DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR ANTIMONY

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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

David Dorman, DVM, PhD, DABVT, DABT
Professor, Toxicology
School of Veterinary Medicine
North Carolina State University

Nelson Belzile, PhD
Full Professor, Chair
Dept. Chemistry & Biochemistry
Laurentian University
Sudbury, Canada

Jeffrey L Burgess, MD, MPH, MS
Professor, Associate Dean for Research
Mel & Enid Zuckerman College of Public Health
University of Arizona

Comments provided by Peer Reviewer #1

COMMENT 1 (page 5, line 33): The Reviewer states "Stibine is mentioned for the first time but not defined. I recommend adding (antimony hydride) directly afterwards."

RESPONSE: *The suggested revision was made.*

COMMENT 2 (page 7, line 23): The Reviewer states "Can a common name, possibly hexahydroxoantimonate, be added for $Sb(OH)_6$?"

RESPONSE: *The suggested revision was made.*

COMMENT 3 (page 14, lines 22-24): The Reviewer notes "The text states that "Because cancer effects could occur at lower exposure levels, Figure 3-1 also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA". However, only the exposure concentration appear to be illustrated in Figure 3-1 for the relevant studies."

RESPONSE: *The referenced sentence was deleted*

COMMENT 4 (Table 3-1): The Reviewer states "For Figure key 3 the NOAEL is 122 mg/m^3 and the less serious LOAEL is 1,395 mg/m^3. This is confusing at there was an intermediate exposure concentration of 799 mg/m^3, which would be expected to be a NOAEL or LOAEL. Please provide further information of effects or lack thereof at 799 mg/m^3, and if corrections are needed please make sure that they are included in Figure 3-1 as well.

RESPONSE: *The data summary tables for the best available copy of this unpublished study are illegible; thus, data in the profile are extracted from the qualitative discussion of the results. In this discussion, the investigator noted that renal and/or pulmonary lesions were observed in four animals (species was not reported) in the mid-concentration group (799 mg/m^3). Given this limited information, a determination could not be made as to whether this concentration was a NOAEL or a LOAEL. The lowest concentration was categorized as a NOAEL based on the investigator's statement "the lowest level did not produce any untoward effects."*

COMMENT 5 (Table 3-1): The Reviewer states "For Figure key 5 the NOAEL is 6.3 mg/m^3 for CS, BW and OW. However, in the Results section text field the lower exposure concentration of 3.1 mg/m^3 was associated with increases in relative lung weights. This would appear to be a LOAEL effect, which brings into question the higher concentration exposure of 6.3 mg/m^3 being listed as the NOAEL. Please explain this apparent inconsistency, and if corrections are needed please make sure that they are included in Figure 3-1 as well."

RESPONSE: *CS, BW, and OW are the parameters measured in the study; NOAEL and LOAEL categorizations are based on whether adverse effects were observed at a particular exposure level. The increase in relative lung weight in the absence of histological damage was not considered an adverse effect; thus, 3.1 and 6.3 mg/m^3 were considered NOAELs.*

COMMENT 6 (Table 3-1): The Reviewer states "For Figure key 6, the acronym OF is written under the Parameters monitored column, but the acronym is not defined in the table footnotes. I assume that this is organ function. If so, please add the acronym to the table footnotes.

RESPONSE: *The definition of the acronym OF (organ function) was added to the table footnote.*

COMMENT 7 (Table 3-1): The Reviewer states "In the footnote, the term $BMCL_{10}$ is used but not defined elsewhere in the table or footnote. Please add it to the list of acronyms near the end of the footnote."

RESPONSE: *The definition of the acronym $BMCL_{10}$ (lower confidence limit of the benchmark concentration) was added to the table footnote.*

COMMENT 8 (Figure 3-1): The Reviewer states "The study listed in Table 3-1 used to determine the chronic-inhalation MRL (Figure key 19) was 0.05 mg/m^3, which is inconsistent with the MRL shown in Figure 3-1. Given that the NOAEL for respiratory effects in Table 3-1 is 0.05 mg/m^3, which is inconsistent with the positioning of the 19R data point for respiratory effects in Figure 3-1, I suspect that the positioning of the data point in the figure is incorrect"

RESPONSE: *The MRL was based on a $BMCL_{10}$ of 0.10 rather than the NOAEL; this is noted in the footnote in Table 3-1.*

COMMENT 9 (page 26, line 1): The Reviewer states "I recommend adding that at an antimony smelter conjunctivitis was reported in 28% of workers (Potkonjak and Pavlovich 1983)."

RESPONSE: *Since the ocular effect was likely due to direct contact, Potkonjak and Pavlovich (1983) was added to the discussion of ocular effects in the dermal exposure section*

COMMENT 10 (page 28, line 11): The Reviewer states "Please add that in both of these studies arsenic was reported as a co-exposure."

RESPONSE: *The suggested revision was made.*

COMMENT 11 (page 30, line 22): The Reviewer states "Please delete the words "however" and "only", as an exposure explaining 6.2% of a population risk for a multifactorial condition such as high blood pressure is actually quite impressive"

RESPONSE: *The suggested revision was made.*

COMMENT 12 (page 34, lines 1-3): The Reviewer states "Please add the Dunn study to Table 3-2."

RESPONSE: *The Dunn study was not added to the LSE table (Table 3-2) because it is a case report with crude estimates of exposure levels*

COMMENT 13 (Table 3-3): The Reviewer states "For Figure key 7, only the exposure concentrations for male mice are listed in the NOAEL column. Should the higher concentrations to which the female mice were exposed also be included, assuming they were also NOAELs?"

RESPONSE: *The practice is to use the lower of the male and female NOAEL values since it is not known whether the higher dose would also be a NOAEL in the other sex.*

COMMENT 14 (Table 3-3): The Reviewer states "For Figure key 10, some explanation should be provided for why the "Other" effects concentration of 0.56 mg/m^3 on the spleen (mild sinus congestion) is considered a NOAEL and not a LOAEL. Under the hepatic effects text under the Results column, observed changes at the NOAEL concentration were described as being adaptive and not biologically significant. If the same is true of the changes seen in the spleen, this should be mentioned as well."

RESPONSE: *The error in the Table was corrected; the NOAEL for other systemic effects was 0.06 mg/kg/day.*

COMMENT 15 (Figure 3-2): The Reviewer states "The acute MRL for effects other than cancer in the figure (Figure key 2M) is not mentioned in Table 3-3. This information needs to be added to Table 3-3 (both in the main part of the table and the footnotes) or fixed in the figure, whichever is in error."

RESPONSE: *The footnote was added to the LSE table*

COMMENT 16 (Figure 3-2): The Reviewer states "The intermediate MRL for effects other than cancer in the figure (Figure key 10R) is not mentioned in Table 3-3. This information needs to be added to Table 3-3 (both in the main part of the table and the footnotes) or fixed in the figure, whichever is in error."

RESPONSE: *The footnote was added to the LSE table*

COMMENT 17 (Figure 3-2): The Reviewer states "For Figure keys 4, 11 and 20-22 the acronym OF is written under the Parameters monitored column, but the acronym is not defined in the table footnotes. I assume that this is organ function. If so, please add the acronym to the table footnotes."

