RESPONSE: *The paragraph was revised as follows:*

> *Several occupational studies have demonstrated exposure-response relationships for silicosis and mortality due to silicosis. However, a NOAEL for silicosis has not been defined, with silicosis and death due to silicosis observed for the lowest cumulative exposure ranges reported. For the lowest cumulative exposure range reported in the available literature (0–0.2 mg/m^3-year), silicosis was observed in 5 of 3,330 gold miners (Steenland and Brown 1995a). At the cumulative exposure range of 0.1–1.23 mg/m^3-year, death due to silicosis was observed in 2,857 of 74,040 mining and pottery workers in China (Chen et al. 2012). Cumulative exposure levels reported in other occupational studies report are higher than those by Chen et al. (2012) and Steenland and Brown (1995).*

COMMENT 3: Page 11, line 25: This is strange. When you say 'next highest' one expects the next highest in Steenland and Brown 1995a, which was 0.2-0.5 mg/m3-year. Why the switch to a different study (Churchyard). This should be changed.

RESPONSE: *The paragraph was re-written as indicated in the Response to Comment 2.*

COMMENT 4: Page 11, line 27: This paragraph mixes risks of silicosis morbidity during follow up period along with a ratio of mortality rate. Might be better to give the absolute mortality rate or the number of deaths per person time in the lowest cumulative exposure for Chen et al, so the data are more comparable. The studies cited seems to be strange sampling of the entirety of the data as seen in Table 3.3. This paragraph needs re-writing.

RESPONSE: *The paragraph was re-written as indicated in the Response to Comment 2.*

COMMENT 5: Page 12, line 16: The study by Liu et al. in China provides evidence that silicosis is not required. This is the perhaps the best evidence to date. See a fuller discussion of this below on page 52.

Liu Y, Steenland K, Rong Y, Hnizdo E, Huang X, Zhang H, Shi T, Sun Y, Wu T, Chen W. Exposure-response analysis and risk assessment for lung cancer in relationship to silica exposure: a 44-year cohort study of 34,018 workers. Am J Epidemiol. 2013 Nov 1; 178(9):1424-33.

RESPONSE: *The following sentence was added to this paragraph: "Results of a cohort study of over 30,000 workers in China indicate that c-silica can induce lung cancer in the absence of silicosis (Liu et al. 2013)."*

COMMENT 6: Page 12, line 18: Not clear what is meant by 'association' here. Those with silicosis have higher silica exposure and therefore more lung cancer, in terms of either rates or risk. But the exposure-response for silica and lung cancer, i.e., the rate per unit does, does not appear to differ between those with silicosis and those without silicosis, as per the Liu et al paper cited above.

RESPONSE: *The sentence was deleted.*

COMMENT 7: Page 12, line 20: In our 2001 paper we gave some evidence that smoking was not acting as a confounder in studies in which there was some data on smoking, for internal comparisons in which workers are compared to workers. I think more could be said about this. For example, in Liu et al. 2013, the exposure-response coefficient for silica and lung cancer, adjusted for smoking (0.055, log cumexp lagged 15 years), was quite similar to to the same metric in our paper in 2001 (0.062) (Steenland et al. 2001). In internal analyses confounding by smoking is a priori unlikely and is clearly not a valid explanation of the positive exposure response trends found to date.

RESPONSE: *The following revision was made: "Smoking, as in all studies of potential lung carcinogens, could be a confounding factor in studies examining the relationship between c-silica exposure and lung cancer (Hessel et al. 2000). However, results of a pooled analysis of over 65,000 workers show that smoking was not a confounder in studies with data on smoking (Steenland et al. 2001)."*

COMMENT 8: Page 14, line 19: Spell out LOAEL it this is first occurrence?

RESPONSE: *Abbreviations for both NOAEL and LOAEL are spelled out at the first occurrence in the document.*

COMMENT 9: Page 14, line 22: I can't follow this sentence. Can this be further clarified?

RESPONSE: *The following was added to the beginning of Section 2.2.*

No information on the effects of oral a-silica in humans was identified, and very few studies evaluating adverse effects of a-silica in animals have been conducted. Available animals studies either do not identify adverse effects at the doses tested or do not provide sufficient evidence to determine the toxicological significance of observed effects (e.g., changes in organ weights in the absence of histopathological changes). Therefore, available data for a-silica are insufficient to derive oral MRLs for a-silica for any exposure duration.

At the location identified above in Comment 9, the following was added:

As discussed in Section 2.2, no information on the effects of oral a-silica in humans was identified, and animals studies either do not identify adverse effects at the doses tested or do not

provide sufficient data to determine the toxicological significance of observed effects. Therefore, available data for a-silica are insufficient to derive oral MRLs for a-silica for any exposure duration.

COMMENT 10: Page 19, line 11: I don't think this is true with regard to lung cancer. The evidence is pretty consistent for lung cancer, negative studies are the exception. For this reason IARC classified the epi evidence as 'sufficient', which means chance and confounding can be ruled as the cause of the positive associations between silica and lung cancer.

RESPONSE: *The profile was revised as follows.*

Silicosis does not result from inhalation of any other substance, including a-silica, and is not associated with incidental exposure to low levels of c-silica in the environment (e.g., at beaches). Numerous occupational exposure studies provide evidence that inhaled c-silica causes lung cancer, and the International Agency for Research on Cancer (IARC 2012), National Institute for Occupational Safety and Health (NIOSH 2002), and National Toxicology Program (NTP 2014) classify c-silica as a carcinogen. Although the studies on kidney disease and connective tissue disease are not as extensive as those for silicosis and lung cancer, available evidence supports an association between occupational exposure to c-silica and increased risks for these effects.

COMMENT 11: Page 21, line 5: While you correctly focus on other end-points, you do not mention heart disease in this review, although there is now a large published study focusing on this outcome in exposed workers, which concludes, "Low-level crystalline silica exposure was associated with increased mortality from heart disease, including pulmonary heart disease and ischemic heart disease, whereas high-level exposure mainly increased mortality from pulmonary heart disease. Current permissible exposure limits for crystalline silica in many countries may be insufficient to protect people from deaths due to heart disease."

Liu Y, Rong Y, Steenland K, Christiani DC, Huang X, Wu T, Chen W. Long-term exposure to crystalline silica and risk of heart disease mortality. Epidemiology. 2014 Sep;25(5):689-96.

RESPONSE: *The following sentence was added. "Results of a recent study of over 42,000 workers in China showed a significant positive trend for cumulative c-silica exposure and mortality from heart disease (Liu et al. 2014).*

COMMENT 12: Page 25, line 23: Probably should say something here (and below) about whether these are lifetime risks, or risks through the end of a certain period of follow-up. Cumulative risks will vary depending on length of follow-up, as you note below in reference to Muir. Rates are not as sensitive to this.

