

**Disposition of Peer Review Comments for
Toxicological Profile for
Hydrogen Sulfide and Carbonyl Sulfide**

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 Hydrogen Sulfide and Carbonyl Sulfide were:

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Review comments provided by Reviewer #1:

COMMENT: Regarding the question of whether there are any data relevant to child health and developmental effects that have not been discussed in the profile, the Reviewer commented that “the Profile acknowledges deficiencies in the database for hydrogen sulfide (H₂S), and more especially so for carbonyl sulfide (COS). In view of missing definitive data, the Profile presents an apparently exhaustive survey of the limited available information. I am unaware of any additional, relevant literature on the health hazards to children from exposure to H₂S or COS.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there are any general issues relevant to child health that have not been discussed in the profile, the Reviewer commented that “the Profile presents a satisfactory accounting of the general scientific bases for special concerns (for childhood exposures and early life susceptibilities). I have no suggestions for other general issues related to children’s health concerns.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether Chapter 1 presents the important information in a non-technical style suitable for the average citizen, the Reviewer commented that “the “tone” of the Profile is certainly “factual;” in any case, I’m not sure how to respond to the request to assess whether the Profile is in any way “judgmental.” The many interpretations are certainly judgments regarding the weight of evidence, the adversity of observed effects, the relevance to human health safety assessment, etc. Whatever the intent of the question, the Profile does not include inflammatory and or unsubstantiated statements. Regarding the goal of presenting “...the important information in a non-technical style suitable for the average citizen...” The public health statements include the necessary use of some semi-technical information (e.g., chemical names) and some clinical terminology (e.g., “respiratory distress”); without accompanying explanations, such terms are not likely to be fully understood by a reader who is unfamiliar with the topics. The Profile mentions occupational exposure guidelines but does not address their role (or lack) in the determination of MRLs. More to the point, the Public Health Statement might benefit from a brief discussion of the common belief that occupational exposure limits (OELs) should apply primarily (if not solely) to otherwise-healthy workers, who are subject to direct exposure-management options (i.e., engineering controls and or personal protection equipment), and who are subject to medical monitoring for signs of developing problems. In other words, OELs may not be useful for safety assessment for non-worker populations that may include potentially extra-susceptible individuals (e.g., the very young, very old, chronically ill, handicapped, etc.) and for whom no simple means of exposure management is available and for whom medical monitoring is significantly more challenging than in the work environment.”

RESPONSE: *It is beyond the scope of the Public Health Statement to include a discussion of the healthy worker effect or the applicability of occupational exposure guidance values to non-workers. The text was revised to clarify that the OSHA and NIOSH values are for workers.*

COMMENT: Regarding the question of whether the answers to the questions in Chapter 1 adequately address the concerns of the lay public, whether the summary statements are consistent and supported by the technical discussion in the remainder of the text, and whether there are any general issues relevant to child health that have not been discussed in the profile, the Reviewer commented: “other than the

suggestions above, I have no quarrel with either the questions or the answers to them in the Public Health Statement.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the scientific terms used in Chapter 1 are too technical or require additional explanation, the Reviewer commented: “see comments above re “unavoidable semi-technical language” and “clinical terminology.” On the whole, the Public Health Statement is sound.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer agrees with the discussion in Chapter 2 on effects known to occur in humans, the Reviewer commented: “I agree with the assessments of potential effects as stated in the Profile.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the effects only observed in animals are likely to be of concern to humans, the Reviewer commented: “In the most general terms, the effects of H₂S that were observed in laboratory animals have been confirmed by both the nature and severity of effects in humans. Acute effects of very high concentrations (between 100 and 1,000 ppm) led to severe intoxication including death in animals and humans. For those effects that were observed in animals but have been documented in humans, the only prudent interpretation is to assume that in the absence of clear evidence to the contrary, an adverse finding in animal tests provides evidence of a POTENTIAL hazard in humans. Re COS. There is a dearth of available information on exposures or effects in humans. In the absence of evidence to the contrary, a prudent interpretation is that any adverse effect from COS observed in laboratory animals should be assumed to reveal a POTENTIAL hazard to humans.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether exposure conditions are adequately described, the Reviewer commented: “No. It would significantly improve the utility of the Profile to harmonize the exposure dimensions (aka, “units”) throughout the document. NOTE: both H₂S and COS are gases under ambient conditions (of temperature and pressure). Given that fact, my suggestion is report all concentrations in “ppm” (parts per million); if there are overriding reasons to include other dimensions (e.g., ug/m³), the Profile should list both...ppm and ug/m³. My principal criticism of the Profile (specifically with respect to exposure characterization) is the frequent use of imprecise descriptors. For example (many more could be cited), see Section 202, page 17, lines 23 to 25, where the Profile cites the literature as reporting “Respiratory distress and pulmonary edema...associated with very high concentrations of hydrogen sulfide.” [emphasis added] No information is provided to better characterize the imprecise term “very high.” See also page 18, line 13 (“lower levels”) and page 19, line 22 (“very high”) and line 29 (“low”). All available quantitative values should be reported for these and other citations in the Profile. Alternatively, if quantitative data are not available from the source, that fact should be stated explicitly.”

RESPONSE: *The profile predominantly uses ppm (or ppb) units to report air concentrations; in the rare cases where mg/m³ is reported, the concentration is also reported in ppm units. The use of qualitative descriptors of exposure levels are used to give the reader some perspective on the thresholds for different effects and are often followed by a more detailed description of the exposure levels. In some cases, actual exposure levels are not known; this is the case for the example the Reviewer gave on page 17, lines 23–25 and page 19, line 22.*

COMMENT: Regarding the question of whether adequately designed human studies are identified in Chapter 3 and if the study(ies) are not adequately designed are the major limitations of the studies sufficiently described in the text, the Reviewer commented: “For context, the presumed scope of this peer review does NOT involve critical reviews of the original/primary research sources, but rather is limited to providing an expert opinion on the reasonableness of the interpretations that are present in the Toxicological Profile. With that said, the Profile appears to have surveyed the literature for reports of studies in humans AND appears to have accurately and succinctly summarized the critical findings from the original/primary source. The text (of the Profile, itself) presents the authors’ critical comments in only summary fashion. With brevity as a primary goal, such summaries are entirely reasonable. Furthermore, the Profile appears to present a satisfactorily balanced review of the strengths and weaknesses of the cited studies.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the conclusions drawn by the authors of the studies are appropriate and accurately reflected in the profile, the Reviewer commented: “Without sufficient resources (time/support) to read and review the original/primary sources, I cannot attest in detail to the appropriateness and accuracy of the summaries in the Profile. With that said, there seems good reason to believe that the Profile’s surveys are comprehensive and that the summaries are balanced.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether all appropriate NOAELs and/or LOAELs are identified for each study, the Reviewer commented: “Hardly ever did the authors of the Profile explicitly identify, in the text of the Profile, the relevant NOAELs or LOAELs; nevertheless, the text of the Profile is clear on the NOAEL/LOAEL values for the “critical effects” in the “critical studies” (i.e., those that were the basis of deriving MRLs). Furthermore, all the NOAELs/LOAELs and other toxicity indicators are displayed in Table 3.1 And Figure 3.1.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether appropriate statistical tests are used in the studies, the Reviewer commented: “for context, the presumed scope of this review does NOT include critical reviews of the original/primary research sources, but rather is limited to providing an expert opinion on the reasonableness of the interpretations that are presented in the Toxicological Profile. The limited time and resources that were committed to this peer review preclude detailed review of original/primary sources. In any case, Chapter 3 provides almost no information on the sorts of statistical tests that might have been conducted (by the original investigators) and only very few bits of information on the results of statistical tests (i.e., the level of statistical significance of the study’s findings).”

RESPONSE: *The emphasis of Chapter 3, particularly Section 3.2, is to provide the reader with a synthesis and evaluation of the weight of evidence available rather than detailed descriptions of individual studies.*

COMMENT: Regarding the question of whether the Reviewer is aware of other studies which may be important in evaluating the toxicity of the substance, the Reviewer commented: “I am not aware of any such studies.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether adequately designed animal studies are identified in the text, the Reviewer commented: “For context, the presumed scope of this review does NOT include critical reviews of the original/primary research sources, but rather is limited to providing an expert opinion on the reasonableness of the interpretations that are present in the Toxicological Profile. The limited time and resources that were committed to this peer review preclude detailed review of original/primary sources. With that said, there are few (if any) specific critical references to the designs of the original/primary research studies. I don’t recall any specific reference to the adequacy of the numbers of animals in a study...nor to the adequacy of the numbers of exposure groups...nor to whether the exposure levels were appropriately chosen (or not). I have no recollection of any mention of “good animals care” (or the lack) nor of “accounting for competing causes of death.”

RESPONSE: *As noted previously, the emphasis of Section 3.2 is the synthesis and evaluation of the weight of evidence. A detailed description of the animal studies is presented in the Supplemental Document.*

COMMENT: Regarding the question of whether the animal species is appropriate for the most significant toxicological endpoint of the study, the Reviewer commented: “In general, the critical studies were conducted in appropriate animal models.

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the conclusions drawn by the authors of the animal studies are appropriate and accurately reflected in the text, the Reviewer commented: “For context, the presumed scope of this review does NOT include critical reviews of the original/primary research sources, but rather is limited to providing an expert opinion on the reasonableness of the interpretations that are present in the Toxicological Profile. The limited time and resources that were committed to this peer review preclude detailed review of original/primary sources; consequently, specific comments on the appropriateness of the conclusions that were drawn by the original investigators are beyond the scope of this peer review of the Profile. Nevertheless, the overall quality of the Profile is consistent with the inference that its authors of the Profile were diligent in assessing the appropriateness of the original investigators’ conclusions.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether all appropriate NOAELs and LOAELs are identified for each animal study and whether all appropriate toxicological effects are identified for the studies, the

Reviewer commented: “Hardly ever did the authors of the Profile explicitly identify, in the text of the Profile, the relevant NOAELs or LOAELs; nevertheless, the text of the Profile is clear on the NOAEL/LOAEL values for the “critical effects” in the “critical studies” (i.e., those that were the basis of deriving MRLs). Furthermore, all the NOAELs/LOAELs and other toxicity indicators are displayed in Table 3.1 And Figure 3.1.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is a discussion of the toxicities of the various forms of the substance, the Reviewer commented: “This question does not apply in the cases of H₂S or COS, which occur in only one chemical form...as a gas.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether appropriate statistical tests are used in the interpretation of the animal studies, the Reviewer commented: “For context, the presumed scope of this review does NOT involve critical reviews of the original/primary research sources, but rather is limited to providing an expert opinion on the reasonableness of the interpretations that are present in the Toxicological Profile. The limited time and resources that were committed to this peer review preclude detailed review of original/primary sources; consequently, comments on the appropriateness of statistical analysis by the original investigators are beyond the scope of this peer review. In any case, Chapter 3 provides almost no information on the sorts of statistical tests that might have been conducted (by the original investigators) and only very few bits of information on the results of statistical tests (i.e., the level of statistical significance of the study’s findings).”

RESPONSE: *As noted in the RESPONSE to a similar comment on the human studies, the emphasis of Section 3.2 is a discussion of the weight of evidence available for a particular end point rather than detailed descriptions of individual studies.*

COMMENT: Regarding the question of whether the Reviewer is aware of other animal studies which may be important in evaluating the toxicity of the substance, the Reviewer commented: “I am not aware of any such studies.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the LSE tables and figures are complete and self-explanatory, the Reviewer commented: “The LSE tables appear to be complete. They are not totally self-explanatory; but, when accompanied by the “User’s Guide” (with the illustrations/examples) and carefully studied, the LSE tables are reasonably comprehensible. The task of auditing the LSE tables to assure that the values presented there are accurate transcriptions of those that were presented in the original/primary source would take more time and energy than is justified; I have assumed [1] that the exposure values and dimensions as presented in the text have been checked for agreement with the original publications and [2] that the exposure values and dimensions as presented in T-3.1 and F-3.1 have been transcribed accurately from those original publications. I found the task of reviewing the information in the LSE tables and figures to be VERY tedious. A possible improvement would be to revise the “User’s Guide” to rely on a “current” example (i.e., from the specific Profile), rather than the hypothetical case that is presented. The substantial differences between the current case (H₂S and COS)

and the hypothetical case (“substance ‘X’”) are somewhat confusing. See “Key 1” in Table 3.1 (re hydrogen sulfide). I could not locate an explanation for the “M” notation following the “Serious” effect level exposure value (i.e., 800 ppm). From studying other entries in T-3.1, I came to believe that “M” refers to male animals (and “F” to females). Assuming that’s correct, I was surprised to find no listing of the sex/gender of the subjects in the publication from Jappinen, et al. (“Key 17”)...the “critical study” for deriving the acute exposure MRL.”