RESPONSE: *The acronym was added to the footnote*

COMMENT 18: The Reviewer states "For Figure keys 8-10, 13 and 15, the acronym BI is written under the Parameters monitored column, but the acronym is not defined in the table footnotes. Please correct if this is a typo or add the acronym to the table footnotes."

RESPONSE: *The acronym was added to the footnote*

COMMENT 19 (Table 3-5): The Reviewer states "The acronym OF is written under the Parameters monitored column for two of the studies, but the acronym is not defined in the table footnotes. I assume that this is organ function. If so, please add the acronym to the table footnotes."

RESPONSE: *The acronym is defined under the Parameters section of the footnote*

COMMENT 20 (Table 3-6): The Reviewer states "For the DNA damage row, please add "(gavage)" after "Mouse peritoneal macrophages", assuming this is the route of exposure given in the Lima et. al.2010 study."

RESPONSE: *The suggested revision was made.*

COMMENT 21 (page 62, lines 5-15): The Reviewer states "Please mention why cancer was not included in this Hazard Identification section."

RESPONSE: *The section is a summary of the Systematic Review discussed in detail in Appendix B. The rationale for not including cancer is discussed in the appendix.*

COMMENT 22 (page 70, line 18): The Reviewer states "This chronic inhalation MRL of 0.0003 mg/m^3 does not match with the MRL illustrated in Figure 3.1, as in the figure it appears to be closer to 0.0008 mg/m^3."

RESPONSE: *The figure was adjusted.*

COMMENT 23 (page 85, line 7): The Reviewer states "The word "lower" should be replaced with "higher" as the intermediate-duration inhalation MCL was numerically a higher value than the acute inhalation MCL.:

RESPONSE: *The suggested revision was made.*

COMMENT 24 (page 107, line 2): The Reviewer states "The 300 mg/kg of antimony in PET water bottles is not an exposure, but rather the concentration in the plastic, according to the text on page 137, lines 22-23. Please correct the text on page 107 to state that individuals may be exposed to antimony from PET water bottles, giving the exposure concentration in the water from the PET water bottles if desired but omitting the 300 mg/kg value as it is misleading in this context. The information on page 137 does not need to be changed, however."

RESPONSE: *The suggested revision was made.*

COMMENT 25 (page 130, line 32): The Reviewer states "The minimal detectable mean concentration of 90 mg/m^3 must be an error. Please verify that your units are correct."

RESPONSE: *The unit was corrected to* ng/m^3

COMMENT 26 (page 138, line 16): The Reviewer states "Please note in the text that the urinary antimony concentrations have been decreasing over time as reflected in the NHANES geometric mean and selected percentile values. Please provide any available information to help explain this decrease, as I could not find it discussed elsewhere and such a marked decrease (well over 50%) is important. Also,

assuming this decline is not explained by changes in analytic techniques, which seems unlikely, this reduction in exposure should be mentioned in Chapter 2 and possibly Chapter 1."

RESPONSE: *A note was added regarding the decreasing urine antimony levels in the NHANES data. There are insufficient data to determine the cause of the decline and statements were not added to Chapters 1 or 2.*

COMMENT 27: The Reviewer states "I recommend adding Van Velzen D, Langenkamp H, Herb G. Antimony, its sources, applications and flow paths into urban and industrial waste: a review. Waste Manag Res. February 1998 vol. 16 no. 1 32-40. This reference is important as it documents the important contribution of antimony in flame retardants as a source of exposure."

RESPONSE: *The van Velzen et al. (1998) paper was added to the profile.*

Comments provided by Peer Reviewer #2:

General Comments

COMMENT 1: The Reviewer states **"**Chapter 1 has not been written at an 8-10th grade level. Using the readability statistics available in Word this chapter has an 11.3 Flesch-Kincaid grade level and a 39.7 reading ease. Flesch Reading Ease does not provide a standard grade level difficulty interpretation, although the higher the number, the easier the text is to read and scores between 60 and 70 are considered easily understood by 8th and 9th graders. (http://www.readabilityformulas.com/flesch-reading-ease-readability-formula.php). Grade levels determined using Flesch-Kincaid methods may under predict readability grade levels predicted by other methods (e.g., Simple Measure Of Gobbledygook [SMOG]) used to estimate grade level readability (e.g., see Fitzsimmons PR, Michael BD, Hulley JL, Scott GO. A readability assessment of online Parkinson's disease information. J R Coll Physicians Edinb 40(4):292-296, 2010).

For example consider rewording: (Page 2): The concentration of antimony that is dissolved in rivers and lakes is very low, usually less than 1 micrograms per liter (µg/L) (USGS 2011). Antimony does not appear to accumulate in fish or other aquatic animals (EPA 1980). Soil usually contains very low concentrations of antimony, although soils near occupational sites, such as mining and production sites, contain antimony levels as high as 17,500 milligrams per kilogram (mg/kg) (Scheinost et al. 2006). – as written this paragraph 16.5 grade level. The following changes lower the Flesch-Kincaid grade to 8.9: The amount of antimony that is found in rivers and lakes is very low (USGS 2011). They are usually less than 1 micrograms per liter (µg/L). Antimony amounts do not increase in fish or other animals that live in water (EPA 198). Soil also contains very low concentrations of antimony. Soils near mines and other work sites may contain high levels of antimony (Scheinost et al. 2006).
This simple example illustrates how the use of shorter sentences and shorter words can improve the documents readability."

RESPONSE: *Chapter 1 was revised; the Flesch-Kincaid grade level of the revised text (excluding boilerplates) was 10.3.*

COMMENT 2 (page 3): The Reviewer states "*After you eat or drink very large doses of antimony, you may vomit. This will prevent most of the antimony from entering through the stomach and intestines into your blood*. Is there data to support the claim that > 50% of the antimony will be removed? This statement is inconsistent with many clinical studies showing lower recovery rates following the administration of an emetic – also it does not address whether antimony is a reliable emetic or not.

RESPONSE: *The referenced statement was deleted.*

COMMENT 3 (page 3): The Reviewer states "*Antimony can also cause heart problems, including damage to the heart muscle and changes in electrocardiogram (EKG) readings (Brieger et al. 1954).* It is unclear what level of evidence was used by the ATSDR to decide that a causal association could be drawn. This can be especially problematic for relying on an older study like Brieger.

RESPONSE: *The results of the Brieger et al (1954) study is supported by the findings of parenteral exposure in laboratory animals (Alvarez et al. 2005; Bromberger-Barnea and Stephens 1965; Cotten and*

Logan 1966) and reports in humans treated with antimony compounds (Dancaster et al. 1966; Honey 1960; Lawn et al. 2006; Neves et al. 2009; Sundar et al. 1998; Thakur 1998).

COMMENT 4 (page 4): The Reviewer states "*There is also limited information suggesting that antimony can damage the developing cardiovascular system in rats (Angrisani et al. 1988; Rossi et al. 1987).* Was there evidence of damage (pathology) in this study or changes in cardiovascular function when challenged with a cardioactive drug?"