RESPONSE: *The paragraph has been revised to note that Figure 3-2 shows cumulative risks for the follow-up periods of the studies and that cumulative risk can be expected to depend on the length of the follow-up period*

COMMENT 13: Page 27, line 4: This is the only time your mention this issue of length of follow up for risks. Park et al. did this not by observing people throughout their lifetime, but by converting rates to risk and extrapolating out through age 85. Most of the other studies you cite did not do this, although there is a lot of variation on methods of calculating risks.

RESPONSE: *Sentence has been revised to note that the risks were extrapolated to age 85 years.*

COMMENT 14: Page 27, line 15: As noted above, this is very strange wording. "At the next highest cumulative exposure range" is taken from a different study than the previous exposure range, and is not the next highest exposure range in Steenland and Brown (1995a). I think this paragraph needs re-writing

RESPONSE: *The paragraph was revised as follows:*

For the lowest cumulative exposure range reported in the available literature (0–0.2 mg/m^3-year), silicosis was observed in 5 of 3,330 gold miners (Steenland and Brown 1995a). Churchyard et al. (2004) reported that at a cumulative exposure range of 0–0.80 mg/m^3-year, 11/520 gold miners were diagnosed with silicosis.

COMMENT 15: Page 27, line 20: Incidence usually refers to morbidity, not mortality. See comment below regarding exposure-response data, for which you provide only categorical results, not continuous. Categorical results are good to present, but are not directly comparable to each other as referent groups differ across studies.

RESPONSE: *The title of the section was revised to: Silicosis Mortality: Exposure-Response Data.*

COMMENT 16: Page 27, line 34: New relatively high silica exposure is occurring in fracking, you cite Esswein 2013 article below in Section 5.3; you might mention it here.

RESPONSE: *Revised as suggested.*

COMMENT 17: Page 28, line 11: Might mention that OSHA seeks to keep excess lifetime risk of serious disease down below 1/1000, to put this in context.

RESPONSE: *Revised as suggested.*

COMMENT 18: Page 28, line 25: You might note that the authors conducted the 6 cohort analysis in Mannetje et al. 2002a, which has more detailed analysis than the 2002b paper, while excluding 4 cohorts which were in the 2002b paper. Reasons for exclusion were:

Four other cohorts, one from South Africa and three from China, for which quantitative exposure estimates of silica were available, were included in the pooled analysis for lung cancer. However, they were not included in this analysis because of a differential definition for silicosis in coding of causes of death: the three Chinese studies did not use the International Classification of Disease (ICD) system to code death certificates, and there is uncertainty regarding how to apply the original categories for silicosis, pneumoconiosis, and silicotuberculosis in the pooled analysis. Furthermore, the principal investigators of the Chinese cohorts are preparing their own report on silicosis and therefore preferred not to include their data on silicosis mortality in this pooled analysis. In the case of the South African study, there were no deaths coded with silicosis as underlying cause, despite the documentation of high rates of silicosis in this cohort. Discussions with the principal investigator (personal communication, Eva Hnizdo) suggested that in South Africa silicosis was not generally considered an underlying cause of death. It is of note that we found in this cohort strong exposure-response related trends in mortality from related causes of death—that is, tuberculosis and non-specific chronic obstructive pulmonary disease.

RESPONSE: *The summary of the Mannetje et al (2012b) study has been revised to include more detail on the selection of the data used to estimate mortality rates as suggested.*

COMMENT 19: Page 28, line 2: See comment on Table. Reference exposure levels should be given. The results presented are not comparable to each other due to different referent groups. Not sure this Table adds anything for the prior 2 Tables. Exposure-response coefficient, available in a number of studies, are probably more informative.

RESPONSE: *Page 28, line 2 refers to Table 3-4. No comments from the Reviewer were found in Table 3-4. Regarding the Reviewer's comment that reference exposure levels should be given, these are provided in the column titled "Cumulative Exposure." All references in Table 3-4 were reviewed for exposure-response coefficients; none were identified. Table 3-4 was retained in the profile as it is the only table that is specific for mortality due to nonmalignant respiratory diseases in workers exposed to c-silica. The "prior 2 Tables" evaluate exposure-response data for silicosis.*

COMMENT 20: Page 33, line 29: It is one thing to say the disease is rare, which is true, and another to say the cases are few, which is not always true in some of these studies, especially pooled analyses. The percent of subjects in a cohort with kidney disease is low in many studies, but this is true also for lung cancer, and for silicosis mortality.

RESPONSE: *The following was deleted from the profile: "; however, the number of cases of renal disease observed in c-silica-exposed workers from these studies is low (<1%)."*

COMMENT 21: Page 34, line 4: Steenland 2005 is a review article and probably does not belong here, I don't think it reports any new findings.

RESPONSE: *Change made as suggested.*

COMMENT 22: Page 34, line 18: Seems like you ought to add the morbidity findings for end stage renal disease here, from Steenland et al. 2001b (which also include some mortality findings).

RESPONSE: *Discussion of morbidity findings reported for end-stage renal disease reported in Steenland et al. (2001b) was added to the morbidity section.*

COMMENT 23: Page 34, lines 20-34: This section belongs under the 'mortality' section below. These same studies are discussed again there.

RESPONSE: *Lines noted above were deleted from the profile, as the same data are discussed in the mortality section.*

COMMENT 24: Page 36, line 20: They seem reasonably consistent to me

RESPONSE: *The sentence was revised as follows. "Several other studies without quantitative exposure data have evaluated SMRs due to nonmalignant renal diseases. Increased SMRs and/or SMRs and/or*

mortality odds ratios were reported in industrial sand workers, and gold, lead, and zinc miners (Cocco et al. 1994; McDonald et al. 2001; Wyndham et al. 1986). However, SMRs were not increased in pottery workers (Birk et al. 2009), granite cutters (Steenland et al. 1992), or workers from various industries categorized as having high or very-high c-silica exposure (Calvert et al. 2003)."

COMMENT 25: Page 44, line 32: What does this mean? The denominator here is all workers in the cohort. The numerator is the number of arthritis among decedents. The denominator should be decedents. Furthermore, this statistic is not particularly relevant. Simply stating the number of cases would suffice.

RESPONSE: *Revised to state the number of cases only.*

COMMENT 26: Page 45, line 24: Not clear what 'lack of statistical analysis' means…

RESPONSE: *Phrase changed to "statistical analysis not conducted."*

COMMENT 27: Page 50, line 3: Should probably note that there was a significant positive trend using the log of cumulative exposure lagged 15 years (p=0.015), coefficient 0.062.