RESPONSE: *ATSDR will consider the suggested revision to the User’s Guide in future revisions to the profile guidance document. The M and F are used to designate gender differences or to indicate that only one gender was tested. If no gender differences were noted, the M and F do not appear.*

COMMENT: Regarding the question of whether the Reviewer agrees with the categorization of “less serious” and “serious” effects cited in the LSE tables, the Reviewer commented: “Since no MRLs were derived for carbonyl sulfide, the only important distinctions (between “less serious” and “serious”) are those that were the bases for deriving the acute and intermediate duration MRLs for hydrogen sulfide. Regarding the acute MRL for H₂S...I agree with the interpretation in the Profile, i.e., that the “increased airway resistance and decreased specific airway conductance in 2/10 asthmatics” can be characterized a “less serious” effect. NOTE: I am not an expert in the area of clinical/medical respiratory physiology. The magnitude of the changes in respiratory physiology is listed in the text ONLY as “>30%” change (no additional information is provided in the Profile, itself). However, a note from the relevant passage in the Supplemental Document (page 17) indicates that “[T]hese changes were suggestive of bronchial obstruction.” [emphasis added] Whether changes of the reported magnitude should be regarded as “less serious” or even non-significant (from a clinical/medical perspective) should be evaluated by a specialist in clinical pulmonology.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the MRLs are justifiable and if no MRLs were derived, do the data support deriving MRLs, the Reviewer commented “Yes, the values for the 2 MRLs that were derived (acute and intermediate duration MRLs for H₂S by inhalation exposure) are consistent with current science policies at the Agency; in that context, the values are justifiable. Furthermore, I agree with decisions NOT to derive MRLs for oral or dermal exposure to H₂S. Likewise, I agree with the decision NOT to derive MRLs for COS. However, I believe that a provisional MRL for chronic-duration exposures to H₂S could be derived. The process would involve downward adjustment of the “intermediate” term MRL in order to account for the prolonged exposure duration and the limited range of information on other possible adverse health effects that were not identified in the sub-chronic tests in laboratory animals.”

RESPONSE: *ATSDR disagrees with the Reviewer that a chronic-duration inhalation MRL can be derived for hydrogen sulfide by downwardly adjusting the intermediate-duration MRL. It is not the Agency’s practice to use an intermediate-duration study to derive a chronic MRL in the absence of data that could be used to assess whether the point of departure for the intermediate-duration MRL (NOAEL of 10 ppm for olfactory neuron loss) would be protective for chronic exposure or whether chronic exposure will result in additional adverse effects.*

COMMENT: Regarding the question of whether the major limitations of the studies have been adequately and accurately discussed, the Reviewer commented: “Overall, the discussions appear to be adequate and balanced. The limited time and other resources that were committed to this review precluded detailed reviews of the original research literature. Such detailed reviews of the original source would be required in order to confirm the exact accuracy and completeness of the Profile’s summary.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the effect or key endpoint has been critically evaluated for its relevance in both humans and animals, the Reviewer commented: “Given the stated desire for brevity, the discussions of relevance are, themselves, abbreviated. Nevertheless, the evaluations seem to be reasonably complete and balanced.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether “bottom-line” statements have been made regarding the relevance of the endpoint for human health, the Reviewer commented: “I’m not at all sure what this question is seeking. Perhaps the question could be reframed, “have the Profile authors stated unequivocally – for each cited reference – that the information is (or is not) relevant to human health safety assessment?” If that is the question, that answer is, “no.” However, such conclusive statements may not be necessary.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the conclusions are appropriate given the overall database, the Reviewer commented: “Again, I’m not sure what this question is seeking. What “conclusions” (other than the MRLs, themselves) does this question refer to?”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether adequate attention has been paid to dose-response relationships for both human and animal data, the Reviewer commented: “Relatively little information is available on dose-response relationships as revealed by studies on human subjects. For example, the results data from Jappinen, 1990 (i.e., the key study in humans) provides no information on dose-response; the study employed on a single exposure level. For the dose-response relationship as revealed in results from the key animal study (Brenneman, 2000), the Profile provides a seemingly complete and balanced accounting, with supporting arguments.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the animal data has been used to draw support for any known human effects, the Reviewer commented: “A very peculiar question. If the question were reframed as, “have data from animal toxicity tests tended to confirm the effects that have been observed in humans?” The answer would be a qualified affirmative. The principal effects on the ocular, respiratory and nervous systems have been observed in humans have also been observed in laboratory tests. The Profile provides accurate confirmation of the findings in both humans and lab animals.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is an adequate discussion of absorption, distribution, metabolism, and excretion of the substances, the Reviewer commented: “Given the limited array of data that are available on the ADME of H₂S, the Profile’s reviews seem reasonably complete. Almost no data are available on “high- vs low-level exposures”...nor on whether males and females respond similarly (or not)...nor whether there are potentially significant differences between laboratory animal and humans.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the major organs, tissues, etc in which the substance is stored have been identified, the Reviewer commented: “The question is an odd one when applied to H₂S...which is not stored in significant quantities; rather, H₂S is rapidly absorbed, metabolized, and excreted. Hardly anything is known with any real certainty about the ADME (PBPK) of carbonyl sulfide.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether all applicable metabolic parameters have been presented and all available PB/PK models have been presented, the Reviewer commented: “Given the caveats above, the answer is “yes.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is adequate discussion of the differences in toxicokinetics between animals and humans, the Reviewer commented: “Given the caveats above, the answer is “yes.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether all applicable metabolic parameters have been presented and all available PB/PK models have been presented, the Reviewer commented: “The Profile does not make direct comparisons or contrasts between humans and animals. However, even without direct statements of equivalence or difference, the discussions are adequate to provide the salient information.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is an adequate discussion of the relevance of animal toxicokinetic information for humans, the Reviewer commented: “See comments above”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is a discussion of the toxicokinetics of different forms of the substance, the Reviewer commented: “Not applicable.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether all possible mechanisms of action have been discussed, the Reviewer commented: “This is an impossible question. If all possible mechanisms of action were discussed, the document would be massive...even more massive than the present.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether all the biomarkers of exposure are specific for the substance or are general for a class of substances, the Reviewer commented: “The possible biomarkers for exposure are not specific for H₂S, and the Profile should explicitly acknowledge that fact. No biomarkers for COS exposure were identified.”

RESPONSE: *A notation was made that the blood sulfide level is not specific for hydrogen sulfide; the existing discussions of biomarkers of exposure explicitly state that they are not specific for hydrogen sulfide.*

COMMENT: Regarding the question of whether there are valid tests to measure the biomarkers of exposure, the Reviewer commented: “According to the Profile, there are valid test methods available for the proposed biomarkers of exposure. Nevertheless, the markers are not specific for H₂S or COS, and the quantitative relationships between exposure concentrations and the results of biomarker tests have not been developed. No biomarkers for COS exposure were identified.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is an adequate discussion of the interactive effects with other substances, the Reviewer commented: “The discussion of possible interactions with other chemical exposures is adequate. The most relevant data on possible interactions has been taken from studies of humans who were exposed to mixtures of H₂S and other chemicals in the workplace. This section of the Profile (regarding possible interactions) does NOT concentrate on effects that might occur specifically at hazardous waste sites.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text discusses the mechanisms of interactions with other substances, the Reviewer commented: “The evidence for potential interactions following co-exposure to other chemicals is not conclusive. Consequently, no discussion of mechanisms of action is possible.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is a discussion of populations at higher risk because of biological differences which make them more susceptible, the Reviewer commented: “The Profile includes a very limited discussion of possible genetic and/or medical conditions that may render some individuals more susceptible to the adverse effects of H₂S...specifically to effects on the respiratory system. I agree that the available evidence suggests (but is not conclusive) that prior-existing diseases/conditions of the respiratory system can predispose to more severe responses to H₂S exposures. I am not aware of any additional studies on this particular topic.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the management and treatment discussed in Section 3.11 is specific for the substance or is general for a class of substances, the Reviewer commented: “H₂S (and presumably, COS as well) are rapidly absorbed. No incontrovertibly effective means exists for reducing absorption (during or following exposure) and no known means to beneficially alter distribution after exposure. Oxygen supplementation and symptomatic care are apparently the only suggested modes of clinical therapy.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is any controversy associated with the treatment and whether it is well accepted, the Reviewer commented: “The recommended treatment nodes are not specific to either H₂S or to COS. Oxygen supplementation may (or may not) be effective.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there are any hazards associated with the treatment of populations that are unusually susceptible to the substances, the Reviewer commented: “Within broad limits, the working assumption seems to be that children and adults respond to H₂S (or COS?) exposures in essentially the same fashion. Apart from differences (between adults and children) in respiratory rates and volumes, body weights, and behaviors that can influence exposure, children and adults seem likely to respond similarly; the Profile should refer the reader to the introductory paragraphs of Section 6.6 for a more complete discussion.”

RESPONSE: *The discussion of the response of children to hydrogen sulfide exposure is presented in Section 3.7, which contains a more detailed overview of physiological differences between children and adults than does the discussion in the introduction to Section 6.6.*

COMMENT: Regarding the question of whether there are treatments available to prevent the specific substance from reaching the target organ, the Reviewer commented: “H₂S (and presumably, COS as well) are rapidly absorbed, distributed, metabolized, and the metabolites excreted. There are no known methods by which to reduce the overall body burdens of either H₂S or COS. Furthermore, there appear to be no confirmed “blockers” (neither physiological nor biochemical) that would reduce the amount of H₂S (or COS?) that reaches the target organs.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is any controversy associated with the treatment for preventing the substance from reaching the target organ, the Reviewer commented: “H₂S (and presumably, COS as well) are rapidly absorbed. No incontrovertibly effective means exists for reducing absorption (during or following exposure) and no known means to beneficially alter distribution after exposure. Oxygen supplementation and symptomatic care are apparently the only suggested modes of clinical therapy.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there are any hazards associated with the treatment for preventing the substance from reaching the target organ in populations unusually susceptible to the substance, the Reviewer commented: “No, other than the possibly greater susceptibility of children (especially those with cardiac defects) to the adverse consequences of methemoglobin formation following nitrite administration.”

RESPONSE: *A statement was added to Section 3.11.3, that the induction of methemoglobinemia for the treatment of hydrogen sulfide toxicity has only been evaluated in adults; given the increased sensitivity of young children to the development of methemoglobinemia from exposure to nitrates, care should be taken in using this approach.*

COMMENT: Regarding the question of whether there are any treatments to prevent adverse effects as the substance is being eliminated from the major organs/tissues where it has been stored, the Reviewer commented: “The profile does not include an assessment that would guide a response to this question. However, the following appears to be the case with H₂S (and possibly with COS, as well). H₂S is rapidly absorbed and distributed, relatively rapidly metabolized (time measured in minutes to hours); the metabolic products are excreted over slightly longer periods (from hours to a few days). Neither H₂S nor its principal metabolites are believed to be actively sequestered and stored in the body for extended periods. Furthermore, the principal toxic effects (from H₂S exposure) are attributed to the parent compound, not to the metabolite(s); consequently, any retained metabolites may be assumed to be non-hazardous (at a minimum, much less hazardous than the un-metabolized parent compound).”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there are treatments available to prevent the specific substance from reaching the target organs, the Reviewer commented: “There appear to be no confirmed “blockers” (neither physiological nor biochemical) that would reduce the amount of H₂S (or COS?) that reaches the target organs.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is any controversy associated with the treatment to prevent the substance from reaching target organs, the Reviewer commented: “There appear to be no well accepted treatments that would reduce the adverse potency of H₂S (or COS?). Oxygen supplementation and symptomatic/supportive care are apparently the only suggested modes of clinical therapy. The effectiveness of oxygen therapy is uncertain.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there are any hazards associated with treatment to prevent the substance from reaching target organs in populations unusually susceptible to the substance, the Reviewer commented: “No, other than the possibly greater susceptibility of children (especially those with cardiac defects) to the adverse consequences of methemoglobin formation following nitrite administration.”

RESPONSE: *As noted in the previous RESPONSE to this comment, a statement was added to Section 3.11.3, that young children have an increased sensitivity to nitrate exposures leading to the development of methemoglobinemia and that care should be taken in using this approach for the treatment of hydrogen sulfide toxicity.*

COMMENT: Regarding the question of whether the Reviewer knew of other studies which may fill a data gap, the Reviewer commented: “I have no comments on Figure 2-X, except to offer that the example (of Substance “X”) is quite different from the situation with H₂S and COS...sufficiently different that the example may be confusing. Regarding H₂S and COS, I am not aware of any additional studies that would fill any significant data gaps.”

RESPONSE: *ATSDR will consider the Reviewer’s comment in future revisions to the profile guidance document.*

COMMENT: Regarding the question of whether the data needs are presented in a neutral, non-judgmental fashion, the Reviewer commented: “Yes, the Profile seems essentially unbiased.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer agrees with the identified data needs, the Reviewer commented: “In general, I agree with the recommendations. I strongly urge ATSDR to address questions of the relative priority of each specific recommendation. For example, I agree with the statement on p 105, lines 30 to 31; the authors suggest that the available evidence (i.e., lack of genotoxic activity) indicates that long-term carcinogenicity studies on H₂S are a low priority. In contrast, the passage that begins on page 106, line 33, suggests that carbonyl sulfide should be retested in laboratory animals for possible effects on female reproduction. A more compelling justification is needed IF such testing is to be regarded as a high priority. Similarly, the passage that begins on page 107, line 18 implies that testing should be done for developmental effects from exposure to H₂S by the oral and dermal routes. Since H₂S is very rarely encountered by oral or dermal exposure, what priority should be given to the suggested studies? The same question (about testing for hazards from oral or dermal exposure) applies to the passage on page 108, lines 26 to 29; given the rare exposure by oral or dermal routes, what priority should be given to testing H₂S for neurotoxicity...by those routes of exposure?”

RESPONSE: *The purpose of this section of the toxicological profile is to identify data gaps and needs. As noted in the Introduction to Section 3.12, the data needs identified in the profile will be evaluated and prioritized at a later time.*

COMMENT: Regarding the question of whether the text indicates whether any information on the data need exists, the Reviewer commented: “The Profile provides limited information on currently available data.”