RESPONSE: *The studies found cardiovascular alterations in a challenge test.*

COMMENT 5 (page 4): The Reviewer states **"***Use bottled water if you have concerns about the presence of antimony in your tap water*. This doesn't seem to be very prudent especially if the person was to use a PET-based plastic bottle."

RESPONSE: *Although antimony can be present in PET-based plastic bottles, FDA has set an allowable level of antimony in bottled water. This was considered an alternative to consuming tap water with high levels of antimony.*

COMMENT 6 (Section 2.1, line 18): The Reviewer states "*Levels of antimony have increased in ambient waters due to anthropogenic activity such as mining activities, and coal and municipal waste combustion (Jablonska-Czapla et al. 2014).* In looking at this reference I noted there was no primary citation provided in the manuscript by Jablonska-Czapla – moreover it is not clear whether this observation extends to most water systems or US waterways. It would also be useful to provide the time frame that this statement refers to.

RESPONSE: *The statement was based on foreign monitoring data and was deleted from this section.*

COMMENT 7 (page 8, line 4): The Reviewer states *"Currently, antimony compounds are used to treat two parasitic diseases, schistosomiasis and leishmaniasis."* Is this statement correct for example the use of antimony is not included as a treatment by the CDC (see: http://www.cdc.gov/parasites/schistosomiasis/treatment.html). I believe this is a historical use rather than a current application given the use of modern drugs.

RESPONSE: *The text was revised to indicate that currently it is used to treat leishmaniasis.*

COMMENT 8 (page 8, line 26): The Reviewer states "*In laboratory animals, the lung effects include the accumulation of antimony particles in the lungs, increases in alveolar/intra-alveolar macrophages (Newton et al. 1994; NTP 2016),* ***decreases in lung clearance times*** *(Newton et al. 1994), chronic interstitial inflammation (Brieger et al. 1954; Newton et al. 1994; NTP 2016), and interstitial fibrosis (Groth et al. 1986; Newton et al. 1994; Watt 1983).* I presume that the statement about decreased lung clearance applies to the clearance of antimony from the lung (as stated in Newton) – please clarify this since some studies look at bacterial clearance as a test of immunological pulmonary responses."

RESPONSE: *The suggested revision was made.*

COMMENT 9: The Reviewer states "I do not agree with the ATSDR's classification that: antimony is suspected to cause cardiovascular health effects, specifically myocardial and EKG alterations, in humans. As the ATSDR notes in Appendix B: "Although the hazard identification for myocardial and EKG alterations **should be not classifiable** based on inadequate evidence in humans and low evidence in animals, the level of the hazard identification was raised to suspected health effect based on consistent evidence of EKG alterations in patients treated with injected trivalent or pentavalent antimony compounds (Dancaster et al. 1966; Honey 1960; Lawn et al. 2006; Neves et al. 2009; Sundar et al. 1998; Thakur 1998) and in animal studies involving parenteral administration (Alvarez et al. 2005; Bromberger-Barnea and Stephens 1965; Cotten and Logan 1966)." According to the description of the way the systematic review was conducted data from parenteral exposure would be considered "supporting" (see Table B1). Moreover the ATSDR has seemingly pooled EKG changes as if they represent a single clinical outcome when in reality changes in the EKG can be quite variable and should be more explicitly described in the text.

RESPONSE: *The cardiotoxicity of the antimony has not been well investigated in laboratory animal studies. However, human and laboratory animal studies have consistently reported EKG alterations, particularly prolongation of the QT interval. Thus, it was considered a suspected potential effect for humans.*

COMMENT 10: The Reviewer states "The discussion concerning developmental effects in animals needs to discuss whether maternal effects are significant enough to question whether the reported effects represent maternal or developmental toxicity. For example Rossi et al., 1987 state: "Antimony exposure decreased maternal and pup body weight."

RESPONSE: *A statement was added that a decrease in maternal weight gain was also observed at the doses associated with decreases in pup body weight.*

COMMENT 11: The Reviewer states "I do not agree with the inclusion of the study by Rossi et al., 1987 as a developmental toxicity study per se (despite their use of a perinatal exposure). No structural changes were observed and their main finding was an alteration in vascular responses following pharmacological manipulation (e.g., decreased pressor response following administration of 1-noradrenaline and hypotensive response following administration of 1-isoprenaline). The work by Angrisani also appears to not fit the typical definition of a developmental toxicity effect per se."

RESPONSE: *The available data do not allow for an assessment of whether the cardiovascular effects are due impaired development of the cardiovascular system or another mechanism. These effects were discussed under developmental toxicity and mentioned in the cardiovascular effects section of Section 3.2.2.2).*

COMMENT 12: The Reviewer states "The ATSDR also needs to be extremely cautious in its interpretation of the change (decreased) in blood glucose seen following antimony exposure (Poon et al., 1998) as an adverse health effect. The original data (Table 1) from the study suggests that blood glucose levels in male and female rats were around 240 to 250 mg/dl. These values are quite high when compared with other studies (e.g., see Nowland MH, Hugunin KM, Rogers KL. Effects of short-term fasting in male Sprague-Dawley rats. Comp Med. 2011 Apr;61(2):138-44; also http://www.taconic.com/rat-model/sprague-dawley) which show that blood glucose concentrations are qualitatively in line with those seen in humans and other mammals. I also feel here and elsewhere the authors should clearly indicate when a response occurs in one sex (e.g., Poon reported changes in females only)."

RESPONSE: *The text was revised to indicate that decreases in blood glucose were observed in female rats in the Poon et al. (1998) study and in males and females in the Schroeder et al. (1970) study. A note was added to indicate that the serum glucose levels in all groups (including controls) was higher than the normal range reported by the animal supplier.*

COMMENT 13: The Reviewer states **"**Chapter 2 has very little specific exposure dose and duration data provided. Overall exposure conditions has not been adequately described"

RESPONSE: *It is beyond the intended scope of the Relevance to Public Health chapter to provide detailed descriptions of the study including exposure durations; this information is provided in Chapter 3.*

COMMENT 14 (Chapter 3): The Reviewer states "The ATSDR has provided a robust literature search and the chapter is organized well and follows guidelines for this type of document. I am not aware of any human or animal studies that should have been included in their review. Conclusions drawn by the authors of the cited manuscripts appear to be adequately described in the ATSDR document."

RESPONSE: *No suggested revisions.*

COMMENT 15: The Reviewer states "The discussion on PBPK models and inclusion of Figure 3-3 seems overlong given that no PBPK models for antimony was found. Is this merely required boilerplate?"

RESPONSE: *This is the required boilerplate for this section.*

COMMENT 16 (Table 3-11): The Reviewer states "the NOAELs and LOAELs only provide the exposure concentration not the duration (e.g., hr/day, day/wk – etc). Also note the Table legend is really incomplete – e.g., exposure route and concentrations are not provided. In general data could easily be tabulated to reduce the amount of text used. Even though the ATSDR document covers 'all' antimony species – it would be helpful if summary tables indicate the chemical form of antimony that was used in the study."