RESPONSE: *Added note on positive trend as suggested.*

COMMENT 28: Page 50, line 23: Lacasse is an analysis of cohorts of silicotics, and has no data on non-silicotics. The other three generally confine themselves to comparisons of exposed workers (either with silicosis or without) vs non-exposed referent populations, and calculated meta-analytis SMRs. These analyses are not particularly informative. We know siloctics have higher exposure, we know exposed causes lung cancer, so we know a prior that silicotics will have a higher RR compared to a non-exposed referent population than silica-exposed worker without silicosis. For example, in the most recent of these meta analyses Erren et al. 2009b), silica exposed workers without silicosis have an RR of 1.2, while those with silicosis has an RR of 2.1. This is entirely to be expected and is not inconsistent with the hypothesis that silica can cause lung cancer among people with silicosis. The more relevant data are those for exposure-response among silica exposed without silicosis. There both Checkoway (1999) and Liu (2013) (which supersedes Chen 2005) show positive significant exposure-response coefficients in internal analysis of silica exposed workers without silicosis. Hence while you can say that the question remains controversial, this conclusion is based on the wrong data. The best data point to silica causing lung cancer in the absence of silicosis.

RESPONSE: *Lacasse et al. (2005) was deleted from this discussion. The paragraph was revised as follows:*

> *Numerous studies have explored the relationship between silicosis and increased risk of lung cancer (Brown 2009; Checkoway 2000; Checkoway and Franzblau 2000; Cox 2011; NIOSH 2002; Pelucchi et al. 2006; Smith et al. 1995; Soutar et al. 2000; Steenland and Ward 2014). Details of recent meta- or pooled analyses providing information on the relationship between silicosis status and the increased risk of lung cancer are provided in Table 3-15 (Erren et al. 2009b; Kurihara and Wada 2004; Pelucchi et al. 2006). In general, studies show that the risk of lung cancer is increased in workers with and without silicosis, but the association between workers with silicosis and lung cancer is stronger than for workers without silicosis. For*

workers with silicosis, risk ratios or SMRs (95% CI) ranged from 1.52 (1.02, 2.26) to 4.47 (3.17, 6.30), compared to a range of 0.97 (0.69, 1.38) to 1.2 (1.0, 1.4) for workers without silicosis.

COMMENT 29: Page 52, lines 3-9: This language is not appropriate. The question is do never smokers show a positive exposure response similar to ever-smokers, between silica and lung cancer. And is it similar to that of smokers? The best data on this are in Liu et al, in Table 4. I believe you are mis-interpreting the data in that Table. Note that the reference group for the ever-smokers in that table is low silicia exposed workers who *never smoked.* So of course the RRs by silica category are higher than the corresponding ones for never smokers. Although the data are a bit sparse for silica expose never smokers (always the case for lung cancer), the RR of 1.60 in the uppermost category does not differ markedly from the ratio of the uppermost category of ever smokers to the lower most category of never smokers (5.07/2.75=1.84). This is reflected by the fact that the interaction terms for multiplicative interaction was not rejected (p=0.25), meaning that on a RR scale the exposure response in never smokers and ever smokers was not significantly different.

RESPONSE: *The "*Crystalline Silica, Smoking and Lung Cancer*" section was revised as follows: Adjusting for potential confounding bias from smoking is important in studies examining the association between c-silica and lung cancer, because smoking is a risk factor for lung cancer (Brown 2009; Cox 2011; NIOSH 2012). However, smoking may also interact with silica to produce lung cancer. Results of a retrospective study in China showed increased lung cancer risk in never-smokers in association with c-silica exposure and that the change in risk with increasing exposure was similar in never-smokers and ever-smokers (Table 3-16) (Liu et al. 2013). The study authors stated that "the joint effect of [c-]silica and smoking on lung cancer was more than additive and close to multiplicative."*

COMMENT 30: Page 52, lines 9-15 (starting with the reference Steenland): This paragraph does not belong here. It is about adjusting for confounding using partial data on smoking, not about the effect of silica on smokers vs nonsmokers (interaction, or effect modification).

RESPONSE: *Removed sentences.*

COMMENT 31: Table 3-3 (referring to Cumulative Exposure (mg/m^3-year)): Is this the reference category in these studies?

RESPONSE: *Correct. This heading was used in all tables. No change.*

COMMENT 32: Table 3-6: The effect estimates in this Table are generally not comparable to each other, as the referent groups differ; probably should note referent group somewhere in Table. It would make more sense to present exposure-response coefficients per mg/m3-year, when available, these would be more comparable to each other. Eg, for Chen et al. it would be an RR of 1.07 per each mg/m3-yr increase, while for Mannetje et al. had an RR of 1.04 per each mg/m3-year. Park et al. had an RR of 1.20. Not sure this Table adds anything to Tables 3-4 and 3-5.

RESPONSE: *No change was made to Table 3-6. Table 3-6 is included as a tool for the reader to quickly review the exposure-response data for silicosis mortality due to silicosis. The intent is not to compare across studies. The following sentence was added in the text discussing results summarized in Table 3-6. "Note that effect estimates in Table 3-6 generally are not comparable to each other, as reference groups differ."*

COMMENT 33: Table 3-8 (referring to Steenland and Brown, 1995b): This is a mortality study, not a morbidity study, and hence the Table is mislabeled on this point.

RESPONSE: *The Steenland and Brown (1995b) study was removed from Table 3-8. In addition, in the discussion of "*Renal Disease: Incidence and Exposure-Response Data*," the sentence referring to Steenland and Brown (1995b) was deleted.*

COMMENT 34: Table 3-8: Most of the findings in this Table regarding Steenland 2001b are for mortality, and are repeated in Table 3.10 below. I suggest you limit the data here to the findings for morbidity, i.e., the SIRs for end stage renal disease.

RESPONSE: *Mortality data from Steenland (2001b) were removed from Table 3-8.*

COMMENT 35: Table 3-9: This pooled study is a study of mortality, not incidence.

RESPONSE: *"Incidence" deleted from Table 3-9 title.*

COMMENT 36: Table 3-11: This table includes mortality results as well as morbidity.

RESPONSE: *The title of Table 3-11 was changed to "Autoimmune Disease in Workers exposed to Respirable c-Silica."*

COMMENT 37: Table 3-11 (with reference to Steenland and Brown, 1995b): Mortality study.

RESPONSE: *No change. See response to Comment 36.*

COMMENT 38: Table 3-11 (with reference to Steenland et al, 2001b): Mortality not morbidity.

RESPONSE: *No change. See response to Comment 36.*

COMMENT 39: Table 3-11 (with reference to Steenland and Brown, 1995b): Mortality not morbidity.

RESPONSE: *No change. See response to Comment 36.*

COMMENT 40: Table 3-12: How can you have a relative risk from a case series?