RESPONSE: *An updated literature search was conducted in February 2013 and relevant studies were added to the profile. The Reviewer did not identify specific studies that should be included in the profile.*

COMMENT: Regarding the question of whether the text adequately justifies why further development of the data needs would be desirable or justifies the inappropriateness of developing the data need at present, the Reviewer commented: “The justifications (i.e., the anticipated “value added” from the proposed research) would strengthen the Profile.”

RESPONSE: *The purpose of this section of the profile is to assess whether adequate information on the health effects of hydrogen sulfide and carbonyl sulfide is available and to identify data needs and data gaps. The profile does not include a justification for why the data needs/gaps should be filled or a prioritization of the data needs.*

COMMENT: Regarding the question of whether the Reviewer is aware of any chemical and physical property information or values that are wrong or missing, the Reviewer commented: “I am not aware of any additional studies that would fill any significant data gaps with respect to physical or chemical properties.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer is aware of any information on the production, import/export, use or disposal of the substance that is wrong or missing, the Reviewer commented: “I am not aware of any missing information.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text appropriately traces the substance from its point of release to the environment until it reaches the receptor population, the Reviewer commented: “The sources of H₂S and COS are both natural and anthropogenic...and widely dispersed. On a broad environmental scale, contributions from natural sources are said to far exceed those from human activities. With that said, the principal anthropogenic point sources being industrial and/or agricultural process facilities. Given 2 facts...[1] that there are multiple background sources of both chemicals, and [2] ATSDR’s focus is primarily on the relatively infrequent occurrence of waste sites as significant sources, it is not a simple matter to trace the path and media between specific sources and targets/receptors. NOTE: the Profile provides sufficient information to document and characterize the relatively infrequent occurrence of H₂S (found at 35 of 1,689 waste sites) and COS (found at 3 of 1,689 sites). I am not aware of other relevant information.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text covers pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media, the Reviewer

commented: “While confirming that the principal sources of H₂S and COS are natural, the Profile also provides substantial information on the media (i.e., air, water, soils/sediments) to which H₂S and/or COS are released from anthropogenic sources. The Profile also provides substantial information on the environmental fate, transport, deposition and degradation of H₂S and COS in the various media. I am not aware of any additional relevant information.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text provides information on levels monitored or estimated in the environment (including background levels), that proper units are used for each medium, and that the information includes the form of the substance measured, the Reviewer commented: “The Profile provides substantial information on measured levels of H₂S (and to a lesser degree, for COS, as well). The information includes measurements of “background levels” from very large-scale atmospheric sampling programs. Although the Profile reports the units (aka, dimensions) in appropriate term, the Profile could be incrementally improved by harmonizing the units of concentration. My preference would be to express the concentrations in air in units of ppm (parts per million; vol/vol) AND in mg/m³...the concentrations in water in units of ppm (wt/wt) AND in mg/kg...and the concentrations in soils/sediments in units of ppm (wt/wt) AND in mg/kg (for both “dry weight” and “wet weight” whenever the full set data is available). The “form” of the substances that were analyzed were reported in the correct terms...as a gas (in air), and a dissolved gas (in water), or as a adsorbed gas (in soils/sediments). The discussions are adequate. I am not aware of any additional relevant information.”

RESPONSE: *Throughout the toxicological profile, ATSDR has attempted to use consistent units; for example, air levels are reported in ppm units. ATSDR disagrees with the Reviewer’s suggestion of reporting monitoring data in ppm and mg/m³ or mg/kg units and believes that reporting both units will not add any value to the toxicological profile and will decrease the readability of the document. Unit conversion factors are presented in Chapter 4.*

COMMENT: Regarding the question of whether the text describes sources and pathways of exposure for the general population, occupations involved in the handling of the substance, and populations with potentially high exposures, the Reviewer commented: “The Profile provides a good deal of information on potential human exposures in both ambient (general background levels as well as levels near point sources) and occupational/workplace environments. I agree with the selection of the subject populations. I am not aware of any high exposure (i.e., high risk) populations that were not addressed in the Profile.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding questions on Chapter 7, the Reviewer commented: “NOTE: I am not an expert in analytical chemistry. Consequently, I cannot comment meaningfully on the information presented in Chapter 7.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer is aware of additional methods that should be added to the profile, the Reviewer commented: “See NOTE above.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the methods have been included for measuring key metabolites previously mentioned in the text, the Reviewer commented: “See NOTE above.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether unique issues related to sampling for the substance exist and have been adequately addressed in the text, the Reviewer commented: “See NOTE above.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the identification of data needs for analytical methods is adequately presented in the profile, the Reviewer commented: “See NOTE above.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer is aware of other regulations or guidelines that may be appropriate for Table 8-1, the Reviewer commented: “I am not aware of other relevant regulations or advisories.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there are additional references that provide new data or if there are better studies than those already in the text, the Reviewer commented: “I am not aware of any additional relevant references.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question on the adequacy of design, methodology, and reporting of unpublished studies, the Reviewer commented: “The study reports present results of tests that would have been considered “state-of-the-science” designs at the time the studies were conducted. The methods that were applied would also have been considered “state-of-the-science” by contemporary standards. Furthermore, each of the Monsanto-sponsored study reports includes reference to compliance with the provisions of the “Good Laboratory Practices” regulations. That fact, alone, lends assurance that the studies were performed with care. The reporting was the – and now – routine.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question on the validity of results and author’s conclusions for the unpublished studies, the Reviewer commented: “The results (as reported) are consistent with the original investigators’ conclusions.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question on the study inadequacies or confounding for the unpublished studies, the Reviewer commented: “There were no obvious confounding factors in the reports of the unpublished studies.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question asking the Reviewer to provide a summary of their conclusions and whether the Reviewer agrees or disagrees with those of the author, the Reviewer commented: “It’s unclear whether this request is for agreement (or lack) with the conclusions of the authors of the unpublished studies OR with the conclusions of the authors of the toxicological Profile. In any case, I agree with the conclusions from both the unpublished reports and the Profile.”

RESPONSE: *No revisions were suggested.*

COMMENT: “Overall, the research advisory sections (aka, “Data needs”) are the weakest. In general, they provide less-than-sufficient explanation of the “value added” from the proposed research/testing. Framed as a question, “how exactly would the results of the recommended research be expected to reduce uncertainty in the overall safety assessment?”

RESPONSE: *As noted in the previous RESPONSE to this comment, the toxicological profile identifies data needs and data gaps in the information needed to evaluate the health effects associated with exposure to hydrogen sulfide or carbonyl sulfide and the potential for human exposure to these compounds. In a separate document, a Priority Data Needs document, ATSDR re-evaluates these data needs/gaps to determine whether they should be filled and prioritizes the data needs.*

COMMENT: “Multiple (repeated) citations to the same data and source is basically sound. Although tending to test the patience of a reader of the entire document, the practice makes it possible for a reader who has a more special or narrower interest to see a more comprehensive review of the available information.”

RESPONSE: *No revisions were suggested.*

COMMENT: “It is not at all clear whether the authors of the Profile actually consulted the original literature...OR relied on the summaries from the “Supplemental Document” (apparently prepared by scientists at SRC, Inc., an extramural contractor). If the latter were the case, then as a matter of good scholarship and accurate documentation, the citations in the bibliography should clearly state that the sources are “secondary,” not “primary.” More specifically, if the summary (from SRC, Inc.) is the principal sources of information on the findings from Jappinen, et al, 1990, then the bibliography should reflect that relationship, i.e., Jappinen, P, et al. 1990. *Exposure to hydrogen sulphide and respiratory function. Br J Ind Med* 47:824-828. (summarized in Supplemental Document for Hydrogen Sulfide and Carbonyl Sulfide. SRC, Inc. 2013)”

RESPONSE: *The profile authors reviewed the primary literature during the preparation of the supplemental document and the profile.*

COMMENT: “As a matter of science policy, the decision NOT to develop a chronic-duration MRL for H₂S is reasonable. But, the net effect is to leave a vacuum of useful information for long-term human health safety assessment. A case can be made for applying a downward adjustment of the intermediate-duration MRL to provide some minimal measure of guidance for safety assessment from prolonged exposures.”

RESPONSE: *As noted previously, the lack of reliable chronic-duration inhalation studies precludes determining if the point of departure for the intermediate-duration MRL (NOAEL of 10 ppm for olfactory neuron loss) would be protective for chronic exposure or whether chronic exposure will result in additional adverse effects. It is not ATSDR’s practice to divide an intermediate-duration inhalation MRL by an uncertainty or modifying factor to account for the shorter exposure duration in the absence of relevant data to support the use of this factor.*

COMMENT: “I recommend a more careful review and a more thorough discussion of the findings from Inserra, et al. 2004 (as listed in the text; 2002 as listed in the bibliography). See page 60, lines 20 to 28. Inserra’s findings apparently showed no significant effects from prolonged human exposures in the range of 100 ppb to 1,000 ppb. At a very minimum, those findings deserve greater attention and discussion. Regarding “priorities” for data needs, and given the findings by Inserra, et al., what level of priority (urgency) should be placed on the suggestion that additional epidemiology studies be done on people who are more highly exposed?”

RESPONSE: *The Inserra et al. (2004) study examined the possible association between exposure to hydrogen sulfide and neurobehavioral effects in residents living in Dakota City, Nebraska. Although no significant alterations were found, interpretation of the study is limited by poor exposure characterization; this is discussed in the toxicological profile on page 60, lines 20–28. The study did not investigate the possible association between hydrogen sulfide exposure and respiratory effects. Given the limitations of the study, including a limited number of health outcomes evaluated and poor exposure monitoring, the Inserra et al. (2004) does not address the need for additional epidemiology studies.*

COMMENT: “Although the studies from Monsanto have not been published, the results could be applied to derive acute and intermediate-duration MRLs.”

RESPONSE: *The unpublished studies by Monsanto, as well as the published literature, were considered as a basis for MRLs for carbonyl sulfide. However, ATSDR determined that the database was not suitable for identifying the critical targets of toxicity and establishing dose-response relationships.*

Review comments provided by Reviewer #2:

COMMENT: “PubMed, Toxline, and Google search were performed looking for additional references. The only two retrieved that are not referenced in the current document are:

Bartholomaeus AR, Haritos VS. Review of the toxicology of carbonyl sulfide, a new grain fumigant. Food Chem Toxicol 2005; Dec; 43(12):1687-1701.

- This is a review article regarding replacement of phosphine and methyl bromide as grain fumigants. The authors note that the toxicology database for COS is deficient in many respects.
- *I do not think including this review article would improve the Toxicological Profile.*

Sills RC, Harry GJ, Valentine WM, Morgan DL. Interdisciplinary neurotoxicity inhalation studies: carbon disulfide and carbonyl sulfide research in F344 rats. Toxicol Appl Pharmacol 2005; Sep 1; 207(2 Suppl):254-250.

- This article describes MRM (Magnetic Resonance Microscopy) studies showing that COS targets the auditory pathway in the brain. Electrophysiological studies showed decreased auditory brainstem evoked responses. A decrease in cytochrome oxidase activity was considered by the authors to be a contributing factor to the pathogenesis of COS neurotoxicity in the rat.
- While this is an interesting article, the current document cites other studies by the same group and these findings are already reviewed in the Toxicological Profile Draft
- *I do not think including this article would improve the Toxicological Profile.”*

RESPONSE: *The Bartholomaeus and Haritos (2005) and Sill et al. (2005) papers are review articles. Both papers were evaluated to determine whether they identify studies that were relevant to the toxicological profile.*

COMMENT: “Additionally, for this review I have reviewed the appropriate National Library of Medicine ToxID Plus and Hazardous Substances Data Bank (HSDB) documents, as well as the August 1994 Chemical Summary for Carbonyl Sulfide prepared by the US EPA Office of Pollution Prevention and Toxics. It is of note that much of the toxicity of COS seems to be due to its metabolic conversion to H₂S (Hydrogen Sulfide) by the enzyme carbonic anhydrase, although from experimental animal inhalation studies COS clearly has toxicity of its own as well.”

RESPONSE: *No revisions were suggested.*

COMMENT (page 51): “The slate-grey skin discoloration in H₂S-exposed rabbits noted in the 1942 Lang and Draize study might well have been due to induction of sulfhemoglobinemia or sulfmethemoglobinemia, as this description is classical for the presence of sulfhemoglobinemia in humans. On blood analysis by co-oximetry, sulfhemoglobin (and perhaps sulfmethemoglobin) may be falsely reported as methemoglobin.”

RESPONSE: *The Laug and Draize (1942) study reported increased sulfhemoglobin levels in rabbits exposed for at least 20 minutes; this information was added to the profile.*

COMMENT: “A problem with the Rotorua, New Zealand studies is that the categories of disease/illness are so broad that they do not seem to be able to take into account *all* of the pathophysiological mechanisms (i.e., "other diseases of the brain"; "disorders of the eyes and adnexa") which renders any conclusions about any relationship (particularly potentially causal) between exposure to any specific chemical or group of chemicals essentially impossible, especially as no concurrent air monitoring or individual breathing zone monitoring was done. It is certainly proper to summarize these studies in the current Toxicological Profile draft, but cautionary statements as to interpretation could be more strongly stated taking the above comments into account.”