RESPONSE: *The table was revised to indicate that the studies involved chronic duration inhalation exposure and the exposure durations were added as footnotes.*

COMMENT 17: The Reviewer states "I'm confused by the data presented in the ATSDR document and the on-line NTP (2016) report – ATSDR indicates a 2.5 mg/m3 concentration was used but in the draft NTP document they report the concentration is 3 mg/m3 (e.g., see: NTP TR 590 – summary of findings). It would be useful for the ATSDR references to include the links to these documents and accession dates since the NTP does not appear to have been finalized yet)."

RESPONSE: *The concentrations reported in the profile are in terms of antimony (mg antimony/m^3) whereas NTP reports antimony trioxide concentrations*

COMMENT 18: The Reviewer states "The study by Newton et al shows a large variation (> 3 fold) in the atmospheric antimony concentrations that were generated on each day (see Figure 1 that paper)."

RESPONSE: *The reported mean and standard deviations for the antimony trioxide levels in the 1-year study were 0.06±0.04, 0.51±0.13, and 4.50±1.33 mg/m^3.*

COMMENT 19: The Reviewer states "Statistical analyses performed by Rossi et al (1987) do not appear to have considered maternal (litter effects) – indeed there was a crossover design that does not describe how pups were allocated to treatment groups. This may draw into question the utility of the study (this likely also applies to Angrisani et al., 1988). "

RESPONSE: *The crossover design along with the gestational, lactational, and postnatal exposure precluded analysis on a litter basis. Although not specified, it is assumed that pups were exposed to the same antimony trichloride concentration pre- and postnatally.*

COMMENT 20: The Reviewer states "Poon et al (1998) did some cursory evaluation of thyroid hormone levels that might be applicable to section 3.7."

RESPONSE: *The thyroid effects observed in the Poon et al. (1998) study are discussed under Endocrine Effects in Section 3.2.2.2. There is no evidence that antimony is an endocrine disruptor, thus these effects were not discussed in Section 3.7.*

COMMENT 21 (Section 3.12.2): The Reviewer states "The use of BAL as a chelator is supported by a 1946 study performed in rabbits given lethal doses of antimony by Eagle et al (BAL in antimony poisoning in JPET)."

RESPONSE: *The Eagle et al. (1947) study was added to the profile.*

COMMENT 22 (Figure 3-4): The Reviewer states "Figure 3-4 – I was surprised that ATSDR considered there to be data available for neurologic effects since no neurotoxicity studies (beyond an assessment of brain pathology) has been performed. Criteria used to make these decisions seems lacking."

RESPONSE: *Figure 3-4 identifies endpoints which have been evaluated in toxicity studies regardless of the quality of the study. As discussed in Section 3.13.2, available studies do not adequately address the potential neurotoxicity of antimony and neurotoxicity is an identified data gap.*

COMMENT 23 (Chapter 4): The Reviewer states "I am not aware of any information or values that are wrong or missing in the chemical and physical properties tables and adequate physicochemical information has been provided on the various forms of the substance."

RESPONSE: *No suggested revisions.*

COMMENT 24 (Chapter 5): The Reviewer states "I am not aware of any incorrect or missing information"

RESPONSE: *No suggested revisions.*

COMMENT 25 (Chapter 6): The Reviewer states "A picky point but the preamble to this chapter indicates that: "Antimony and antimony-containing compounds have been identified in at least **579** of the 1,699 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2007). However, the number of sites evaluated for antimony and compounds is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, **573** are located within the United States and **2** are located in the Commonwealth of Puerto Rico (not shown)" – but subsequent information) only accounts for 575 of these 579 sites."

RESPONSE: *The text was revised to indicate that 5 were located in Puerto Rico and 1 was located in Guam.*

COMMENT 26 (page 107): The Reviewer states **"**Page 107: *Individuals can be exposed to as high as 300 mg/kg antimony in polyethylene terephthalate (PET) water bottles (Belzile et al. 2011).* This statement needs clarification since this is the concentration found in the plastic versus quantity that leaches from it (this data is provided by Belzile et al. 2011 showing higher antimony water concentrations when PET bottles are used to store water (as discussed in section 6.4.4)."

RESPONSE: *The text was revised to delete the concentration in the PET bottles.*

COMMENT 27: The Reviewer states "Other media: the description of studies evaluating antimony from mattresses seems incomplete since some studies (e.g., Warnock et al., 1995) suggest that this could be a source of bacterial-generated gaseous form of antimony. This is warranted since there were some attempts to link this observation to a toxic gas cause for SIDS (and mentioned as a general concern on page 149."

RESPONSE: *The text was revised to indicate the possible source of the stibine and the findings of several studies which did not find increases in brain or liver antimony levels in infants dying from SIDS.*

COMMENT 28: The Reviewer states "I realize that ATSDR is not the source of the data presented in Table 6-3 but the level of precision is hard to believe (e.g., Mobile, commercial marine vessels: 69.72685 lb)."

RESPONSE: *Many of the values reported in the National Emissions Inventory dataset are reported with this many significant figures.*

COMMENT 29 (page 116): The Reviewer states "Provide a reference for the following statement: *Antimony Kd values ranged from 1 to 2,065 L/kg in a sorption study investigating plant uptake of antimony*."

RESPONSE: *The citation (Nakamaru and Sekine 2008) was added.*

COMMENT 30 (page 117): The Reviewer states "*Bioconcentration factors for antimony ranged from 0.15 to 390 (Acquire 1989; Callahan et al. 1979).* Is there an explanation for this wide range (e.g., form of antimony, species, etc)?"

RESPONSE: *The range reflects difference in bioconcentration factors across species.*

COMMENT 31 (Chapter 6): The Reviewer states" Overall this chapter has done a very good job of compiling the exposure data. I am not aware of any data that is missing."

RESPONSE: *No suggested revision.*

COMMENT 32 (Chapter 7): The Reviewer states "The introduction to the chapter could clearly indicate the methods used to detect total antimony versus those used to speciate this metal (e.g., this is adequately discussed on page 152). Likewise Table 7-1 could indicate when total antimony concentration is being estimated (e.g., add to Table legend)."

RESPONSE: *Footnotes were added to Table 7-1 to indicate whether the method measured total antimony or antimony species.*

COMMENT 33 (Chapter 7): The Reviewer states "This chapter appears to be complete"

RESPONSE: *No revisions suggested.*

COMMENT 34 (Chapter 8): The Reviewer states "This chapter appears to be complete"

RESPONSE: *No revisions suggested.*

COMMENT 35 (Table A-2): The Reviewer states "I found this Table confusing since the model with the lowest AIC (see page A-4, and Table footnote e) the Table A-3 uses a different criteria (most conservative – lowest BMCL10). The rationale for using a combination of these two approaches does not to be well spelled out."