RESPONSE: *In Table 3-12, the CERR of 1.01 (95% CI 0.94, 1.08) reported for "case-series" was revised to "mortality studies."*

COMMENT 41: Table 3-14 (with reference to the table heading): Suggest you cut out 'with undefined silicosis status', these are usually just called silica-exposed cohorts.

RESPONSE: *Change made as suggested.*

COMMENT 42: Table 3-14 (with reference to the table heading): Should be 'lung cancer.'

RESPONSE: *Change made as suggested.*

COMMENT 43: Table 3-15: See comment in text on this question. I don't think the data in these meta-analysis get at the real question.

RESPONSE: *Text was revised as indicated in Response to Comment 28.*

COMMENT 44: Table 3-15 (with reference to Lacasse et al. 2005): This paper has no data on non-silicotics and does not belong in this Table.

RESPONSE: *Lacasse et al. (2005) was deleted from Table 3-15.*

COMMENT 45: Table 3-15 (with reference to table heading): You mean 'lung cancer' not 'cancer' here, I believe.

RESPONSE: *Change made as suggested.*

COMMENT 46: Table 3-16: How does Table 3.16 differ from Table 3.15?

RESPONSE: *Table 3-16 was deleted from the profile.*

COMMENT 47: Table 3-17: The only study in this table which has data on risk of lung cancer for silica exposed workers who are either smokers or non-smokers is Liu et al, the others do not belong here.

RESPONSE: *Now Table 3-16. Except for Liu et al. (2013), all other studies were deleted from Table 3-16.*

COMMENT 48: Table 3-17 (with reference to Berry et al. 2004): Berry et al. does not belong here. They do not provide data on lung cancer risk for silica exposed workers who are either smokers or non-smokers. Furthermore their data is restricted to silicotics.

RESPONSE: *Now Table 3-16. Except for Liu et al. (2013), all other studies were deleted from Table 3-16.*

COMMENT 49: Table 3-17 (with reference to Kurihara and Wada 2004): Also does not belong here

RESPONSE: *Now Table 3-16. Except for Liu et al. (2013), all other studies were deleted from Table 3-16.*

COMMENT 50: Table 3-17 (with reference to Lacasse et al. 2005): Again this study does not belong here. You are confusing 'adjusting for smoking' and 'interaction, or effect modification'. Only the Liu study has relevant data to the latter question, which is the question posed by the title of this table.

RESPONSE: *Now Table 3-16. Except for Liu et al.(2013), all other studies were deleted from Table 3-16.*

COMMENT 51: Table 3-17 (with reference to Steenland and Greenland 2004): Again, not relevant to the question of effect modification by smoking.

RESPONSE: *Now Table 3-16. Except for Liu et al. (2013), all other studies were deleted from Table 3-16.*

Comments provided by Reviewer #3:

GENERAL COMMENTS

Well written.
I have tracked changes throughout the document and written 59 comments.
Document is comprehensive except lacks information on the risk of COPD. Information on TB risk is inadequate. Information on exposure response for mortality from renal disease is also incomplete.
Specific items need to be addressed related to medical issues such as "immune disease", treatment, terminology for PMF, description of accelerated silicosis, repeatedly saying silica does not cause acute disease than talking about acute silicosis.

The repeated way the cancer risk from silica exposure vs. the cancer risk among those with silicosis is characterized is contradictory.

The document is missing any reference to state environmental regulations regarding silica exposure.

Section 6.7 Populations with Potentially High Exposures does not include any reference to the health disparity literature that African Americans are at increased risk of silicosis from past discriminatory hiring practices.

"Silica has been identified in at least 38 of the 1,699 hazardous waste sites…"
This statement needs to be better explained since silica is probably at most if not all sites based on its presence in soil. What is particular about these 38 sites?

RESPONSE: *Please see the Additional Comments section for responses to these general comments.*

ADDITIONAL COMMENTS

COMMENT 1: Page 1, lines 9-10: Given that silica is in the earth's crust. I would expect silica at all sites involving soil. Presumably there is a particular concern about silica at these 38 sites?

RESPONSE: *The section was revised to better represent the information for silica.*

COMMENT 2: Page 3, line 9: Add during drilling involving fracking.

RESPONSE: *Addition made as requested.*

COMMENT 3: Page 3, line 23: Add foundries.

RESPONSE: *Addition made as requested.*

COMMENT 4: Page 4, line 16: COPD is now more common than silicosis:

Begin R, Filion R, Ostiguy G. 1995. Emphysema in silica- and asbestos-exposed workers seeking compensation: a CT scan study. *Chest* 1995; 108:647-655.

- This study found an association between emphysematous changes observed on a CT scan and silica exposure in workers applying for compensation.

Brüske I, Thuering E, Heinrich J, Huster KM, Nowak D. 2014. Respirable quartz dust exposure and airway obstruction: a systematic review and meta-analysis. *Occup Environ Med* 71:583-589.

- This paper reported on a meta-analysis that showed a statistically significant increase in measures of airway obstruction and with increasing occupational exposure to silica. Selected studies had quantitative data to calculate an exposure response effect.

Cowie RL, Hay M, Thomas RG. 1993. Association of silicosis, lung dysfunction, and emphysema in gold miners. *Thorax* 48:746-749.

- This study of black South African gold miners found emphysema on CT scan in cigarette and non -cigarette smokers and in in individuals with and without radiographic changes of silicosis.

Ehrlich RI, Myers JE, te Water Naude JM, Thompson ML, Churchyard GJ. 2011. Workplace: Lung function loss in relation to silica dust exposure in South African gold miners. *Occup Environ Med* 68:96-101.

- This study quantitated the loss pulmonary function by exposure levels of silica among black South African gold miners and found that silica dust levels had a greater impact on pulmonary function results than the development of silicosis.

Hertzberg VS, Rosenman KD, Reilly MJ, Rice CH. 2002.The effect of occupational silica exposure on pulmonary function. *Chest* 122:721-728.

- This study quantitated an exposure response effect between silica exposure and obstructive changes on pulmonary function testing among silica exposed foundry workers without radiographic evidence of silicosis.

Hnizdo E. 1990. Combined effect of silica dust and tobacco smoking on mortality from chronic obstructive lung disease in gold miners. *Br J Ind Med* 47:656-64.

- This study calculated that among white South African gold miners that 5% of the attributable risk of mortality from COPD was from silica, 34% from cigarette smoking and 59% from the combined effect of silica and cigarette smoking.

Hnizdo E, Vallyathan V. 2003. Chronic obstructive pulmonary disease due to occupational exposure to silica dust: a review of epidemiological and pathological evidence. *Occup Environ Med* 60:237–243.

- A review of the studies summarizing the occurrence of obstructive changes in pulmonary function, emphysematous changes on radiographs, chronic bronchitis, mortality from COPD among workers with silica exposure.