RESPONSE: *The toxicological profile was revised to ensure that whenever the health effects data from the Bates et al. (1997, 2002) studies of the Rotorua population were discussed, it was noted that interpretation of the findings is limited by the lack of monitoring data and the potential exposure to other compounds.*

COMMENT: “As both H₂S and COS are *gases* at standard atmospheric pressure and temperature, oral exposure would be extremely unlikely, particularly for the general population.”

RESPONSE: *ATSDR agrees with the Reviewer that the likelihood of oral exposure to hydrogen sulfide or carbonyl sulfide is very small.*

COMMENT (page 81, lines 9 and 14): “Should similar statements be added regarding COS as well?”

RESPONSE: *A statement is made in Section 3.4.4 that no information was located on the elimination and excretion of carbonyl sulfide; therefore, statements are not necessary in each subsection.*

COMMENT (Page 150, lines 10-14): “This quotes data from the 1995 TESS Toxic Exposure Surveillance System)/NPDS (National Poison Data System) compiled by the AAPCC (American Association of Poison Control Centers) and comprises collected data on *poison exposures* reported to participating Poison Centers in the US (note that *poison exposure does not equate to poisoning*). These data in varying formats have been published annually since 1983.

It would seem proper to at least include the most current published data which can be found in:

Bronstein AC, Spyker DA, Cantilena LR Jr, Rumack BH, Dart RC. 2011. Clin Toxicol (Phila) 2012 Dec; 50(10):911-1164.

The 2012 data will likely be published in the same journal in December 2013.

It might also be better to retrieve the reports and summarize the last 5 or 10 years of data, at least for H₂S, to better characterize the available data on exposure to this gas. When I do so, I usually list the total number of exposures and separate them by age range categories, list the causes for exposure, consider the number of patients who were evaluated/treated in a health care facility (a surrogate measure of concern/severity), list the number of patients who were asymptomatic and those who had mild, moderate, or severe exposure, and the number of deaths. I also scan the brief reports of fatal cases included in these reports at the end for descriptions of any fatal cases for the chemical of concern.

It does need to be born in mind that in studies of this database, occupational and environmental exposures are generally under-represented as are cases where the exposed person was dead on arrival to the hospital/ED. There is no mechanism in place for coroners/medical examiners to report such cases to the NPDS.”

RESPONSE: *The profile was updated to include data from the most recent annual report of the National Poison Control System (2012). Additionally, information from the 2010, 2005, and 2000 reports were added to the profile.*

COMMENT: “I have no comments or corrections for Figures 3-1 and 3-2; I have no comments or corrections for Tables 3-1 and 3-2.”

RESPONSE: *No revisions were suggested.*

COMMENT: “I agree with the derived MRLs, the methodology used to derive them, and the appropriateness of the references used.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the Supplemental Document, “The summaries are well done by SRC, Inc. and they are quite useful for interpreting and reviewing the draft Toxicological Profile. The only comment I have is that there is a tremendous amount of redundancy in these tables with multiple individual entries for the same study(ies) with exactly or nearly exactly the same text in each entry in the Descriptions, Results, and Comments sections. This is somewhat confusing. Could not at least some of these be combined into a single entry for easier and less time-consuming reading?”

RESPONSE: *The Supplemental Document follows the same format as Section 3.2 of the profile and the LSE Tables, which can result in repetition of a study that examined multiple end points. ATSDR will consider the Reviewer’s comments in future revisions of the profile guidance.*

COMMENT: Regarding the question of whether any relevant data to child health and developmental effects have not been discussed in the profile, the Reviewer commented: “None to my knowledge. I did not find any additional information on these issues in the literature searches I performed.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether any general issues relevant to child health have not been discussed in the profile, the Reviewer commented: “None to my knowledge. I did not find any additional information on these issues in the literature searches I performed.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether Chapter 1 presents the important information in a non-technical style suitable for the average citizen, the Reviewer commented: “Yes, the chapter does present the important information in a non-technical style suitable for the average citizen.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the answers to the questions in Chapter 1 adequately address the concerns of the lay public, whether the summary statements are consistent and supported by the technical discussion in the remainder of the text, and whether there are any general issues relevant to child health that have not been discussed in the profile, the Reviewer commented: “Please see my comments made on the document pages itself which will be found on the appropriate pages in the .pdf files which will accompany this report. Other than comments as noted directly above, the answers to the questions do adequately address the concerns of the lay public. The summary statements are consistent and are supported by the technical discussions in the remainder of the text.”

RESPONSE: *The responses to Reviewer’s annotated page comments are discussed in the next section of this document.*

COMMENT: Regarding the question of whether the scientific terms used in Chapter 1 are too technical or require additional explanation, the Reviewer commented: “Other than specific comments made on the accompanying .pdf files, the scientific terms used are not too technical and do not require additional explanation.”

RESPONSE: *The responses to Reviewer’s annotated page comments are discussed in the next section of this document.*

COMMENT: Regarding the question of whether the Reviewer agrees with the discussion in Chapter 2 on effects known to occur in humans, the Reviewer commented: “I agree with those effects known to occur in humans as reported in the text. I found only 2 potentially relevant studies that are not cited in the Toxicological Profile. However, other studies by the same authors are cited and the two I found would not add any significant information not already covered in the Toxicological Profile.”

RESPONSE: *ATSDR assumes that the Reviewer is referring to the Bartholomaeus and Haritos (2005) and Sills et al. (2005) review articles. These papers were not included in Chapter 2 because they are review articles; neither study identified primary literature not included in the profile.*

COMMENT: Regarding the question of whether the effects only observed in animals are likely to be of concern to humans, the Reviewer commented: “The effects only observed in animals are likely to be of concern in humans, particularly for carbonyl sulfide (COS) for which there is no human data as discussed in the Toxicological Profile (nor, did I find any human data in my literature searches). In the apparently complete absence of human data, prudence would lead to supposing that similar effects found in animal studies could occur in humans.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether exposure conditions are adequately described, the Reviewer commented: “Yes, known exposure conditions have been adequately described.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether adequately designed human studies are identified in Chapter 3 and if not adequately designed are the major limitations of the study (ies) sufficiently described in the text, the Reviewer commented: “Where available, adequately designed human studies for hydrogen sulfide (H₂S) were described in the text. The major limitations of these studies were sufficiently described in the text. I have made some comments earlier in this report specifically about the limitations of the Rotorua studies. This question does not apply to COS because no human data were found.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the conclusions drawn the authors of the studies appropriate and accurately reflected in the profile, the Reviewer commented: “Yes, the conclusions drawn by the authors of the studies were appropriate and adequately reflected in the Toxicological Profile.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether all appropriate NOAELs and/or LOAELs are identified for each study, the Reviewer commented: “Yes, all appropriate NOAELs and LOAELs were identified for each study where such were reports. In the derivation of MRLs, the reasons for choosing the studies on which they are based and why other values were not utilized are adequately discussed in the Toxicological Profile.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether appropriate statistical tests are used in the studies, the Reviewer commented: “As I am not a biostatistician, all I can state is within what knowledge of biostatistics I do have, the statistical tests were appropriate, other statistical tests would not have been more appropriate, and the statistical tests appeared to have been evaluated appropriately.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer is aware of other studies which may be important in evaluating the toxicity of the substance, the Reviewer commented: “No, I am not aware of other studies which may be important in evaluating the toxicity of, in this case, the two substances.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether adequately designed animal studies are identified in the text, the Reviewer commented: “Yes, adequately designed animal studies were identified in the text. I have made a specific evaluation of the four unpublished studies that were sent to me with the Draft Toxicological Profile and comments and answers to question are found at the end of this report.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the animal species is appropriate for the most significant toxicological endpoint of the study, the Reviewer commented: “Animal species in which H₂S studies cited in the Toxicological Profile are the usual ones used for such testing, as were those available for COS. It is unclear that using other animal species would be more appropriate for either toxic gas.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the conclusions drawn by the authors of the animal studies are appropriate and accurately reflected in the text, the Reviewer commented: “Yes, the conclusions drawn by the authors of the studies were appropriate and adequately reflected in the text.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether all appropriate NOAELs and LOAELs are identified for each animal study and whether all appropriate toxicological effects are identified for the studies, the Reviewer commented: “Yes, all appropriate NOAELs and LOAELs were identified for each study and all appropriate toxicological effects were identified for the studies.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is a discussion of the toxicities of the various forms of the substance, the Reviewer commented: “Both toxic gases covered in this Toxicological Profile are *gases* at normal atmospheric pressure and temperatures. There was one feeding study in pigs, but this is essentially *not* a potential exposure route in humans. There is actually little evidence for any significant systemic absorption resulting in poisoning from dermal exposure.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether appropriate statistical tests are used in the interpretation of the animal studies, the Reviewer commented: “As I am not a biostatistician, all I can state is within what knowledge of biostatistics I do have, the statistical tests were appropriate, other statistical tests would not have been more appropriate, and the statistical tests appeared to have been evaluated appropriately.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer is aware of other animal studies which may be important in evaluating the toxicity of the substance, the Reviewer commented: “No, I am not aware of any other studies that may be important in evaluating the toxicity of, in this case the two, substances.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the LSE tables and figures are complete and self-explanatory, the Reviewer commented: “Yes, the LSE Tables and Figures are complete and self-explanatory. The "User's Guide" does clearly explain how to use them. The exposure levels are accurately presented for the route of exposure. I have no suggestions to improve the effectiveness of the LSE Tables and Figures or the "User's Guide".”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer agrees with the categorization of “less serious” and “serious” effects cited in the LSE tables, the Reviewer commented: “Yes, I agree.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the MRLs are justifiable and if no MRLs are derived, do the data support deriving MRLs, the Reviewer commented “Yes, for H₂S, the derived MRLs values are justifiable. For COS, I agree that the available data do not support such a derivation.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the major limitations of the studies have been adequately and accurately discussed, the Reviewer commented: “Yes, the major limitations of the studies have been adequately and accurately discussed and I find nothing that could be changed to improve or more adequately reflect the proper interpretation of the studies.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the effect or key endpoint has been critically evaluated for its relevance in both humans and animals, the Reviewer commented: “Yes, to the extent possible with available data, the effect, or key endpoint, has been critically evaluated for its relevance in both humans and animals.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether “bottom-line” statements have been made regarding the relevance of the endpoint for human health, the Reviewer commented: “Yes, "bottom-line" statements have been made regarding the relevance of the endpoint for human health.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the conclusions are appropriate given the overall database, the Reviewer commented: “Yes, the conclusions are appropriate given the overall database.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether adequate attention has been paid to dose-response relationships for both human and animal data, the Reviewer commented: “Yes, adequate attention has been paid to dose-response relationships for both human and animal data. Much of the data for H₂S does provide reasonable dose-response relationships in both humans and animals. For COS, only animal data are available, but dose-response relationships have had adequate attention paid given the paucity of data.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the animal data has been used to draw support for any known human effects, the Reviewer commented: “Yes, in the case of H₂S animal data has been used to draw valid support for any known human effects. In the case of COS, no human data were found, so the animal data must be used to suggest possible human effects.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is an adequate discussion of absorption, distribution, metabolism, and excretion of the substances, the Reviewer commented: “Yes, for H₂S, what toxicokinetic data are available are adequately discussed and I do not see any ways to improve the text. In the case of COS, no toxicokinetic data are available.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the major organs, tissues, etc. in which the substance is stored have been identified, the Reviewer commented: “Unlike some toxicants such as heavy metals/metalloids, PCBs and similar compounds, and certain older pesticides, both H₂S and COS are gases and would not be expected to be stored to any significant extent in organs or tissues. For H₂S, some data on tissue distributions are discussed in the Toxicological Profile at short periods after inhalation exposure. Similar data are not available for COS. I see no way to improve the text.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether all applicable metabolic parameters have been presented and whether all available PB/PK models have been presented, the Reviewer commented: “What data are available have been adequately presented. Models of pharmacokinetics/pharmacodynamics have not developed for the two gases covered by this Toxicological Profile.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is adequate discussion of the differences in toxicokinetics between animals and humans, the Reviewer commented: “What data are available have been adequately discussed. There are no other observations that should be made.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is an adequate discussion of the relevance of animal toxicokinetic information for humans, the Reviewer commented: “What data are available have been adequately discussed. There is a paucity of such data for H₂S and none for COS.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is a discussion of the toxicokinetics of different forms of the substance, the Reviewer commented: “This question is not applicable for the two toxic gases discussed in this Toxicological Profile.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether all possible mechanisms of action have been discussed, the Reviewer commented: “So far as data are available, all possible mechanisms of action have been discussed. Please see the accompanying .pdf files for my comments on the issue of sulfhemoglobin inhibiting cytochrome oxidase which is incorrect. H₂S itself inhibits cytochrome oxidase. See also comments above on the metabolism of COS to H₂S which could be added to the text, although from the limited number of animal studies available, COS appears to have direct effects of its own.”