RESPONSE: *As noted in the description of the benchmark dose modeling (page A-4), when the BMCL values are sufficiently close (within 3 fold), the model with the lowest AIC is selected. If the BMCL values are not sufficiently close then the model with the lowest BMCL is selected.*

COMMENT 36 (Table A-10): The Reviewer states "Table A-10 – see my earlier comment about these unusually high control glucose concentrations"

RESPONSE: *The investigators did not discuss why the blood glucose levels in all groups (including controls) were higher than levels measured in other studies. A statement was added that the values in the Poon et al. (1998) study were higher than the normal range for this strain.*

COMMENT 37 (Appendix B): The Reviewer states "Appendix B – I could not find a clearly defined PECO statement that was used to guide the systematic review(s)."

RESPONSE: *In the Problem Formulation section (Section B.1), ATSDR defines the objective of the systematic review which echoes the purpose of the toxicological profile: identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to antimony. Given the broad nature of this objective, specific PECO (Population, Exposure, Comparator, and Outcome) statements were not used.*

COMMENT 38 (Appendix B): The Reviewer states "Table B-1 could be strengthened by indicating explicitly that subject age, sex, and other factors were not exclusion criteria. I can not find a listing of your formal exclusion criteria."

RESPONSE: *ATSDR opted to list inclusion criteria rather than exclusion criteria.*

COMMENT 39 (Section B.2.2): The Reviewer states "– how were the abstracts and full text studies screened? e.g., two independent evaluators? Similar procedural question for your risk of bias evaluation."

RESPONSE: *One independent evaluator screened the literature search and assessed the risk of bias, the systematic review results were then evaluated by the ATSDR chemical manager team.*

COMMENT 40 (Table B-7): The Reviewer states "*Other bias: This question addresses whether the copper levels of the diet met nutritional requirements*. This should be clearly spelled out (i.e., provide nutritional range and species specific reference like NRC's Nutritional Requirements) – how were historical information about diets handled since some have changed over time? It's also unclear why this was considered N/A for the majority of studies that were evaluated for risk of bias since diets were provided in all animal studies.

RESPONSE: *The text was revised to delete the statement regarding copper intake. No specific confounders were identified for antimony. The table was revised to indicate "NA" in all studies for this potential bias.*

COMMENT 41 (Table B-12): The Reviewer states **"***A sufficient number of animals per group were tested*. What criteria were used to determine this – did ATSDR perform a power analysis?"

RESPONSE: *The criteria were 10 animals/sex/group for intermediate duration studies and 50 animals/sex/group for chronic studies.*

COMMENT 42: The Reviewer states "Using a figure similar to Figure B-2 could be a very useful way to summarize the hazard information and allow a reader to quickly understand the source of the data (animal or human) and the level of evidence."

RESPONSE: *ATSDR will consider this suggestion in future versions of the toxicological profile guidance document.*

COMMENT 43 (page B-37): The Reviewer states "*Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility*. It is not clear how (or if) ATSDR did this.

RESPONSE: *This is used on a case-by-case basis to add support or opposition to biological plausibility. One example is the use of parenteral exposure studies to elevate the classification of cardiovascular effects from "not classifiable" to "suspected health effect".*

Comments provided by Peer Reviewer #3:

ATSDR Charge Questions and Responses

CHAPTER 1 – PUBLIC HEALTH STATEMENT

QUESTION: The tone of the chapter should be factual rather than judgmental. Does the chapter present the important information in a non-technical style suitable for the average citizen?

COMMENT: Yes, the tone is factual and not judgmental. Information is presented in non-technical and understandable terms to the average citizen. It is also well indicated where readers can refer to for more information.

RESPONSE: *No revisions were suggested.*

QUESTION: Major headings are stated as a question. In your opinion, do the answers to the questions adequately address the concerns of the lay public? Are these summary statements consistent, and are they supported by the technical discussion in the remainder of the text? Please note sections that are weak and suggest ways to improve them.

COMMENT: The question format is well done and easy to follow. Readers are re-directed to other sections for more details. The information presented in this section appears relevant and sufficient.

RESPONSE: *No revisions were suggested.*

QUESTION: Are scientific terms used that are too technical or that require additional explanation? Please note such terms and suggest alternate wording

COMMENT: Some units might be confusing to the average citizen but they can again refer to the toll-free line or the Agency for clarifications.

RESPONSE: *No revisions were suggested.*

CHAPTER 2 – RELEVANCE TO PUBLIC HEALTH

QUESTION: Do you agree with those effects known to occur in humans as reported in the text? If not, provide a copy of additional references you would cite and indicate where (in the text) these references should be included. -Are the effects only observed in animals likely to be of concern to humans? Why or why not? If you do not agree, please explain.

COMMENT: It is clearly stated that those effects either “have been reported” or “have been observed” and been published in refereed scientific literature. It is also commonly accepted that effects observed in animals are likely to be of concern to humans. I agree that it is important to make people aware of the studies and aware of the toxic potential of antimony and its compounds and not over alarming them. Table 2.1 is very informative and realistic.

RESPONSE: *No revisions were suggested.*

QUESTION: Have exposure conditions been adequately described? If you do not agree, please explain.

COMMENT: Exposure conditions are as well described as they are in literature. It might be good to include a comment on the importance of the oxidation state of Sb (III or V) and it is nice to see that some studies have define LOAELs for respiratory tract effects as a function of a specific antimony valence state.

RESPONSE: *No revisions were suggested.*

CHAPTER 3 –HEALTH EFFECTS

SECTION 3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

Toxicity – Quality of Human Studies

QUESTION: Were adequately designed human studies identified in the text (i.e., good exposure data, sufficiently long period of exposure to account for observed health effects, adequate control for confounding factors)? If not, were the major limitations of the studies sufficiently described in the text without providing detailed discussions? If study limitations were not adequately addressed, please suggest appropriate changes.

COMMENT: Yes, in general although it is not easy to comment on the adequate design or the quality of data for older studies. It could be mentioned in the text that some studies are old and the levels of exposure in some of them might have been exceptional due to the lack of knowledge and protection at that time. It could also be indicated that the exactitude in terms of concentrations might be questionable for older studies due to the difficulty in judging the quality of analyses (precision and limit of detection at lower concentration levels). The exact nature of the antimony compounds that subjects were exposed to is not always indicated. Sometimes a lot of information is coming from one major study, which means that results could be treated with or without extra confidence.

RESPONSE: *There are insufficient data to determine whether older studies inaccurately determined antimony exposure levels, thus the suggested statement was not added. In most cases, the antimony compound is reported. In some human studies, particularly occupational exposure studies, the antimony species were poorly characterized or was not reported.*

COMMENT: Tables 3.1 3.2 provides a lot of details and are very informative but I suggest re-arranging both Tables in chronological order for each sub-sections.

RESPONSE: *The studies are arranged in alphabetical order within each section to allow for easier look-up.*

QUESTION: Were the conclusions drawn by the authors of the studies appropriate and accurately reflected in the profile? If not, did the text provide adequate justification for including the study (e.g., citing study limitations)? Please suggest appropriate changes.

COMMENT: Conclusions are very good in general. See comments and answers to the previous questions.