RESPONSE: *Changes made as indicated by the Reviewer. In addition, a section on COPD, including the citations noted above, was added under Respiratory Effects in Section 3.2.1.2.*

COMMENT 5: Page 4, line 19: Calcined amorphous silica causes silicosis.

RESPONSE: *The literature search for this profile included toxicological data on calcined a-silica. ATSDR did not identify any literature to support the above statement. A targeted update literature search made in response to the Reviewer's comment did not identify any new relevant studies evaluating the potential carcinogenicity of calcined a-silica. According to IARC (1997), the cristabalite [c-silica] content of calcined a-silica is ranges from 10 to 60%. Due to contamination of calcined a-silicia with cristabalite, it is not possible to determine the potential for calcined a-silica to produce silicosis. No other forms of a-silica have been shown to cause silicosis. The Reviewer did not provide a citation for*

the above statement. Therefore, no change has been made in response to this comment.

COMMENT 6: Page 5, line 4: Not true silica is a carcinogen in the absence of silicosis.

Lacasse Y, Martin S, Simard S, Desmeules M. 2005.Meta-analysis of silicosis and lung cancer. *Scand J Work Environ Health* 31: 450-458.

- A meta-analysis that concluded that the effect of cigarette smoking did not explain the increased risk of lung cancer from exposure to silica.

Rice FL, Park R, Stayner L et al. 2001. Crystalline silica exposure and lung cancer mortality in diatomaceous earth industry workers: a quantitative risk assessment. *Occup Environ Med* 58: 38-45.

- This report analyzed multiple different exposure models and found that trends of predictive risk were the same across all the models for a cohort of diatomaceous exposed workers.

Steenland K, Greenland S. *2004.* Monte Carlo sensitivity analysis and Bayesian analysis of smoking as an unmeasured confounder in a study of silica and lung cancer. *Am J Epidemiol* 160: 384-392.

- A sensitivity analysis of the effect of cigarette smoking that continued to show an increased risk of lung cancer among sand and gravel workers.

Steenland K, Mannetje A, Boffetta P et al. International Agency for Research on Cancer. 2001. Pooled exposure–response analyses and risk assessment for lung cancer in 10 cohorts of silica-exposed workers: an IARC multicentre study. *Cancer Causes Control* 12: 773-784.

- This quantitative assessment of lung cancer risk from ten diverse industries with silica exposure found that cumulative crystalline silica exposure (cumulative, unlagged and lagged; log cumulative, unlagged and lagged) showed highly significant trends for lung cancer risk.

RESPONSE: *[Note that page 5, line 4 does not speak to lung cancer.] The paragraph was revised as follows:*

> *Several government agencies have classified c-silica as a lung carcinogen in humans (IARC 2012; NIOSH 2002; NTP 2014). Results of studies indicate that c-silica can cause lung cancer in workers, with increased risks in smokers. (Brown 2009; Checkoway and Franzblau 2000; Cox 2011; Gamble 2011; IARC 2012; NIOSH 2002; Soutar et al. 2000; Steenland 2005; Steenland and Ward 2014). Available evidence supports an association between occupational exposure to c-silica and increased risks of lung cancer, as well as adverse effects to the kidney and autoimmune disorders. Available data in humans and laboratory animals are not sufficient to demonstrate a causal relationship between oral exposure to c-silica and any adverse effect outcome. Adverse effects of dermal exposure to c-silica have not been reported.*

COMMENT 7: Page 5, line 11: I would not consider this up to date on effect on Kidney:

Ibrahim KS, Ahmed SB, Amer NM. 2011. Study of Kidney Dysfunction in Non-Silicotic Egyptian Workers. *Int J Hyg Environ Health* 214: 53-58.

- A cross-sectional study of ceramic workers with silica exposure, which an increase in markers of tubular and glomerular dysfunction in comparison non-silica exposed control group.

Ng TP, Ng YL, Lee HS, Chia KS, and Ong HY. 1992. A study of silica nephrotoxicity in exposed silicotic and non-silicotic workers. *Br J Ind Med* 49:35-37.

- Significantly higher urinary excretions of albumin and macroglobulin were found in quarry

workers exposed to silica.

Millerick-May M, Reilly MJ**,** Schrauben S, Rosenman KD. Silicosis and Chronic Renal Disease. Am J Ind Med 2015; 58: 730-736.

- A review of individuals with silicosis in a population based case registry found an increased prevalence of kidney dysfunction.

Steenland K, Attfield M, and Mannejte A. 2002. Pooled analyses of renal disease mortality and crystalline silica exposure in three cohorts. *Ann Occup Hyg* 46:4-9.

- Based on the results of three cohorts, the estimated excess risk of death from renal disease was calculated to be 1.8% (0.8%–9.7%). There was a statistically significant exposure-response trends for acute and chronic renal disease mortality.

Vuppurturi S, Parks CG, Nylander-French LA, Owen-Smith A, Hogan SL, Sandler DP. 2012. Occupational Connective tissue disease: Gómez-Puerta JA, Gedmintas L, Costenbader KH. 2013. The association between silica exposure and development of ANCA-associated vasculitis: systematic review and meta-analysis. *Autoimmune Rev* 12:1129-35.

- A meta-analysis of six case-control studies that found a statistically significant risk of the ANCA-associated vasculitides with ever exposure to silica.

Makol A, Reilly MJ, Rosenman KD. 2011. Prevalence of Connective Tissue Disease in Silicosis. *Am J Ind Med* 54:255-262.

- This paper is an analysis of the prevalence of connective tissue disease in a registry of individuals with the diagnosis of silicosis. Rheumatoid arthritis was the most frequently diagnosed connective disease while anti-neutrophil cytoplasm antibody (ANCA) vasculitis was the condition with the highest risk.

Parks CG, Conrad K, Cooper GS. 1999. Occupational exposure to crystalline silica and autoimmune disease. *Environ Health Persp* 107(Suppl 5): 793-802.

- A review of the epidemiological studies performed examining an association between silica exposure and CTD with discussion of possible biological mechanism.

Rocha-Parise M, Santos LM, Damoiseaux JG, Bagatin E, Lido AV, Torello CO, Cohen Tervaert JW, Queiroz ML. 2014. Lymphocyte activation in silica-exposed workers. *Int J Hyg Environ Health* 217:586-591.

- A study of immune activation in silica exposed workers that examines the effect of silica exposure on lymphocyte activation.

Silica Exposure and Chronic Kidney Disease. Vuppurturi S et al. 2012. *Ren Fail* 34:40-46.

- A case-control study of individuals with chronic renal disease that found a dose-response to silica exposure estimates based on industrial hygiene evaluation of lifetime work histories.