RESPONSE: *The responses to Reviewer’s annotated page comments are discussed in the next section of this document.*

COMMENT: Regarding the question of whether all the biomarkers of exposure are specific for the substance or general for a class of substances, the Reviewer commented: “The biomarkers of exposure for H₂S are not specific for the substance. For example, Urinary thiosulfate can also be increased by ingestion of high-sulfur content drinking water as described in the text. Measurement of blood sulfide levels has been proposed as a biomarker -- as described in the text -- but as blood samples must be obtained within 2 hours of exposure, such measurements are of limited clinical utility. For both of the above, no relationship has been found between airborne concentrations of H₂S and either urinary thiosulfate or blood sulfur levels. There is an adequate discussion of the potential use of alterations in blood heme metabolism, but such tests also are not specific for H₂S. Alterations of rather subtle neurological function have been found in case reports of acute H₂S, but these also are not specific for this compound, as is adequately discussed in the text. No biomarkers for COS exposure have been described, as is discussed in the text.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there are valid tests to measure the biomarkers of exposure, the Reviewer commented: “Yes, there are valid tests to measure the biomarkers of exposure and this is consistent with statements made in other sections of the text.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is an adequate discussion of the interactive effects with other substances, the Reviewer commented: “Yes, for H₂S, there is an adequate discussion of

interactive effects with other chemicals. No studies of such potential interactions at hazardous waste sites were available, so having no discussion is appropriate. There are no such data available for COS.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text discusses the mechanisms of interactions with other substances, the Reviewer commented: “There is no discussion of the mechanisms of interactions in the text because no such data are available.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is a discussion of populations at higher risk because of biological differences which make them more susceptible, the Reviewer commented: “There is some data that persons with asthma may be more susceptible to the respiratory effects of H₂S, although this may be confounded by the odor of this toxic gas. This is adequately described in the text. There is also a discussion that bacterial production of H₂S in the gastrointestinal tract might play a role in development of ulcerative colitis and speculation that persons with this disease might be more susceptible to the toxic effects of this gas, although there are no data to support this speculation. No data are available for COS.”

RESPONSE: *A statement was added to Section 3.10 that there are no data to support whether individuals with ulcerative colitis are more susceptible to the toxicity of hydrogen sulfide.*

COMMENT: Regarding the question of whether the management and treatment discussed in Section 3.11 is specific for the substance or is general for a class of substances, the Reviewer commented: “Intravenous administration of sodium nitrite (one of the components of the nitrite/thiosulfate cyanide antidote kits) has in anecdotal case reports appeared to be efficacious. It is not specific for H₂S poisoning. This is adequately discussed in the text. Hyperbaric oxygen also has some anecdotal evidence of efficacy, but is used for many other indications such as carbon monoxide poisoning and a wide variety of non-toxicological medical conditions. This is adequately discussed in the text. Other than supportive and symptomatic treatment which is common in all poisonings, there are no data available for COS.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is any controversy associated with the treatment and whether it is well accepted, the Reviewer commented: “Sodium nitrite treatment for H₂S remains controversial as some authors question whether the induced methemoglobin and subsequent binding of the sulfur moiety to form sulfmethemoglobin would be sufficient to be efficacious. This is discussed in the references already cited in the text, but not made explicit in the text itself. Adding this to the text would be appropriate. Hyperbaric oxygen treatment for H₂S poisoning also remains controversial and this is adequately discussed in the text. Other than supportive and symptomatic treatment which is common in all poisonings, there are no data available for COS.”

RESPONSE: *The text was revised to note that treatment with amyl nitrite or sodium nitrite has only been shown to be effective if administered within the first few minutes of exposure because the sulfide-methemoglobin complex breaks down rapidly in the presence of oxygen.*

COMMENT: Regarding the question of whether there are any hazards associated with the treatment of populations that are unusually susceptible to the substances, the Reviewer commented: “Yes, there are hazards associated with both nitrite administration and utilization of normobaric 100% oxygen or hyperbaric oxygen in children. This is discussed in the references already cited but not discussed in the text. Children may develop excessive methemoglobinemia following nitrite administration, even resulting in death in at least one case; this occurs more frequently if children are anemic or are administered an inappropriately large dose. Adding this to the text would be appropriate. Infants are at risk for developing retrolental fibroplasia when being treated with high concentrations of oxygen. This would be unlikely for the short duration during treatment of H₂S poisoning, It would be appropriate to mention this in the text. Other than supportive and symptomatic treatment which is common in all poisonings, there are no data available for COS.”

RESPONSE: *A statement was added that young children have an increased sensitivity to nitrate/nitrite exposures leading to the development of methemoglobinemia and that care should be taken in using this approach. Additionally, a statement that a medical expert should be consulted when treating children exposed to hydrogen sulfide was added. A statement was also added that the use of hyperbaric oxygen therapy has only been tested in adults and use in children needs further investigation.*

COMMENT: Regarding the question of whether there are treatments to prevent adverse effects as the substance is being eliminated from the major organs/tissues where it has been stored, the Reviewer commented: “As there is no evidence that either toxic gas is stored in organs or tissues, this question is irrelevant.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there are treatments available to prevent the specific substance from reaching the target organ, the Reviewer commented: “None are available, so discussion of such would be irrelevant.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is any controversy associated with the treatment for preventing the substance from reaching the target organ, the Reviewer commented: “As there are no such treatments available, a discussion of such would be irrelevant.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there are any hazards associated with the treatment for preventing the substance from reaching the target organ in populations unusually susceptible to the substance, the Reviewer commented: “As there are no such treatments available, a discussion of such would be irrelevant.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer knew of other studies which may fill a data gap, the Reviewer commented: “I am not aware of any other studies that might fill a data gap.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the data needs are presented in a neutral, non-judgmental fashion, the Reviewer commented: “Yes, the data needs are presented in a neutral, non-judgmental fashion.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer agrees with the identified data needs, the Reviewer commented: “Yes, I agree with the identified data needs.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text indicates whether any information on the data needs exists, the Reviewer commented: “As none exist, there is no need to discuss this in the text.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text adequately justifies why further development of the data needs would be desirable or justifies the inappropriateness of developing the data need at present, the Reviewer commented: “Yes, the text adequately justifies why further development of the data needs would be desirable. ”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer is aware of any chemical and physical property information or values that are wrong or missing, the Reviewer commented: “I have reviewed the appropriate NLM HSBID and ChemID Plus documents and did not find any missing or wrong information. Nothing else need be referenced here.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer is aware of any information on the production, import/export, use or disposal of the substance that is wrong or missing, the Reviewer commented: “I am not aware that any information for this chapter is either wrong or missing.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text appropriately traced the substance from its point of release to the environment until it reaches the receptor population, the Reviewer commented: “Yes, the text has appropriately traced the substances (two in this case) from their point of release into the

environment until they reach the receptor population, so far as can be known from existing data. The text does provide sufficient and technically sound information regarding the extent of occurrence at NPL sites. I do not know of other relevant information.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text covers pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media, the Reviewer commented: “Yes, the text does cover pertinent information relative to transport, partitioning, transformation, and degradation of the substance to all media. I do not know of other relevant information.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text provides information on levels monitored or estimated in the environment (including background levels), whether proper units are used for each medium, and if the information includes the form of the substance measured, the Reviewer commented: “Insofar as data are available, the text does provide information on levels monitored or estimated in the environment, including background levels. Proper units are used for each medium, where data are available. There is an adequate discussion of the quality of the information. I do not know of other relevant information.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text describes sources and pathways of exposure for the general population, occupations involved in the handling of the substance, and populations with potentially high exposures, the Reviewer commented: “To the extent that data are available, the text does 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.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the data needs presented in Section 6.8.1 are presented in a neutral, non-judgmental fashion, the Reviewer commented: “Yes, the data needs are presented in a neutral, non-judgmental fashion.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text adequately justifies why further development of the data needs would be desirable or justifies the inappropriateness of developing the data needs, the Reviewer commented: “Yes, the text adequately justifies why further development of the data needs would be desirable.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding Section 6.8.2, “As the text mentions, there were no identified ongoing studies nor am I aware of any.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer is aware of additional analytical methods that should be added to the profile, the Reviewer commented: “I am not aware of any additional methods not already listed in the draft document.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the methods have been included for measuring key metabolites previously mentioned in the text, the Reviewer commented: “Yes, methods for measuring key metabolites have been included.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether unique issues related to sampling for the substance exist and have been adequately addressed in the text, the Reviewer commented: “Yes, unique issues relating to sampling for (in this case, two) substances have been adequately addressed in the text (i.e., the problems with measuring H₂S because of its high volatility).”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the identification of data needs for analytical methods are presented in a neutral, non-judgmental fashion, the Reviewer commented: “Yes, the data needs are presented in a neutral, non-judgmental fashion.”

RESPONSE: *No revisions were suggested.*

COMMENT: Does the text indicate whether any information on the data needs exists, the Reviewer commented: “As none exist, there is no need to discuss this in the text.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text adequately justifies why further development of the data needs would be desirable or justifies the inappropriateness of developing the data needs, the Reviewer commented: “Yes, the text adequately justifies why further development of the data needs would be desirable. ”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer is aware of other regulations or guidelines that may be appropriate for Table 8-1, the Reviewer commented: “I am not aware of any other regulations or guidelines appropriate for the table.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there are additional references that provide new data, or if there are better studies than those already in the text, the Reviewer commented: “In my literature searches, I did *not* find any additional references that would provide new data or any better studies than those already in the text.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question on the adequacy of design, methodology, and reporting of “Study #1” unpublished study (referenced in the toxicological profile as Monsanto 1985b), the Reviewer commented: “This study lacks organ weight and histopathology findings which were not done at necropsy.”

RESPONSE: *The lack of organ weight and histopathology data limit the usefulness of this study for evaluating potential systemic toxicity targets; ATSDR believes that the study is adequate for evaluating neurotoxicity.*

COMMENT: Regarding the question on the validity of results and author’s conclusions for “Study #1” unpublished study (referenced in the toxicological profile as Monsanto 1985b), the Reviewer commented: “The fact that many of the experimental animals across all study groups had a viral infection that resulted in lacrimation, eye swelling, and nasal discharge may have confounded the possible irritant effects of COS on the eyes and upper respiratory tract tissues.”

RESPONSE: *ATSDR agrees with the Reviewer that the study is not adequate for evaluating the potential irritation due to the background viral infection.*

COMMENT: Regarding the question on the study inadequacies or confounding “Study #1” unpublished study (referenced in the toxicological profile as Monsanto 1985b), the Reviewer commented: “See No. 2 above.” [comments on the study validity]

RESPONSE: *See RESPONSE to the previous COMMENT.*

COMMENT: Regarding the question on the adequacy of design, methodology, and reporting of “Study #2” unpublished study (referenced in the toxicological profile as Monsanto 1985a), the Reviewer commented: “These are adequate for a 4-hour inhalation LC₅₀ study.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question on the validity of results and author’s conclusions for “Study #2” unpublished study (referenced in the toxicological profile as Monsanto 1985a), the Reviewer

commented: “Valid with the exception of the statement about decomposition of COS causing sulfmethemoglobinemia.”

RESPONSE: *The investigators statement regarding hydrogen sulfide generation and the induction of sulmethemoglobinemia was not included in the toxicological profile.*

COMMENT: Regarding the question on the study inadequacies or confounding for “Study #2” unpublished study (referenced in the toxicological profile as Monsanto 1985a), the Reviewer commented: “The lack of histopathology limits the findings, but this was a study to determine the 4-hour inhalation exposure LC₅₀ and this is not a significant inadequacy of the study.”

RESPONSE: *ATSDR agrees with the Reviewer that the lack of histopathology examination does not preclude using the study to evaluate the lethality of carbonyl sulfide.*

COMMENT: Regarding the question on the adequacy of design, methodology, and reporting of “Study #3” unpublished study (referenced in the toxicological profile as Monsanto 1987), the Reviewer commented: “All 6 parts of this study were adequately designed, the methodology was standard and appropriate, and the reporting reflects the raw data obtained.”

RESPONSE: *It is ATSDR’s practice to not include studies only available as an abstract; thus, only the reproductive toxicity study was included in the toxicological profile because this study is fully described.*

COMMENT: Regarding the question on the validity of results and author’s conclusions for “Study #3” unpublished study (referenced in the toxicological profile as Monsanto 1987), the Reviewer commented: “The results are valid and the author's conclusions are justified by the reported raw data and employed statistical methods.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question on the study inadequacies or confounding for “Study #3” unpublished study (referenced in the toxicological profile as Monsanto 1987), the Reviewer commented: “None were noted in my review.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question on the adequacy of design, methodology, and reporting of “Study #4” unpublished study (referenced in the toxicological profile as DuPont 1981), the Reviewer commented: “Although only summary data are provided in the report of this study, the study design, methodology, and reporting appear to be adequate to produce valid results.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question on the validity of results and author’s conclusions for “Study #4” unpublished study (referenced in the toxicological profile as DuPont 1981), the Reviewer commented:

“As can best be determined from the supplied summary data, the study results are valid and the author's conclusions are valid and supported by the results.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question on the study inadequacies or confounding for “Study 4” unpublished study (referenced in the toxicological profile as DuPont 1981), the Reviewer commented: “The complete raw data were not available for review. I do not find inadequacies in the study based on the data provided. There is a potential confounding factor because of potential contamination with the test COS gas reported as: < 3% H₂S and < 35% CS₂. It would be reasonable to assume from the manner in which the potential contaminants that these are the Limits of Detection for the analytical methodology. It is thus not possible from the data provided to make any conclusions about whether these potential contaminants might or might not have confounded the study.”

RESPONSE: *Although no firm conclusions can be made regarding the influence of contaminants of the observed effects, the LC₅₀ value (1111 ppm) is similar to the LC₅₀ value (1082 ppm) reported in the Monsanto (1985a) study.*

Annotated Comments provided by Reviewer #2

Reviewer #2 provided a hard copy of the profile with annotated comments. The referenced profile statements are presented below with the Reviewers suggested insertions and deletions indicated in red; the page and line numbers refer to the third draft of the profile.