RESPONSE: *No revisions were suggested.*

QUESTION: Were all appropriate NOAELs and/or LOAELs identified for each study? If not, did the text provide adequate justification for excluding NOAELs/LOAELs including, but not limited to, citing study limitations? Please suggest appropriate changes.

COMMENT: NOAELs and/or LOAELs are listed when available from the study. It can be easily assumed that they were not put in the list when not given in the study.

RESPONSE: *No revisions were suggested.*

QUESTION: Were the appropriate statistical tests used in the studies? Would other statistical tests have been more appropriate? Were statistical test results of study data evaluated properly? **NOTE**: As a rule, statistical values are not reported in the text, but proper statistical analyses contribute to the reliability of the data.

COMMENT: Most studies report a generally sufficient numbers of individuals tested over many exposure duration and concentrations. It can be expected with good confidence that appropriate statistics have been applied and evaluated properly.

RESPONSE: *No revisions were suggested.*

QUESTION: Are you aware of other studies which may be important in evaluating the toxicity of the substance? Please provide a copy of each study and indicate where in the text each study should be included.

COMMENT: I am not aware.

RESPONSE: *No revisions were suggested.*

Toxicity – Quality of Animal Studies

QUESTION: Were adequately designed animal studies identified in the text (i.e., adequate number of animals, good animal care, accounting for competing causes of death, sufficient number of dose groups, and sufficient magnitude of dose levels)? If not, does the inadequate design negate the utility of the study? Please explain.

COMMENT: All studies identified in the text were adequately designed and presented with all the required and detailed information. Tables are clearly presented and Figures are nicely and clearly illustrated and coded. Each subsection of Tables should be arranged chronologically.

RESPONSE: *No revisions were suggested.*

QUESTION: Were the animal species appropriate for the most significant toxicological endpoint of the study? If not, which animal species would be more appropriate and why?

COMMENT: Except for older studies, the selected animal species are the most commonly used for toxicological studies.

RESPONSE: *No revisions were suggested.*

QUESTION: Were the conclusions drawn by the authors of the studies appropriate and accurately reflected in the text? If not, did the text provide adequate justification for including the study (e.g., citing study limitations)?

COMMENT: Yes, in general. It might be appropriate again to indicate that levels of exposure may be high in some cases and that not all forms (read also oxidation states) of antimony have been systematically tested.

RESPONSE: *A statement was added to 3.1 to indicate that most of the available studies evaluated the toxicity of trivalent antimony, in particular antimony trioxide.*

QUESTION: Were all appropriate NOAELs and LOAELs identified for each study? Were all appropriate toxicological effects identified for the studies? If not, please explain.

COMMENT: NOAELs and/or LOAELs are listed when available from the study. It can be easily assumed that they were not put in the list when not given in the study.

RESPONSE: *No revisions were suggested.*

QUESTION: If appropriate, is there a discussion of the toxicities of the various forms of the substance? If not, please give examples of toxicological effects that might be important for forms of the substance.

COMMENT: Yes

RESPONSE: *No revisions were suggested.*

QUESTION: Were the appropriate statistical tests used in the interpretation of the studies? If not, which statistical tests would have been more appropriate? Were statistical test results of study data evaluated properly?

COMMENT: Most studies report a generally sufficient numbers of individuals tested over many exposure duration and concentrations. It can be expected with good confidence that appropriate statistics have been applied and evaluated properly.

RESPONSE: *No revisions were suggested.*

QUESTION: Are you aware of other studies that may be important in evaluating the toxicity of the substance? If you are citing a new reference, please provide a copy and indicate where (in the text) it should be included.

COMMENT: Not to my knowledge

RESPONSE: *No revisions were suggested.*

Levels of Significant Exposure (LSE) Tables and Figures

QUESTION: Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables?

COMMENT: In consideration with the diversity and complexity of all studies, I agree that the chosen categorization represents the best and less alarming way to differentiate the effects.

RESPONSE: *No revisions were suggested.*

QUESTION: If MRLs have been derived, are the values justifiable? If no MRLs have been derived, do you agree that the data do not support such a derivation?

COMMENT: I agree.

RESPONSE: *No revisions were suggested.*

Evaluation of Text

QUESTION: Have the major limitations of the studies been adequately and accurately discussed? How might discussions be changed to improve or more accurately reflect the proper interpretation of the studies?

COMMENT: As previously mentioned, it might be appropriate to indicate that older studies (before the 1960's for instance) might in some cases contain less details and may have used less sensitive techniques than those available nowadays.

RESPONSE: *The suggested statement was not added because it is an overgeneralization of older literature. Limitations of specific studies are discussed in Section 3.2.*

QUESTION: Has the effect, or key endpoint, been critically evaluated for its relevance in both humans and animals?

COMMENT: Yes.

RESPONSE: *No revisions were suggested.*

QUESTION: Have "bottom-line" statements been made regarding the relevance of the endpoint for human health?

COMMENT: Yes.

RESPONSE: *No revisions were suggested.*

QUESTION: Are the conclusions appropriate given the overall database? If not, please discuss your own conclusions based on the data provided and other data provided to you but not presented in the text.

COMMENT: Yes, conclusions are appropriate.

RESPONSE: *No revisions were suggested.*

QUESTION: Has adequate attention been paid to dose-response relationships for both human and animal data? Please explain.

COMMENT: Yes, when it was possible to do so.

RESPONSE: *No revisions were suggested.*

QUESTION: Has the animal data been used to draw support for any known human effects? If so, critique the validity of the support.

COMMENT: Except for older studies, the selected animal species are the most commonly used for toxicological studies.

RESPONSE: *No revisions were suggested.*

SECTION 3.4 TOXICOKINETICS

QUESTION: Is there adequate discussion of absorption, distribution, metabolism, and excretion of the substance? If not, suggest ways to improve the text.

COMMENT: Yes, in consideration of all available valid studies.

RESPONSE: *No revisions were suggested.*

QUESTION: Have the major organs, tissues, etc. in which the substance is stored been identified? If not, suggest ways to improve the text.

COMMENT: Yes, in consideration of all available valid studies.

RESPONSE: *No revisions were suggested.*

QUESTION: Have all applicable metabolic parameters been presented? Have all available pharmacokinetic /pharmacodynamic models and supporting data been presented? If not, please explain.

COMMENT: Yes, to my knowledge.

RESPONSE: *No revisions were suggested.*

QUESTION: Is there adequate discussion of the differences in toxicokinetics between humans and animals? What other observations should be made?

COMMENT: Yes, in consideration of all available valid studies.

RESPONSE: *No revisions were suggested.*

QUESTION: Is there an adequate discussion of the relevance of animal toxicokinetic information for humans? If not, please explain.

COMMENT: Yes, in consideration of all available valid studies.

RESPONSE: *No revisions were suggested.*

QUESTION: If applicable, is there a discussion of the toxicokinetics of different forms of the substance (e.g., inorganic vs. organic mercury)?

COMMENT: Yes, in consideration of all available valid studies.

RESPONSE: *No revisions were suggested.*

SECTION 3.5 MECHANISMS OF ACTION

QUESTION: Have all possible mechanisms of action been discussed? If not, please explain.