RESPONSE: *In response to the comment that the kidney section of Section 2.2 is not up to date regarding renal effects, Section 2.2 is intended to be a high-level overview of the health effects of silica compounds, with more detailed information provided in Section 3.2. As such, no changes were made to the discussion of renal effect in Section 2.2. All studies listed above for renal effects were cited in Section 3.2.1.2 (Inhalation, Systemic Effects, Renal Effects); therefore, no changes were made to the renal section of Section 3.2.1.2. Regarding studies listed above for autoimmune effects (Makol et al. 2911; Parks et al. 1999), these studies are cited in Section 3.2.2.3 (Immunological and Lymphoreticular*

Effects). Rocha-Parise et al. (2014) is a publication on the mechanism of toxicity; Rocha-Parise et al. (2014) was added to Section (3.5.2, Mechanism of Toxicity).

COMMENT 8: Page 6, lines 5-6: Contradicts statement on acute silicosis.

RESPONSE: *The sentence was revised as follows. "Health effects of c-silica and a-silica have been shown only to occur in people working in silica industries, most typically following prolonged exposure."*

COMMENT 9: Page 6, lines 13-15: Missing tests for TB, kidney function and connective tissue disease.

RESPONSE: *The following sentence was added. "Workers should also be evaluated for tuberculosis, kidney function, and autoimmune disorders."*

COMMENT 10: Page 7, line 5: This is not the Federal Government. Some state agencies (Wisconsin, Texas) have set environmental limits on silica exposure. I added to regulation section at end.

RESPONSE: *Reference to the American Conference of Governmental Industrial Hygienists (ACGIH) was removed from this section. Regarding regulations set by state agencies, ATSDR typically does not cite state regulations; no change was made in response to this comment.*

COMMENT 11: Page 9, line 4: The Reviewer requested adding "Granite and engineered stone kitchen counter tops" to the list of commercial products containing silica.

RESPONSE: *Change made as requested.*

COMMENT 12: Page 9, line 21: Silicosis very insensitive biomarker rather silica content on biopsy.

RESPONSE: *The following was deleted from this paragraph. "; therefore, silicosis is an important biomarker of exposure to c-silica dust by inhalation (IARC 2012)."*

COMMENT 13: Page 10, line 20: COPD more common than silicosis.

RESPONSE: *No change. The sentence was revised as follows. "Of these, silicosis and lung cancer pose the greatest concern to human health due the potential for death as an outcome."*

COMMENT 14: Page 10, line 26: Not true Calcined a-silica causes silicosis.

RESPONSE: *The literature search for this profile included toxicological data on calcined a-silica. ATSDR did not identify any literature to support the above statement. A targeted update literature search made in response to the Reviewer's comment did not identify any new relevant studies evaluating the potential carcinogenicity of calcined a-silica. According to IARC (1997), the cristabalite [c-silica] content of calcined a-silica is ranges from 10 to 60%. Due to contamination of*

calcined a-silica with cristabalite, it is not possible to determine the potential for calcined a-silica to produce silicosis. No other forms of a-silica have been shown to cause silicosis. The Reviewer did not provide a citation for the above statement. Therefore, no change has been made in response to this comment.

COMMENT 15: Page 10, line 27: Called Progressive massive fibrosis (PMF) not complicated.

RESPONSE: *Change made as requested.*

COMMENT 16: Page 10, line 29: Not true accelerated is simple or PMF occurring sooner, pathology not different.

RESPONSE: *The portion of the sentence indicated above was deleted.*

COMMENT 17: Page 11, line 1: May continue not true for all patients.

RESPONSE: *Change made as requested.*

COMMENT 18: Page 11, line 11: I am not aware of uncertainty on the number of deaths. Uncertainty on the number of cases.

RESPONSE: *The sentence was revised as follows. "In the United States, 13,744 deaths were attributed to silicosis from 1968 to 1990 and 4,313 deaths were attributed to silicosis from 1979 to 1990 (Beckett et al. 1997; Castranova and Vallyathan 2000)."*

COMMENT 19: Page 12, lines 12-14: This is not true. IARC addresses this. Silica would not be considered a human carcinogen if silicosis required.

RESPONSE: *The paragraph was revised in response to the comment above and to Reviewer #2, Comments 5-7.*

> *Compared to other occupational lung carcinogens, such as asbestos, the occupational risk of c-silica-induced lung cancer is low, requiring large study populations to achieve adequate power to detect and quantify c-silica-related cancer risk. Results of pooled and meta-analyses, which provide the strongest support for the carcinogenicity of c-silica in the lung, show increased risks of lung cancer in c-silica workers, with risks exhibiting dependence upon cumulative exposure (Finkelstein 2000; Lacasse et al. 2009; Steenland 2005; Steenland et al. 2001a). Results of a cohort study of over 30,000 workers in China indicate that c-silica can induce lung cancer in the absence of silicosis (Liu et al. 2013). Smoking, as in all studies of potential lung carcinogens, could be a confounding factor in studies examining the relationship between c-silica exposure and lung cancer (Hessel et al. 2000). However, results of a pooled analysis of over 65,000 workers show that smoking was not a confounder in studies with data on smoking (Steenland et al. 2001).*

COMMENT 20: Page 12, lines 16-18: This is true and contradicts the previously highlighted statement.

RESPONSE: *The sentence was deleted.*

COMMENT 21: Page 12, line 23: Throughout document needs to be described as connective tissue disease. As written adverse effect on immune system would say silica causes immunodeficiency – not true.

RESPONSE: *Throughout the profile, "adverse effects on the immune system" or" immune effects" was replaced to indicate the effects of note are autoimmune effects (autoimmune disorders or diseases). These effects are reviewed in Chapter 3 under the Heading "Immunological and Lymphoreticular Effects," as this is where readers would most likely look for this information given the current outline of ATSDR toxicological profiles.*

COMMENT 22: Page 13, line 11: Not true can occur with silica exposure alone without silicosis.

RESPONSE: *The sentence was deleted.*

COMMENT 23: Page 13, line 12: Need additional paragraphs on COPD and tuberculosis.

RESPONSE: *Section 2.2 is intended to be a high-level overview of the health effects of silica compounds, with more detailed information provided in Section 3.2. As such, COPD and tuberculosis are mentioned in Section 2.2. Silicotuberculosis is reviewed in more detail in Section 3.2.1.2 (Inhalation, Systemic Effects, Respiratory effects). A new section on COPD was added to Section 3.2.1.2.*

COMMENT 24: Page 13, line 14: Need to add some discussion on calcined amorphous.

RESPONSE: *The literature search included toxicological data on calcined a-silica. ATSDR did not identify any literature indicating that calcined a-silica causes silicosis. According to IARC (1997), the cristabalite [c-silica] content of calcined a-silica ranges from 10 to 60%. Due to contamination of calcined a-silica with cristabalite, it is not possible to determine the potential for calcined a-silica to produce silicosis. No other forms of a-silica have been shown to cause silicosis. Therefore, no change has been made in response to this comment.*

COMMENT 25: Page 14, line 6: Not true. Certainly effects on pulmonary function results before silicosis.