COMMENT (Page 1, line 7): However, the possibility remains that as more sites are evaluated, the number of sites at which hydrogen sulfide and carbonyl sulfide are found may increase.

RESPONSE: *The text was revised to delete carbonyl sulfide from the sentence.*

COMMENT (Page 1, line 8): Harm might also depend on whether you’ve been exposed to any other chemicals, as well as your age, ~~sex~~ gender, diet, family traits, lifestyle, and state of health.

RESPONSE: *The correct term is sex; no changes were made to the profile.*

COMMENT (Page 9, line 8): Harm might also depend on whether you’ve been exposed to any other chemicals, as well as your age, ~~sex~~ gender, diet, family traits, lifestyle, and state of health.

RESPONSE: *The correct term is sex; no changes were made to the profile.*

COMMENT (Page 11, line 6): How carbonyl sulfide enters your body

RESPONSE: *The suggested revision was made.*

COMMENT (Page11, line 7): The Reviewer noted “at least from one non-human study, carbonic anhydrase may catalyze the conversion of COS to H₂S and CO₂ which would be eliminated as [illegible word] (Haritos & Dojchnov, 2005)”

RESPONSE: *Haritos and Dojchnov (2005) examined the metabolism of carbonyl sulfide in insects; the relevance of these data to humans is not known. No revisions were made to the text.*

COMMENT (Page 11, line 8): Studies in animals show that nervous system effects can occur after short- or long-term exposure to high levels.

RESPONSE: *The suggested revision was made to line 9.*

COMMENT (page 16, line 10): Regarding the sentence “However, at concentrations of ≥ 100 ppm, individuals may not detect hydrogen sulfide odor due to damage to olfactory tissue.”, the Reviewer questioned whether it was damage or olfactory paralysis.

RESPONSE: *The text was revised to olfactory paralysis.*

COMMENT (page 22, line 2): When exposed males were allowed to recover for 10 weeks prior to mating with unexposed females, no reproductive effects were observed

RESPONSE: *The suggested revision was made.*

COMMENT (page 21, line 19): Acute effects noted included coma, dysequilibrium, and respiratory insufficiency with pulmonary edema.

RESPONSE: *Both spellings are correct, no change was made to the document.*

COMMENT (page 42, line 27): However, the respiratory epithelium was not adversely affected in rats similarly exposed 3 hours/day for 5 days (Brenneman et al. 2002).

RESPONSE: *The suggested revision was made.*

COMMENT (page 47, lines 9-10): No morphological alterations were observed in the coronary arteries, aortic arch, descending thoracic aorta, or pulmonary arteries (Hugod and Astrup 1980; Kamstrup and Hugod 1979) and no ~~ultrastructural changes~~ myocardial ultrastructural changes (Hugod 1981) were found in rabbits continuously exposed to 54 ppm carbonyl sulfide for 7 weeks.

RESPONSE: *The suggested revision was made.*

COMMENT (page 50, line 8): No changes in serum protein, lactate dehydrogenase (LDH), serum glutamic-oxaloacetic transaminase (~~serum glutamic oxaloacetic transaminase~~ [SGOT]; aspartate aminotransferase),

RESPONSE: *The suggested revision was made.*

COMMENT (page 51, line 28): Slate-grey skin discoloration and erythema were noted in rabbits exposed to unspecified concentrations of hydrogen sulfide for 2 hours (Laug and Draize 1942). This skin discoloration might have been due to induction of sulfhemoglobinemia.

RESPONSE: *A statement was added that the slate-grey skin discoloration may have been related to increased sulfhemoglobin levels.*

COMMENT (page 61, line 4): The ORs for a 1-ppb change in hydrogen sulfide were 1.18 (95% CI=1.08–1.30) for stress or annoyance and 1.12 (995% CI=1.08–1.30) for feeling nervous or anxious.

RESPONSE: *The suggested revision was made.*

COMMENT (page 61, line 10): Alterations in tests of balance sway with eyes open or closed, color discrimination, visual field performance, cognition, and reaction time were observed in residents living near a hog manure lagoon, as compared to an out-of-state control group (Kilburn 2012).

RESPONSE: *The suggested revision was made.*

COMMENT (page 65, lines 23 and 25): The investigators noted that the observed alterations of brainstem auditory-evoked responses peak generation indicated alterations in the region of the olivary complex-lateral lemniscus region of the brainstem, but with normal function of the auditory nerve and cochlear nucleus region.

RESPONSE: *The suggested revisions were made.*

COMMENT (page 65, line 31): Reflex modification of audiometry or visual evoked potentials after 10 exposures (6 hours/day, 5 days/week, testing conducted 11 days postexposure) and peripheral...

RESPONSE: *The suggested revision was made.*

COMMENT (page 70, line 1): New Zealand, these researchers also examined their data stratified by ethnicity and ~~sex~~ gender and found a significantly increased risk of cancers of the trachea, bronchus, ...

RESPONSE: *The correct term is sex; no changes were made to the profile.*

COMMENT (page 71, line 9): The Reviewer questioned whether the statement should also include carbonyl sulfide.

RESPONSE: *A statement in Section 3.2.2 indicates that there were no oral studies for carbonyl sulfide. The statement in question is specific to hydrogen sulfide.*

COMMENT (page 81, lines 9 and 14): The Reviewer questioned whether the statements should also include carbonyl sulfide.

RESPONSE: *These statements are specific for hydrogen sulfide; there is a statement in Section 3.4.2 that there are no distribution studies for carbonyl sulfide.*

COMMENT (page 97, lines 29-31): In a study in rats, found that hyperbaric treatment for 100 minutes initiated within 20 minutes of termination of a 60-minute exposure to 300 ppm hydrogen sulfide did not significantly alter partial pressure of oxygen, as compared to animals similarly exposed and not undergoing hyperbaric treatment (Wu et al. 2011).

RESPONSE: *This sentence was revised.*

COMMENT (page 102, lines 16-19): Death occurred following a single inhalation exposure in rats (DuPont 1981; Monsanto 1985a) or repeated inhalation exposures in rats (Morgan et al. 2004) and rabbits (Hugod 1981; Hugod and Astrup 1980; Kamstrup and Hugod 1979). Neurotoxicity, including overt signs of toxicity and histological alterations in the brain, was ~~were~~ observed in rats exposed by inhalation once or up to 12 times...

RESPONSE: *The suggested revisions were made.*

COMMENT (page 103, line 4): Although CIIT (1983b, 1983c) did not report increases in the of occurrence histological lesions...

RESPONSE: *The suggested revision was made.*

COMMENT (page 104, line 2): ...a study examining morphological changes in the lungs, heart, and aorta of rabbits (Kamstup and Hugod 1979)...

RESPONSE: *The suggested revision was made.*

COMMENT (page 106, line 30): Immunological effects infrequently observed after human hydrogen sulfide exposure appear to result from infection due to the aspiration or ingestion of manure or ~~vomit~~ (Osbern and Crapo 1981).

RESPONSE: *The suggested revision was made.*

COMMENT (page 107, line 29): Additionally, there is ~~antidotal~~ anecdotal evidence that some individuals experience permanent or persistent neurological symptoms...

RESPONSE: *The suggested revision was made.*

COMMENT (page 108, line 3): The effects ranged from severe signs of neurotoxicity, including ataxia and hypothermia, to necrosis and neuronal loss in parietal cortex, thalamus, and other midbrain structures, to impaired performance on neurophysiological tests and motor function tests...

RESPONSE: *The suggested revision was made.*

COMMENT (page 108, line 16): Some chronic-duration epidemiological studies (Ahlborg 1951; Haahtela et al. 1992; Horton et al. 2009; Inserra et al. 2004; Jaakkola et al. 1990; Jappinen et al. 1990; Marttila et al. 1994b; Schechter et al. 1989; Tenhunen et al. 1983)...

RESPONSE: *The suggested revision was made.*

COMMENT (page 109, line 16): There are no studies examining biomarkers of exposure to carbonyl sulfide, and studies are needed.

RESPONSE: *The sentence in question was revised.*

COMMENT (page 111, lines 25-26): The available data are insufficient to characterize on the toxicity of carbonyl sulfide; ~~although~~ There is a potential for human exposure to carbonyl sulfide, and studies designed to evaluate methods for reducing toxic effects should be done after the critical targets of toxicity and modes of action have been identified.

RESPONSE: *The sentence in question was revised.*

COMMENT (page 112, line 25): The study will examine 1,800 adults living in Rotorua, New Zealand with high, medium, or low exposures to hydrogen sulfide ~~for~~ from geothermal fields.

RESPONSE: *The suggested revision was made.*

COMMENT (page 123, lines 5-7): Hydrogen sulfide has been found in at least 35 of the 1,689 ($\approx 2\%$) waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) and carbonyl sulfide was detected in at least 3 of the 1,689 (0.2%) waste sites (HazDat 2007).

RESPONSE: *Since the number of sites that monitored hydrogen sulfide or carbonyl sulfide is not known, the percentage of sites was not added.*

COMMENT (page 128, line 19): Annually, 100–324 million tons of hydrogen sulfide are released from natural sources with half from volcanoes, flooded ground, or hydrogeologically sources, and the other half from the oceans (Pouliquen et al. 1989).

RESPONSE: *The suggested revision was made.*

COMMENT (page 149, line 8): ...petrochemical plants, coke oven plants, kraft paper mills, food processing plants, landfills, manure treatment facilities, waste water treatment facilities, and tanneries may be more likely to be exposed to higher levels of hydrogen sulfide.

RESPONSE: *The suggested revision was made.*

COMMENT (page 150, lines 10-14): The Reviewer noted “why not update with the most current published version of the NPDS?”

RESPONSE: *The text was revised to include data from the 2012NPDS report (most recent), as well as data from the 2010, 2005, and 2000 reports.*

COMMENT (page 153, line 5): The main exposure concerns are typically associated ~~to~~ with occupational settings where carbonyl sulfide is produced and used, such as for a chemical intermediate (EPA 1994d), and in this context, childhood exposure may be limited.

RESPONSE: *The suggested revision was made.*

COMMENT (page 160, Table 7-1): Weight sample; homogenize in aqueous zinc acetate using a rotostator at 18,000 rpm for 20 seconds; dilute with borate buffer; convert to methylene blue.

RESPONSE: *The suggested revision was made.*

COMMENT (page 161, footnote for Table 70-1): The Reviewer questioned whether the definition of MS should be mass spectrometry or spectroscopy.

RESPONSE: *The definition was corrected to mass spectrometry.*

COMMENT (page 166, Table 7-3): Trap H₂S in an aqueous NaOH and ascorbic acid in a midget impinger; titrate resulting sulfide ion with CdSO₄ solution

RESPONSE: *The suggested revision was made.*

COMMENT (page 172, line 11): These include methylene blue/colorimetric methods, gravimetry, and potentiometry with an ion-selective electrode.

RESPONSE: *The suggested revision was made.*

COMMENT (page 175, line 14): In another study, samples of seawater were obtained using 1,000 mL vacuum extraction flasks, constructed of Erlenmeyer flasks with a Kovar-to-glass seal on the top connected to a valve.

RESPONSE: *The suggested revision was made.*

COMMENT (page 176, line 11): In another study, samples of seawater were obtained using 1,000 mL vacuum extraction flasks, constructed of Erlenmeyer flasks with a Kovar-to-glass seal on the top connected to a valve.

RESPONSE: *The suggested revision was made.*

COMMENT (page 175, line 14): Methods are available for measuring sulfide in blood (Puacz et al. 1995; Richardson et al. 2000) and brain tissue (Goodwin et al. 1989) and for measuring sulfur volatiles in saliva (Solis and Volpe 1973).

RESPONSE: *The suggested revision was made.*

COMMENT (page 189, line 28): *Bandy AR, Thornton DC, Driedger AR, III. 1993. Airborne measurements of sulfur dioxide, dimethyl sulfide, carbon disulfide, and carbonyl sulfide by isotope dilution gas chromatography/mass spectrometry. ~~Journal of Geophysical Research~~ *Atmospheres* 98(D12):23423-23433.

RESPONSE: *The suggested revision was made.*

COMMENT (page 191, line 6): Blanchette AR, Cooper AD. 1976. Determination of hydrogen sulfide and methyl mercaptan in mouth air at parts-per-billion level by gas chromatography. *Anal Chem* 48:729-731.

RESPONSE: *The suggested revision was made.*

COMMENT (page 191, lines 11-12): Boon AG. 1992. Septicity in sewers: Causes, consequences and containment. ~~Water and Environmental Management~~ 6:79-90.

RESPONSE: *The suggested revision was made.*

COMMENT (page 192, line 5): Broderius SJ, Smith LL Jr, Lind DT. 1977. Relative toxicity of free cyanide and dissolved sulfide forms to the fathead minnow (*Pimephales promelas*). ~~Journal of the Fisheries Research Board of Canada~~ 34:2323-2332.

RESPONSE: *The suggested revision was made.*

COMMENT (page 203, lines 2-6): The Reviewer noted that the references for EPA 2013e and EPA 2013f should be moved after the EPA 2013d reference.

RESPONSE: *The suggested revision was made.*

COMMENT (page 203, line 37): Fiedler N, Kipen H, Ohman-Strickland P, et al. 2008. Sensory and cognitive effects of acute exposure to hydrogen sulfide. *Environ Health Perspect* 116(1):78-85.