COMMENT: Yes, Figure 3-3 is simple and useful.

RESPONSE: *No revisions were suggested.*

SECTION 3.6 HAZARD IDENTIFICATION AND MINIMAL RISK LEVELS

COMMENT: Good summary (also in Appendix B).

RESPONSE: *No revisions were suggested.*

SECTION 3.9 BIOMARKERS OF EXPOSURE AND EFFECT

QUESTION: Are the biomarkers of exposure specific for the substance or are they for a class of substances? If they are not specific, how would you change the text?

COMMENT: Text is appropriate.

RESPONSE: *No revisions were suggested.*

QUESTION: Are there valid tests to measure the biomarker of exposure? Is this consistent with statements made in other sections of the text? If not, please indicate where inconsistencies exist.

COMMENT: For Sb, those presented and available are valid.

RESPONSE: *No revisions were suggested.*

QUESTION: Are the biomarkers of effect specific for the substance or are they for a class of substances? If they are not specific, how would you change the text?

COMMENT: Few results are available but likely specific considering the nature of the metal.

RESPONSE: *No revisions were suggested.*

QUESTION: Are there valid tests to measure the biomarker of effect? Is this consistent with statements made in other sections of the text? If not, please indicate where inconsistencies exist.

COMMENT: Yes, likely.

RESPONSE: *No revisions were suggested.*

SECTION 3.10 INTERACTIONS WITH OTHER CHEMICALS

QUESTION: Is there adequate discussion of the interactive effects with other substances? Does the discussion concentrate on those effects that might occur at hazardous waste sites? If not, please clarify and add additional references.

COMMENT: Discussion is short but adequate.

RESPONSE: *No revisions were suggested.*

QUESTION: If interactive effects with other substances are known, does the text discuss the mechanisms of these interactions? If not, please clarify and provide any appropriate references.

COMMENT: There might be a few studies considering or discussing interactions of Sb with other elements but those are related to plants and not, to my knowledge, to animals or humans.

RESPONSE: *No revisions were suggested.*

SECTION 3.11 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

QUESTION: Is there a discussion of populations at higher risk because of biological differences which make them more susceptible? Do you agree with the choices of populations? Why or why not? Are you aware of additional studies in this area?

COMMENT: Discussion is short but appropriate in consideration of the available studies and reports.

RESPONSE: *No revisions were suggested.*

SECTION 3.11 METHOD FOR REDUCING TOXIC EFFECTS

QUESTION: Is the management and treatment specific for the substance, or is it general for a class of substances?

COMMENT: It is based on two studies that are specific to antimony.

RESPONSE: *No revisions were suggested.*

QUESTION: Is there any controversy associated with the treatment? Is it a "well accepted" treatment?

COMMENT: No and it is an accepted treatment.

RESPONSE: *No revisions were suggested.*

QUESTION: Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)?

COMMENT: Not specifically.

RESPONSE: *No revisions were suggested.*

QUESTION: Are treatments available to prevent the specific substance from reaching the target organ(s), or are the actions general for a class of substances?

COMMENT: Not specifically.

RESPONSE: *No revisions were suggested.*

QUESTION: Is there any controversy associated with the treatment? Is it a "well-accepted" treatment? If the discussion concerns an experimental method, do you agree with the conceptual approach of the method?

COMMENT: Not specifically.

RESPONSE: *No revisions were suggested.*

QUESTION: Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)?

COMMENT: Not specifically.

RESPONSE: *No revisions were suggested.*

QUESTION: Are there treatments to prevent adverse effects as the substance is being eliminated from the major organs/tissues where it has been stored (e.g., as a substance is eliminated from adipose tissue, can we prevent adverse effects from occurring in the target organ[s])?

COMMENT: Not specifically.

RESPONSE: *No revisions were suggested.*

QUESTION: Are treatments available to prevent the specific substance from reaching the target organ(s), or are the treatment's actions general for a class of substances?

COMMENT: Not specifically.

RESPONSE: *No revisions were suggested.*

QUESTION: Is there any controversy associated with the treatment? Is it a "well accepted" treatment? If the discussion concerns an experimental method, do you agree with the conceptual approach of the method?

COMMENT: Not specifically.

RESPONSE: *No revisions were suggested.*

QUESTION: Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)?

COMMENT: Not specifically.

RESPONSE: *No revisions were suggested.*

SECTION 3.13 ADEQUACY OF THE DATABASE

Existing Information on Health Effects of Antimony

QUESTION: Do you know of other studies that may fill a data gap? If so, please provide the reference.

COMMENT: No. However, it might be interesting to include for each dot the numbers of studies included.

RESPONSE: *ATSDR is in the processing of revising the format of the toxicological profile, in future versions of the profile, the number of studies examining an endpoint will be included.*

Identification of Data Needs

QUESTION: Are the data needs presented in a neutral, non-judgmental fashion? Please note where the text shows bias.

COMMENT: Data needs are presented in a neutral, non-judgemental fashion and no bias can be detected in the wording.

RESPONSE: *No revisions were suggested.*

QUESTION: Do you agree with the identified data needs? If not, please explain your response and support your conclusions with appropriate references.

COMMENT: I do agree with the identified data needs and glad to see that the aspect of oxidation state of the element considered is clearly mentioned.

RESPONSE: *No revisions were suggested.*

QUESTION: Does the text indicate whether any information on the data need exists?

COMMENT: *Yes, it does.*

RESPONSE: *No revisions were suggested.*

QUESTION: Does the text adequately justify why further development of the data need would be desirable; or, conversely, justify the "inappropriateness" of developing the data need at present? If not, how can this justification be improved.

COMMENT: *Yes, it does.*

RESPONSE: *No revisions were suggested.*

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

QUESTION: Are you aware of any information or values that are wrong or missing in the chemical and physical properties tables? Please provide appropriate references for your additions or changes.
Is information provided on the various forms of the substance? If not, please explain.

COMMENT: It might be appropriate to cite one of our paper for more detailed information of Sb complexes in solution. Filella M, Belzile N, Chen, Y. 2002. Antimony in the environment: a review focused on natural waters. II. Relevant solution chemistry. Earth-Sci Rev 595:262-285.

RESPONSE: *Filella et al. (2002) was added to Chapter 6.*

CHAPTER 5. PRODUCTION, IMPORT/EXPORT, USE AND DISPOSAL

QUESTION: Are you aware of any information that is wrong or missing? If so, please provide copies of the references and indicate where (in the text) the references should be included.

COMMENT: It appears to be up to date.

RESPONSE: *No revisions were suggested.*

CHAPTER 6. POTENTIAL FOR HUMAN EXPOSURE

QUESTION: Has the text appropriately traced the substance from its point of release to the environment until it reaches the receptor population? Does the text provide sufficient and technically sound information regarding the extent of occurrence at NPL sites? Do you know of other relevant information? Please provide references for added information.

COMMENT: Text is appropriate and sufficient. See minor comments/suggestions in red.