Hertzberg VS, Rosenman KD, Reilly MJ, et al. 2002. Effect of occupational silica exposure on pulmonary function. Chest 122(2):721-728.

RESPONSE: *The sentence was revised as follows. "Effects on the respiratory system are the most sensitive effects of inhaled c-silica."*

COMMENT 26: Page 19, lines 4-9: *Repeat of same text and same comments as before.*

RESPONSE: *The introduction to this paragraph was revised as follows. "Health effects associated with inhalation of respirable c-silica are silicosis, lung cancer, renal toxicity, and autoimmune disorders. Silicosis, a progressive fibrotic, potentially fatal lung disease caused by occupational exposure to respirable c-silica, is a well-established effect that has been recognized since ancient times."*

COMMENT 27: Page 21, line 33: Not true of acute silicosis.

RESPONSE: *"Prolonged" was deleted from the sentence.*

COMMENT 28: Page 22, lines 9-11: Same comment as before.

RESPONSE: *Sentence revised to: "Silicosis is not a single disease entity, but is classified as different types (simple silicosis, progressive massive fibrosis [PMF], acute silicosis, and accelerated silicosis)."*

COMMENT 29: Page 22, line 22: IPF does not mimic silicosis.

RESPONSE: *Change made as requested.*

COMMENT 30: Page 22, lines 22-24: Certainly there are patterns associated with silica and silicosis just not unique to silica or silicosis.

RESPONSE: *Change made as requested.*

COMMENT 31: Page 23, line 15: Not terminology commonly used. PMF should come first.

RESPONSE: *Change made as requested.*

COMMENT 32: Page 24, lines 16-17: Not true. It is chronic silicosis occurring after a short time.

RESPONSE: *This paragraph was revised as follows.*

> *Accelerated silicosis, associated with intense exposure to fine c-silica dusts, is a rapidly progressive form of simple (chronic) silicosis. It develops 5–10 years after the start of exposure and is associated with intense exposure to fine c-silica dusts. Symptoms are similar to those of simple silicosis. Accelerated silicosis is associated with significant morbidity and mortality.*

COMMENT 33: Page 24, lines 17-24: Disagree. See comment 32.

RESPONSE: *Paragraph was revised as shown in Response to Comment 32.*

COMMENT 34: Page 24, line 33: Whole literature on interaction of silica:

TB and HI V in South Africa Rees D, Murray J. 2007. Silica, silicosis and tuberculosis. *Int J Tuberc Lung Dis* 11: 474-484.

- A review of the association between tuberculosis, silicosis and silica exposure with discussion of management and prevention.

teWaterNaude JM, Ehrlich RI, Churchyard GJ, Pemba L, Dekker K, Vermeis M, White NW, Thompson ML, Myers JE. 2006. Tuberculosis and silica exposure in South African gold miners. *Occup Environ Med* 63: 187-192.

- This study found that the risk of tuberculosis was related to quantitative estimates of silica exposure regardless of the radiographic presence of silicosis.

Cowie RL. 1994. *T*he epidemiology of tuberculosis in gold miners with silicosis. *Am J Respir Crit Care Med* 150: 1460-1462.

- This report describes the increased risk of tuberculosis in black South African gold miners with and without silicosis even before the spread of HIV.

RESPONSE: *The studies noted above were added to the discussion of silicotuberculosis in Section 3.2.1.2 (Inhalation, Systemic Effects, Respiratory Effects)*

COMMENT 35: Page 25, line 3: More recent data has shown no decrease in hospitalization for silicosis in the US:
Filios MS, Mazurek JM, Schleiff PL, Reilly MJ, Rosenman KD, Lumia ME, Worthington K. Surveillance for Silicosis — Michigan and New Jersey, 2003-2010. MMWR 2015; 62:81-85.

RESPONSE: *The following was added: "Recent surveillance data for silicosis showed no decrease in hospitalization due to silicosis in the United States over the time period 1993–2011 (Filios et al. 2015)."*

COMMENT 36: Page 34, line 25: Millerick-May M, Reilly MJ**,** Schrauben S, Rosenman KD. Silicosis and Chronic RenalDisease. Am J Ind Med 2015; 58: 730-736.

RESPONSE: *Citation above was added as suggested.*

COMMENT 37: Page 36, line 27: Millerick-May M, Reilly MJ**,** Schrauben S, Rosenman KD. Silicosis and Chronic RenalDisease. Am J Ind Med 2015; 58: 730-736.

RESPONSE: *Citation above was added as suggested.*

COMMENT 38: Page 42, line 7: I disagree with the use of the word particularly.

RESPONSE: *Change made as suggested.*

COMMENT 39: Page 51, lines 17-18: Maybe after 1997 IARC not true now. Subsequent sentences contradict.

RESPONSE: *Change made as suggested.*

COMMENT 40: Page 82, lines 6-7: Not sure why suggests important, could be a minor excretory pathway.

RESPONSE: *Sentence was revised as follows. "Urine is an excretory pathway for silica absorbed from the respiratory tract."*

COMMENT 41: Page 86, line 21: Need COPD and tuberculosis also.

RESPONSE: *The following was added regarding mechanisms of toxicity for COPD.*

> *"COPD, characterized by airflow restriction due to chronic bronchitis or emphysema, is associated with exposure to c-silica dust even in the absence of silicosis. Possible mechanisms involved in the development of c-silica-induced airway restriction include: (1) cellular damage, generation of reactive oxygen species, and subsequent release of proinflammatory and fibrogenic factors, and (2) injury to epithelial cells, allowing c-silica to penetrate small airway walls and induce localized fibrosis (Hnizdo and Vallyathan 2003)."*

No additions were made to the profile regarding potential mechanisms of silicotuberculosis. As stated Section 3.2 of the Profile, silicotuberculosis is associated with exposure to silica dust. However, the causal agent of tuberculosis is mycobacterium. Thus, discussion of the mechanism of toxicity is beyond the scope of the profile.

COMMENT 42: Page 91, lines 14-16: Sentence not needed and does not adequately summarize data.

RESPONSE: *Change made as suggested.*

COMMENT 43: Page 97, line 21: What about potential carcinogenic effect? Why have state agencies promulgated environmental standards?

RESPONSE: *The sentence was revised to as follows. "Silicosis is considered to be strictly an occupational disease that typically occurs with prolonged (years) of exposure. Adverse effects of c silica have not associated with non-occupational exposures (e.g., exposure to c-silica in ambient air). The same adverse effects observed in adult workers would be expected to occur in children if sufficiently exposed."*

COMMENT 44: Page 98, line 33: Again, why important?