RESPONSE: *The suggested revision was made.*

COMMENT (page 206, lines 28-29): Hartmann K. 1937. [On superficial and deep (disciform) inflammations of the cornea following exposure to hydrogen sulfide of caisson workers on the North Sea shore.] ~~Klinische Monatsblätter für Augenheilkunde~~ 99:456-468. (German)

RESPONSE: *The suggested revision was made.*

COMMENT (page 207, line 27): Higuchi Y, Fukamachi M. 1977. [Behavioral studies on toxicity of hydrogen sulfide by means of conditioned avoidance responses in rats.] ~~Folia Pharmacologica Japonica~~ 73:307-319. (Japanese)

RESPONSE: *The suggested revision was made.*

COMMENT (page 207, lines 49-50): Hollis JP. 1985. Hydrogen sulfide in Louisiana rice fields. ~~Acta Phytopathologica Academiae Scientiarum Hungaricae~~ 20:321-326.

RESPONSE: *The suggested revision was made.*

COMMENT (page 209, line 24): Jörgensen BB. 1982. Ecology of the bacteria of the sulphur cycle with special reference to anoxic-oxic interface environments. ~~Philos Trans R Soc Lond B Biol Sci~~ 298:543-561.

RESPONSE: *The suggested revision was made.*

COMMENT (page 210, lines 10-11): Kapala J. 2002. Emission of air pollutants from tanks with volatile substances. ~~Latvian Journal of Physics and Technical Sciences~~ 4:36-42.

RESPONSE: *The suggested revision was made.*

COMMENT (page 216, line 13): Moore JWE, Millard S, Babidge W, et al. 1997. Hydrogen sulphide produces diminished fatty acid oxidation in the rat colo~~en~~ *in vivo*: Implications for ulcerative colitis. ~~Aust NZ J Surg~~ 67:245-249.

RESPONSE: *The suggested revision was made.*

COMMENT (page 216, line 28): Moulin FJ-M, Brenneman KA, Kimbell J, et al. 2002. Predicted regional flux of hydrogen sulfide correlates with distribution of nasal olfactory lesions in rats. ~~Toxicol Sci~~ 66:7-15.

RESPONSE: *The citation in the profile is consistent with the published version of the paper; the suggested revision was not made.*

COMMENT (page 216, line 51): Nicholls P. 1975. The effect of sulphide on cytochrome *aa*₃. Isoteric and allosteric shifts of the reduced a-peak. Biochim Bibophys Acta 396:24-35.

RESPONSE: *The suggested revision was made.*

COMMENT (page 221, line 26): Pitcher MCL, Beatty ER, Harris RM, et al. 1998. Sulfur metabolism in ulcerative colitis: investigation of detoxification enzymes in peripheral blood. Dig Dis Sci 43:2080-2085.

RESPONSE: *The suggested revision was made.*

COMMENT (page 226, line 42): Tabacova A. 1986. Maternal exposure to environmental chemicals. Neurotoxicology 7:421-440.

RESPONSE: *The suggested revision was made.*

COMMENT (page 231, line 32): Yant WP. 1930. Hydrogen sulphide in industry: Occurrences effects and treatment. Am J Public Health 20:598-608.

RESPONSE: *The suggested revision was made.*

Review comments provided by Reviewer #3:

COMMENT: Regarding the question of whether any relevant data to child health and developmental effects were not discussed in the profile, the Reviewer commented: “No.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether any general issues relevant to child health were not discussed in the profile, the Reviewer commented: “No.”

RESPONSE: *No revisions were suggested.*

COMMENT: “The Profile is comprehensive, informative, well organized and presented. Due to the nature of the Profile, targeted at different readers in the same Profile, there are significant redundancies in many sections throughout the whole Profile. The same literatures are described in almost identical ways at numerous places. Many sentences and paragraphs are identical, appearing not at one or two places, but numerous places. I guess this is due to the nature of the Profile and we cannot do anything about it but, regardless, to read it through sentence by sentence is exhaustive. And forgive my frankness; very often the reading is boring because one is reading the same text over and over again.”

RESPONSE: *ATSDR will consider revisions to the format of the toxicological profile when it updates its guidance document.*

COMMENT: Regarding the question of whether Chapter 1 presents the important information in a non-technical style suitable for the average citizen, the Reviewer commented: “Yes.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the answers to the questions in Chapter 1 adequately address the concerns of the lay public, whether the summary statements are consistent and supported by the technical discussion in the remainder of the text, and if there are any general issues relevant to child health that have not been discussed in the profile, the Reviewer commented: “Many question headings are ended with a question mark and many others, not. This inconsistency should be corrected. Otherwise, this chapter is well written and suitable for general public interest.”

RESPONSE: *The text has been revised to remove the question marks.*

COMMENT: Regarding the discussion of how hydrogen sulfide leaves your body, “This description is oversimplified. The removal of hydrogen sulfide via expiration should be added.”

RESPONSE: *ATSDR was unable to locate any data by a relevant route of exposure (inhalation, oral, or dermal exposure) to support the Reviewer’s statement that hydrogen sulfide is eliminated via expiration.*

COMMENT: Regarding the question of whether the scientific terms used in Chapter 1 are too technical or require additional explanation, the Reviewer commented: “No need for alternate wording is noticed.”

RESPONSE: *No revisions were suggested.*

COMMENT: (page xiii) The Reviewer questioned whether 1.1 and 1.2 are identical.

RESPONSE: *This error in the Table of Contents was corrected.*

COMMENT: Regarding the question of whether the Reviewer agrees with the discussion in Chapter 2 on effects known to occur in humans, the Reviewer commented: “YES.”

RESPONSE: *No revisions were suggested.*

COMMENT: Page 15, line 24 regarding the discussion of endogenous production by bacteria present in the intestinal tract and mouth, the Reviewer commented: “This paragraph is clearly outdated and obsolete, especially about the endogenous production of hydrogen sulfide by our own cells and tissues. Over the last decade, hundreds of published papers have demonstrated that hydrogen sulfide can be produced by and affect the functions of almost every organ and system in our body. For a detailed summary in this regard, please refer to [Wang R, Physiological implications of hydrogen sulfide – A whiff exploration that blossomed. *Physiol. Rev.* 92(2):791-896, 2012]. The mechanisms of the cellular effects of hydrogen sulfide are far more than NDMA receptors. For example, hydrogen sulfide stimulates ATP-sensitive K channels [Zhao W, Zhang J, Lu Y, Wang R. The vasorelaxant effect of H₂S as a novel endogenous gaseous K_{ATP} channel opener. *EMBO J.* 20:6008-6016, 2001] to relax vascular tissues. The lack of endogenous hydrogen sulfide leads to the age-dependent development of hypertension in experimental mice [Yang G, Wu L, Jiang B, Yang W, Qi J, Cao K, Meng Q, Mustafa AK, Mu W, Zhang S, Snyder SH, Wang R. H₂S as a physiologic vasorelaxant: Hypertension in mice with deletion of cystathionine gamma-lyase. *Science.* 322:587-590, 2008].”

RESPONSE: *The discussion of the physiological functions of endogenous hydrogen sulfide has been expanded based on the Wang (2012) review article.*

COMMENT: Regarding the question of whether the effects only observed in animals are likely to be of concern to humans, the Reviewer commented: “YES, because the animal observations are under the experimental conditions and these conditions may not be applied to humans for the ethical reasons.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether exposure conditions were adequately described, the Reviewer commented: “YES.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether adequately designed human studies are identified in Chapter 3 and if the study(ies) is/are not adequately designed, and are the major limitations of the studies sufficiently described in the text, the Reviewer commented: “YES. And the major limitations of the studies are sufficiently described in the text.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the conclusions drawn by the authors of the studies are appropriate and accurately reflected in the profile, the Reviewer commented: “The purpose of Chapter 3 should be “providing a summary evaluation of the weight of evidence, rather than on providing detailed descriptions of every relevant study. Scientifically prudent judgments and interpretations are both appropriate and desirable.” Unfortunately, this purpose is not fulfilled. There should be a summary paragraph for each section to summarize what would be the most likely consensus, what are clearly premature, and why there were inconsistencies. As it stands, most text of this Chapter is the list of publications. For example, it appears that at concentrations lower than 10 ppm or 50 ppm hydrogen sulfide did not present obvious hazard to respiratory tract in human or rats, respectively. Taking another example, the peak concentration of hydrogen sulfide appears to be more critical than its average concentration over an extended period of time. These summaries and the like can be added.”

RESPONSE: *A number of sections in Section 3.2 are short and ATSDR does not believe that a summary is necessary. A summary of the respiratory and neurological effects of hydrogen sulfide was added to the toxicological profile; the summary includes the identification of NOAEL values. However, ATSDR disagrees with the Reviewer that there are sufficient data to support the statement that peak concentrations appear to be more critical than average concentrations over an extended period of time. A comparison of the results of the Brenneman et al. (2002) acute studies suggests that duration of exposure may be an important determinant of toxicity. In rats exposed to hydrogen sulfide 3 hours/day for 5 days, olfactory lesions consisting of necrotic olfactory epithelium sloughing was observed at 80 ppm with a NOAEL of 30 ppm. A single 3-hour exposure to 80 ppm did not result in damage to the nasal epithelial tissue; necrosis was observed at 200 ppm.*

COMMENT: Regarding the question of whether all appropriate NOAELs and/or LOAELs are identified for each study, the Reviewer commented: “Adequate information in this regard has been provided.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether appropriate statistical tests are used in the studies, the Reviewer commented: “The text of this Profile mentioned the statistical analysis of the concerned literature reports. However, the text did not evaluate the statistic strength of each literature or conduct statistical analysis of all related literature, which is understandable.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer is aware of other studies which may be important in evaluating the toxicity of the substance, the Reviewer commented: “The text is adequate and inclusive.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether adequately designed animal studies are identified in the text, the Reviewer commented: “The analysis and presentation of literature is adequate.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the animal species is appropriate for the most significant toxicological endpoint of the study, the Reviewer commented: “Most animal studies on the toxicological profile of hydrogen sulfide and carbonyl sulfide were conducted on small animals (rat, mice, or rabbit, etc). To be more relevant to human health, big animals such as pig or dog may be tested. But those experiments are challenged by the cost and other factors. The text of Profile is adequate to address these issues.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the conclusions drawn by the authors of the animal studies are appropriate and accurately reflected in the text, the Reviewer commented: “YES.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether all appropriate NOAELs and LOAELs are identified for each animal study and whether all appropriate toxicological effects are identified for the studies, the Reviewer commented: “Adequate information in this regard has been provided.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is a discussion of the toxicities of the various forms of the substance, the Reviewer commented: “YES.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether appropriate statistical tests are used in the interpretation of the animal studies, the Reviewer commented: “The text of this Profile mentioned the statistical analysis of the concerned literature reports. However, the text did not evaluate the statistic strength of each literature or conduct statistical analysis of all related literature, which is understandable.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer is aware of other animal studies which may be important in evaluating the toxicity of the substance, the Reviewer commented: “The analysis and presentation of literature is adequate.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the LSE tables and figures are complete and self-explanatory, the Reviewer commented: “The analysis and presentation of literature is adequate.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer agrees with the categorization of “less serious” and “serious” effects cited in the LSE tables, the Reviewer commented: “Agree”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the MRLs are justifiable and if no MRLs were derived, do the data support deriving MRLs, the Reviewer commented “The text merely listed the published MRLs from different studies. Some MRLs were provided and some not. There is no consensus on MRLs.”

RESPONSE: *The only MRLs presented in the profile are those derived for hydrogen sulfide. ATSDR believes that the Reviewer may be confusing MRLs with NOAEL/LOAEL values. Although not all NOAEL and LOAEL values are presented in the text, they are all presented in the LSE table and figure.*

COMMENT: Regarding the question of whether the major limitations of the studies have been adequately and accurately discussed, the Reviewer commented: “YES.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the effect or key endpoint has been critically evaluated for its relevance in both humans and animals, the Reviewer commented: “YES”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether “bottom-line” statements have been made regarding the relevance of the endpoint for human health, the Reviewer commented: “In some cases but not in all cases.”

RESPONSE: *For hydrogen sulfide, the animal data confirm the findings observed in the human studies, as is noted in several places in the toxicological profile. For carbonyl sulfide, a statement was added to Section 2.2 that it is assumed that the effects observed in animals are relevant to humans.*

COMMENT: Regarding the question of whether the conclusions are appropriate given the overall database, the Reviewer commented: “No. See my previous comments.”

RESPONSE: *See the RESPONSES to the Reviewer’s previous comments.*

COMMENT: Regarding the question of whether adequate attention has been paid to dose-response relationships for both human and animal data, the Reviewer commented: “Yes .”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the animal data has been used to draw support for any known human effects, the Reviewer commented: “In some cases but not in all cases.”

RESPONSE: *A statement was added to the discussion of the carbonyl sulfide animal studies in Section 2.2 that it is assumed that the observed effects would be relevant. For hydrogen sulfide, it is noted that the animal studies confirm the results of the human studies.*

COMMENT: Regarding the question of whether there is an adequate discussion of absorption, distribution, metabolism, and excretion of the substances, the Reviewer commented: “YES in most parts. For the metabolism of hydrogen sulfide, the 4th mechanism should be mentioned, i.e. expiration and excretion. See - [Wang R, Physiological implications of hydrogen sulfide – A whiff exploration that blossomed. *Physiol. Rev.* 92(2):791-896, 2012].”