RESPONSE: *See RESPONSES to the comments in red in the Annotated Comments section.*

QUESTION: Does the text cover pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media? Do you know of other relevant information? Please provide references for added information.

COMMENT: Pertinent information is covered. Table 6.4 containing too many significant digits for some numbers.

RESPONSE: *This is the number of significant figures reported in EPA 2015a.*

QUESTION: Does the text provide information on levels monitored or estimated in the environment, including background levels? Are proper units used for each medium? Does the information include the form of the substance measured?

COMMENT: Information is given. Some units to be converted to the metric system.

RESPONSE: *See specific responses to this comment in the Annotated Comments section below.*

QUESTION: Is there an adequate discussion of the quality of the information? Do you know of other relevant information? Please provide references for added information.

COMMENT: Discussion on the quality of information is adequate.

RESPONSE: *No revisions were suggested.*

QUESTION: Does the text describe sources and pathways of exposure for the general population and occupations involved in the handling of the substance, as well as populations with potentially high exposures? Do you agree with the selection of these populations? If not, why? Which additional populations should be included in this section?

COMMENT: It is a good description of sources and pathways in consideration of actual knowledge. There has been an appropriate selection of populations.

RESPONSE: *No revisions were suggested.*

CHAPTER 7. ANALYTICAL METHODS

QUESTION: Are you aware of additional methods that can be added to the tables? If so, please provide copies of appropriate references.

COMMENT: All commonly used analytical techniques are mentioned.

RESPONSE: *No revisions were suggested.*

QUESTION: Have methods been included for measuring key metabolites mentioned previously in the text?

COMMENT: Yes.

RESPONSE: *No revisions were suggested.*

QUESTION: If unique issues related to sampling for the substance exist, have they been adequately addressed in the text? What other discussion should be provided?

COMMENT: The determination of antimony and species in tissues, biological fluids, metabolites, etc. include several steps going for the selection of the method, sampling, preservation, storage, analyses and quality control through the use of certified standards to cite a few. It would be valuable to mention all those steps and refer the reader to a critical discussion and evaluation of those in one of our review paper: Filella M, Belzile N, Chen Y. 2013. Human exposure to antimony. III Contents in some human excreted biofluids (urine, milk, saliva). Crit Rev Environ Sci Technol 43:162-214.

RESPONSE: *This level of detail is beyond the scope of this chapter of the profile; the intent of the chapter is to provide a high level summary of the available analytical methods.*

CHAPTER 8. REGULATIONS AND ADVISORIES

QUESTION: Are you aware of other regulations or guidelines that may be appropriate for the table? If so, please provide a copy of the reference.

COMMENT: No.

RESPONSE: *No revisions were suggested.*

CHAPTER 9. REFERENCES

QUESTION: Are there additional references that provide new data or are there better studies than those already in the text? If so, please provide a copy of each additional reference.

COMMENT: Some of our review papers suggested and provided. Tables in appendices are very useful.

RESPONSE: *Filella et al. (2012, 2013a, 2013b) were not added to the profile; these papers are in-depth discussions of analytical methods for measuring antimony in biological media, this level of detail is beyond the scope of Chapter 7. Filella et al. (2002) was added to Chapter 6.*

Annotated Comments

The Reviewer made several editorial suggestions to the profile; unless otherwise noted, the suggested revisions were made.

COMMENT 1: Regarding string references, the Reviewer states "Chronological citation for all cited documents"

RESPONSE: *Consistent with ATSDR's editorial guidance, string references are listed alphabetically.*

COMMENT 2 (page 2, line 21): The Reviewer suggests adding "reviewed in" to the Belzile et al. 2011 citation.

RESPONSE: *The suggested revision was not made, since the citations are removed from Chapter 1 in the final version of the profile.*

COMMENT 3: The Reviewer suggests listing the references in data tables in chronological order

RESPONSE: *The studies are arranged in alphabetical order within each section to allow for easier look-up.*

COMMENT 4 (Table 2-1): The Reviewer suggests including a brief definition of the uncertainty factor

RESPONSE: *The table was revised to include information on the uncertainty factors.*

COMMENT 5 (page 14, lines 33-34 through page 15, line 1): The Reviewer suggests adding information on the valence states.

RESPONSE: *The information on the valence state of the different antimony compounds are presented in previous section (Section 3.1).*

COMMENT 6 (page 30, line 33): The Reviewer suggests adding the phrase "(when supplied)" to the end of the sentence.

RESPONSE: *The CELs are the lowest concentration/dose resulting in a significant increase in the incidence of malignant lesions; these values are listed in Table 3-1 and Figure 3-1.*

COMMENT 7 (Table 3-8): The Reviewer suggests adding standard deviation or associated analytical error if available.

RESPONSE: *The suggested revision was made.*

COMMENT 8 (Figure 3-4): The Reviewer suggests including the number studies for each dot.

RESPONSE: *ATSDR is in the processing of revising the format of the toxicological profile, in future versions of the profile, the number of studies examining an endpoint will be included,*

COMMENT 9 (page 93, line 5): The Reviewer suggests replacing group 5A with Group 15

RESPONSE: *The IUPAC group label was added in parenthesis after group 5A.*

COMMENT 10 (page 93, line 7): The Reviewer suggests adding "in aqueous solutions and biological fluids" to the statement regarding stability.

RESPONSE: *The suggested revision was made.*

COMMENT 11: The Reviewer suggests adding the citation "Filella et al. 2002"

RESPONSE: *Filella et al. (2002) was added to Chapter 6.*

COMMENT 12: The Reviewer questions whether Table 4-2 should appear after Table 4-1.

RESPONSE: *Table 4-2 is called out in the text after Table 4-1, thus the placement is correct.*

COMMENT 13 (Tables 5-1, 5-2, 6-1, 6-2): The Reviewer questions whether the amount on site should also be reported in kg.

RESPONSE: *The amount on site is reported in pounds in TRI, thus no unit conversion was done.*

COMMENT 14 (page 107, line 15): The Reviewer suggests adding "and aquatic sediment"

RESPONSE: *The suggested revision was made.*

COMMENT 15 (page 107, line 35): The Reviewer suggests adding "and some anoxic or poorly oxygenated environments".

RESPONSE: *The suggested revision was made.*

COMMENT 16 (page 110, lines 19-20): The Reviewer suggests also reporting the TRI data in metric tons.

RESPONSE: *Since the release data are reported in pound units, the dose conversion was not made.*

COMMENT 17 (page 115, line 10 and Table 6-3: The Reviewer suggests also reporting the NEI emission data in metric tons.

RESPONSE: *To be consistent with the release data, the emission data were not converted to metric tons.*

COMMENT 18 (Table 6-4): The Reviewer states "certainly too many significant digits for most numbers of daily mean concentrations.

RESPONSE: *Table 6-4 has the same number of significant digits as reported in EPA 2015a.*

COMMENT 19 (page 154, line 24) The Reviewer suggests adding atomic fluorescence spectroscopy (AFS) to the list of commonly employed methods.

RESPONSE: *AFS is mentioned in the paragraph on page 155 discussing methods to determine antimony species.*