RESPONSE: *Change made as suggested.*

COMMENT 45: Page 99, line 28: Foundries – benz pyrene, formaldehyde, asbestos.

RESPONSE: *Change made as suggested.*

COMMENT 46: Page 100, line 12: Populations with increased prevalence of TB at increased risk as well increased HIV –Studies on South African Gold miners!

RESPONSE: *Change made as suggested.*

COMMENT 47: Page 100, line 15: Covered in polymorphisms.

RESPONSE: *Change made as suggested.*

COMMENT 48: Page 101, lines 21-22: Realized this is standard sentence but for silica it would be pulmonary and occupational physicians.

RESPONSE: *Change made as suggested.*

COMMENT 49: Page 103, Figure 3-8: Acute- Acute silicosis.

RESPONSE: *No change. Per ATSDR Guidance, acute effects are those occurring following exposures ≤14 days. Acute silicosis is associated with intermediate-duration exposure (>14 days to <1 year).*

COMMENT 50: Page 105, line 8: Acute silicosis is associated with short duration.

RESPONSE: *The sentence was revised as follows. "Effects of occupational exposure to c-silica typically occur after prolonged (chronic) exposure (years)."*

COMMENT 51: Page 106, line 5: Acute silicosis is associated with short duration.

RESPONSE: *The sentence was revised as follows. "Adverse effects of occupational (inhalation) exposure to c-silica occur after intermediate (> 14 days to <1 year) or chronic exposure (years) and are have not been associated exposure durations of ≤14 days."*

COMMENT 52: Page 109, lines 1-2: Not true.

RESPONSE: *Indicated sentence was deleted.*

COMMENT 53: Page 109, lines 11-12: They are for renal mortality see OSHA background document for new silica standard.

RESPONSE: *Indicated sentence was deleted.*

COMMENT 54: Page 125, line 12: I could not find in document discussion how formed with heat, their presence in foundries and how they have a lower occupational standard. All above info should be added.

RESPONSE:
The following was added to Section 4.2. "Interconversion of the silica polymorphs occurs upon heating or cooling (see Section 6.3.2 for additional information)."

The following was added to Section 5.1 Production Methods. "Cristobalite may be formed from quartz during the pouring of metal in foundries where quartz is used to make moulds and cores (IARC 1997)."

The following was added to Section 6.3.2. "Biogenic silica are converted into cristobalite at approximately 800°C (IARC 1997)."

Discussion of the PELs was added to Chapter 8 based on the information in Table 8-1: "Silica polymorphs may have separate regulations, advisories, and guidelines. For example, general industry PELs for cristobalite and tridymite are lower than general industry PEL for quartz (OSHA 2013a)."

COMMENT 55: Page 127, line 29-30: Some discussion needed on fracking sand.

RESPONSE:
The following was added to Section 5.1. "Demand for hydraulic fracturing sand has resulted in increased industrial sand and gravel production capacity in the United States through ongoing permitting and opening of new mines (USGS 2015)."

The following was added to Section 5.3. "Silica sand is used as a proppant, to prop open fractures and promote hydrocarbon flow and extraction. Water and proppants make up 98–99.5% of typical fracturing fluids. Silica sand with a round spherical shape and commonly graded particle distribution is specifically selected for hydraulic fracturing fluid production. Resin-coated silica is also used as a proppant (Holloway and Rudd 2014)."

COMMENT 56: Page 133, line 5-7: Need some statement why particularly noted in these 38 sites – fly ash? Because expect silica found in all sites involving soil.

RESPONSE: *A sentence was added to indicate that silica is ubiquitous in the environment and that areas of concern are adjacent to mining, processing, and transporting facilities.*

COMMENT 57: Page 147, line 18: There is whole literature on racial disparity related to silica exposure:

Cherniak M. 1986. *The Hawk's Nest incident. America's worst industrial disaster*. New Haven: Yale University press.

- This book is the most comprehensive review of the background and epidemiology of the tunnel drilling operation that occurred in West Virginia in the 1930's and was responsible for causing 764 deaths from silicosis and an unknown number of nonfatal cases.

Cowie RL, Mabena SK. 1991. Silicosis, chronic airflow limitation and chronic bronchitis in South African gold miners. *Am Rev Respir Dis* 143: 80-84.

- This was the first respiratory health study of black South African Gold miners. This study found that 857 (71.6%) of 1,197 black miners had silicosis and 62% had chronic bronchitis including 45% of the miners who had never smoked cigarettes.

Foote CL, Whatley WC, Wright G. 2003. Arbitraging a discriminatory labor market; Black workers at the Ford Motor Company, 1918-1947 *J Labor Econ* 21: 493-532.

- Describes the discriminatory practices used to recruit and locate black workers in certain areas of

the foundry.

Rice C, Rosenman KD, Reilly MJ, Hertzberg VS. 2002. Reconstruction of Silica Exposure at a Foundry for Evaluation of Exposure-Response. *Ann Occup Hyg* 46 (suppl 1):10-13.

- This study in a Midwest foundry found that blacks workers who had the same duration of work as white workers had on the average higher cumulative and average silica exposures metrics.

RESPONSE: *ATSDR agrees that there is a "racial disparity related to silica exposure." However, discussion of socioeconomic factors involving "racial disparity related to silica exposure" is beyond the scope of toxicological profiles.*

COMMENT 58: Page 168, line 5: Similar to previous comment, insensitive. Quantitative amount of silica in lung tissue is a better marker.

RESPONSE: *The following was added. "Silica burden in the lung may provide a more sensitive marker of exposure, although an exposure-lung burden response relationship remains to be established."*

COMMENT 59: Page 170, Table 8-1: State agency guidelines for environmental exposure to silica:

WDNR (Wisconsin Department of Natural Resources). 2012. Silica Sand Mining in Wisconsin. Available: http://dnr.wi.gov/topic/mines/documents/silicasandminingfinal.pdf.

Vermont Department of Environmental Conservation. 1998. Air Toxics Report Available: http://www.anr.state.vt.us/air/airtoxics/htm/AirToxReport1998.htm.

OEHHA (California Office of Environmental Health Hazard Assessment). 2005. Chronic Toxicity Summary. Silica (Crystalline, Respirable). Available: http://www.oehha.org/air/chronic_rels/pdf/silicacrel_final.pdf.

New York State Department of Environmental Conservation. 1997. Policy DAR-1: Guidelines for the Control of Toxic Ambient Air Contaminants. Available: http://www.dec.ny.gov/chemical/30681.html

Texas Commission on Environmental Quality (TCEQ). 2011a. Silica, Amorphous and Other Non-Crystalline Forms Development Support Document. http://www.tceq.state.tx.us/assets/public/implementation/tox/dsd/final/july11/amorphous_silica.pdf.

RESPONSE: *No change. ATSDR typically does not cite state regulations.*