RESPONSE: *ATSDR does not consider expiration and excretion to be a metabolism mechanism; rather, these data are discussed in the Elimination and Excretion sections of the toxicological profile. ATSDR did not identify studies that monitored exhaled hydrogen sulfide following inhalation, oral, or dermal exposure. The Wang (2012) study review discusses a study by Insko et al. (2009), which measured “a significant amount of hydrogen sulfide” in expired air after intravenous administration of sodium sulfide; since the administered compound was not hydrogen sulfide, the study was not considered relevant for the inclusion in the toxicological profile.*

COMMENT: Regarding the question of whether the major organs, tissues, etc. in which the substance is stored have been identified, the Reviewer commented: “YES.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether all applicable metabolic parameters have been presented and all available PB/PK models have been presented, the Reviewer commented: “YES.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is adequate discussion of the differences in toxicokinetics between animals and humans, the Reviewer commented: “YES.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is an adequate discussion of the relevance of animal toxicokinetic information for humans, the Reviewer commented: “YES, based on available literature.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is a discussion of the toxicokinetics of different forms of the substance, the Reviewer commented: “YES.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding Section 3.4.2, “A summary should be provided based on the literature as per which tissue(s) has the greatest distribution after intoxication.”

RESPONSE: *There are limited data on the distribution of hydrogen sulfide; the available data on the relative distribution of hydrogen sulfide is presented in Section 3.4.2.1.*

COMMENT: Regarding Section 3.4.5, “A lengthy description was given for PBPK models. However, only after reading all this description the readers will realize that “No PBPK models have been developed for hydrogen sulfide or carbonyl sulfide.” Therefore, this section can be significantly shortened by at least 50%. ”

RESPONSE: *The Reviewer is referring to the standard boilerplate introduction for this section; ATSDR will consider the Reviewer’s suggestion of deleting this introduction when there are no data when the Agency revises the toxicological profile guidance.*

COMMENT: Regarding the question of whether all possible mechanisms of action have been discussed, the Reviewer commented: “For the metabolism of hydrogen sulfide, the 4th mechanism should be mentioned, i.e. expiration and excretion. See - [Wang R, Physiological implications of hydrogen sulfide – A whiff exploration that blossomed. *Physiol. Rev.* 92(2):791-896, 2012]. A summary should be provided based on the literature as per which tissue(s) has the greatest distribution after intoxication.”

RESPONSE: *As noted previously, expiration and excretion is not considered a metabolism mechanism and this information was not added to Section 3.5.1; this section includes a note that the hydrogen sulfide is primarily excreted as sulfate in the urine. A discussion of the relative distribution of hydrogen sulfide is presented in Section 3.4.2.1.*

COMMENT: Regarding Section 3.6, “Again, a lengthy description was given for this section. After reading this description the readers will realize that this concept has not been associated with H₂S or carbonyl sulfide at all. Therefore, this section is not needed at all.”

RESPONSE: *The Reviewer is referring to the standard boilerplate introduction for this section; ATSDR will consider the Reviewer’s suggestion of deleting this introduction when there are no data when the Agency revises the toxicological profile guidance.*

COMMENT: Regarding the question of whether all the biomarkers of exposure are specific for the substance or general for a class of substances, the Reviewer commented: “Most of the biomarkers described are relatively specific. Exhaled hydrogen sulfide should be included as a biomarker of

hydrogen sulfide exposure [Chen Y, Wang R. The message in the air: Hydrogen sulfide metabolism in chronic respiratory diseases. *Respiratory Physiology & Neurobiology* 184:130–138, 2012].”

RESPONSE: *Section 3.8 Biomarkers of Exposure and Effect of the profile discusses biomarkers that could be used to qualitatively or quantitatively assess external exposure to hydrogen sulfide or to characterize effects caused by exposure to exogenous hydrogen sulfide. The Chen and Wang (2012) paper does not discuss the use of exhaled hydrogen sulfide as a biomarker of exogenous hydrogen sulfide exposure. Rather, the paper discusses the possible use of hydrogen sulfide levels in nasal air as a biomarker of asthma and other respiratory diseases based on the role of endogenous hydrogen sulfide as a gasotransmitter involved in the maintenance of respiratory function.*

COMMENT: Regarding the question of whether there are valid tests to measure the biomarkers of exposure, the Reviewer commented: “YES.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the biomarkers of effect are specific for the substance, the Reviewer commented: “No specific biomarker of effect have been identified.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there are valid tests to measure biomarkers of effect, the Reviewer commented: “Not applicable.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is an adequate discussion of the interactive effects with other substances, the Reviewer commented: “YES.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the discussion on interactions emphasizes effects that might occur at hazardous waste sites, the Reviewer commented: “YES, such as ethanol or carbon disulfide.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the discussion on interactions include a discussion of the mechanisms of interactions, the Reviewer commented: “NO and there is no literature can be refereed.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is a discussion of populations at higher risk because of biological differences that make them more susceptible, the Reviewer commented: “Only asthmatics and ulcerative colitis patients were identified.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer agrees with the choice of unusually susceptible populations, the Reviewer commented: “YES. These two populations have either respiratory problems and gastrointestinal abnormal production of hydrogen sulfide. However, abnormal hydrogen sulfide metabolism in humans has been shown to induce numerous diseases, such as hypertension, inflammation, diabetes, atherosclerosis, etc. (see – [Wang R, Physiological implications of hydrogen sulfide – A whiff exploration that blossomed. *Physiol. Rev.* 92(2):791-896, 2012]. These populations will certainly be more susceptible to hydrogen sulfide exposure.”

RESPONSE: *The Reviewer’s statement that abnormal hydrogen sulfide metabolism has been shown to induce numerous diseases is referring to endogenous hydrogen sulfide. Although links between several diseases and alterations in endogenous hydrogen sulfide have been proposed, it is not clear how exogenous hydrogen sulfide would influence these associations particularly since many are due to low levels of endogenous hydrogen sulfide. Thus, this information was not added to the profile.*

COMMENT: Regarding the question of whether the management and treatment discussed in Section 3.11 is specific for the substance or is general for a class of substances, the Reviewer commented: “There are no specific methods available to reduce the absorption of hydrogen sulfide or carbonyl sulfide following exposure.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is any controversy associated with the treatment and whether it is well accepted, the Reviewer commented: “Not applicable.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there are any hazards associated with the treatment of populations that are unusually susceptible to the substances, the Reviewer commented: “Not applicable.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there are treatments available to prevent the specific substance from reaching the target organ, the Reviewer commented: “There are no known methods for reducing the body burden of hydrogen sulfide or carbonyl sulfide.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is any controversy associated with the treatment for preventing the substance from reaching the target organ, the Reviewer commented: “Not applicable.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there are any hazards associated with the treatment for preventing the substance from reaching the target organ in populations unusually susceptible to the substance, the Reviewer commented: “Not applicable”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there are treatments to prevent adverse effects as the substance is being eliminated from the major organs/tissues where it is stored, the Reviewer commented: “Not applicable.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there are treatments available to prevent the specific substance from reaching the target organ(s), the Reviewer commented: “The described methods are relatively specific for hydrogen sulfide. Direct administration of methemoglobin is another method that should have been included [Van de Louw A, Haouzi P. Inhibitory effects of hyperoxia and methemoglobinemia on H(2)S induced ventilatory stimulation in the rat. *Respir Physiol Neurobiol.* 2012 May 31; 181(3):326-34.]”

RESPONSE: *The findings in the Van de Louw and Haouzi (2012) study are consistent the human data presented in the profile. However, since very high doses of hydrogen sulfide was administered to rats via intravenous injection, its relevance to humans is not known and it was not added to the profile.*

COMMENT: Regarding the question of whether there is any controversy associated with the treatment for blocking the mechanism of toxic action, the Reviewer commented: “YES.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the treatment for blocking the mechanism of toxic action is well accepted, the Reviewer commented: “No.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer agrees with the conceptual approach of the experimental method for the treatment for blocking the mechanism of toxic action, the Reviewer commented: “YES, such as the oxygen therapy.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there are any hazards associated with the treatment for blocking the mechanism of toxic action in unusually susceptible populations, the Reviewer commented: “Not sure.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer knew of other studies which may fill a data gap, the Reviewer commented: “NO.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the data needs are presented in a neutral, non-judgmental fashion, the Reviewer commented: “There is no bias identified.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer agrees with the identified data needs, the Reviewer commented: “YES”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text indicates if any information on the data need exists, the Reviewer commented: “YES and I agree with the judgments.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text adequately justifies why further development of the data need would be desirable or justifies the inappropriateness of developing the data need at present, the Reviewer commented: “AGREE.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer is aware of any chemical and physical property information or values that are wrong or missing, the Reviewer commented: “NO.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether information is provided on the various forms of the substance, the Reviewer commented: “YES.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer is aware of any information on the production, import/export, use or disposal of the substance that is wrong or missing, the Reviewer commented: “NO.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text appropriately traced the substance from its point of release to the environment until it reaches the receptor population, the Reviewer commented: “YES.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text provides sufficient and technically sound information regarding the extent of occurrence at NPL sites, the Reviewer commented: “YES.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer knows of other relevant information, the Reviewer commented: “NO.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text covers pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media, the Reviewer commented: “Hydrogen sulfide release from “Chinese drywall” at a rate above the minimum reported threshold odor level (0.5 ppb) may be worth to mention [Wang R, Physiological implications of hydrogen sulfide – A whiff exploration that blossomed. *Physiol. Rev.* 92(2):791-896, 2012].”

RESPONSE: *The Wang (2012) paper notes “It was claimed that once installed, these [Chinese] drywalls released H₂S at a rate above the minimum reported threshold odor level (0.5 ppb)”;* however, a citation is not provided for this statement. Thus, this statement was not added to the profile. However, information from the Consumer Product Safety Commission on Chinese drywall was added to the profile.

COMMENT: Regarding the question of whether the text provides information on levels monitored or estimated in the environment (including background levels), that proper units are used for each medium, and the information includes the form of the substance measured, the Reviewer commented: YES.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether quality of the monitoring information is discussed, the Reviewer commented: YES.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text describes sources and pathways of exposure for the general population, occupations involved in the handling of the substance, and populations with potentially high exposures, the Reviewer commented: “YES.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of which additional populations should be included in this section, the Reviewer commented: “Please see my comments on Section 3.10.”

RESPONSE: *See the RESPONSE to the COMMENT on Section 3.10.*

COMMENT: Regarding the question of whether the data needs are presented in Section 6.8.1, the Reviewer commented: “The same answers I provided to Sections 3.12.2. and 3.12.3 apply here.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer is aware of additional analytical methods that should be added to the profile, the Reviewer commented: “The methods listed for environmental monitoring of hydrogen sulfide or carbonyl sulfide are adequate. Be aware that numerous methods have been developed and tested for measuring endogenous hydrogen sulfide levels in mammalian blood and various organs and cells [See - Wang R, Physiological implications of hydrogen sulfide – A whiff exploration that blossomed. *Physiol. Rev.* 92(2):791-896, 2012].”

RESPONSE: *The Wang (2012) paper discusses several analytical methods for detecting hydrogen sulfide levels that have been considered by researchers. However, most of these methods, such as nanotubes and sulfur ion-specific electrodes, have not been shown to accurately detect hydrogen sulfide levels in biological samples and may also include sulfides released from proteins during sample preparation. Wang (2012) notes that spectrophotometry-based methods is the choice method to determine tissue or cell production of H₂S and chromatography analysis of hydrogen sulfide is suitable for measurement of hydrogen sulfide in air samples. The toxicological profile discusses several gas chromatography methods as well as the use of potentiometry with ion-selective electrodes for measuring hydrogen sulfide in biological samples*

COMMENT: Regarding the question of whether the methods have been included for measuring key metabolites previously mentioned in the text, the Reviewer commented: “YES.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether unique issues related to sampling for the substance exist and have been adequately addressed in the text, the Reviewer commented: “Yes, When collecting and analyzing air samples, moisture level of the samples should be taken into consideration. See [Wondimu T, Wang R, Ross BM. A comparison of moisture removing strategies for breath samples spiked with trace concentrations of hydrogen sulphide. *Curr. Anal. Chem.* 9(2):312-318(7), 2013. DOI: 10.2174/157341113805218956].”

RESPONSE: *This paper did not contain additional information on analytical methods.*

COMMENT: Regarding the questions on Section 7.3.1 data needs, the Reviewer commented: “The same answers apply here.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the statement in Section 7.3.2 that no ongoing studies for hydrogen sulfide or carbonyl sulfide were identified, the Reviewer commented: “This statement needs to be revised to specify that “no environmental or occupational studies....” because numerous studies on the biological and medical effects of H₂S are ongoing.”

RESPONSE: *The statement was revised to clarify that no ongoing studies examining analytical methods were identified.*

COMMENT: Regarding the question of whether the Reviewer is aware of other regulations or guidelines that may be appropriate for Table 8-1, the Reviewer commented: “NO.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there are additional references that provide new data or if there are better studies than those already in the text, the Reviewer commented: “It is generally adequate. For additional references, I have mentioned them in the answers for previous sections.”

RESPONSE: *ATSDR has reviewed these studies and relevant data were added to the profile.*

COMMENT: Regarding the questions on the unpublished studies, the Reviewer commented: “Not applicable.”

RESPONSE: *No revisions were suggested.*