DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR TRICHLOROBENZENES

Agency for Toxic Substances and Disease Registry
U.S. Public Health Service

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Peer reviewers for the Toxicological Profile for Trichlorobenzenes were:

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ATSDR would like to thank these scientists for their review of the document. When the reviewer's suggestions were followed, or when other revisions obviated the need to respond, no further response is provided herein. Revisions that may have obviated the need to respond included sections that were rewritten, moved, or deleted. Some of the editorial and format suggestions could not be followed without changing ATSDR's established format. Additionally, several stylistic changes that were purely arbitrary were not incorporated. Other suggestions made by the reviewers that ATSDR decided not to follow are discussed below. In the discussion that follows, "PR" refers to the appropriate page of the assembled peer review document and "P" indicates a page number in the Draft of the profile.

Review comments provided by Richard J. Bull, Ph.D.

General Comments

PR5, first paragraph: Dr. Bull states that he found the content awkwardly placed and unnecessarily repetitive. He further states that the relatively exhaustive treatment of the toxicology data in the Summary of Health Effects within the section on Relevance to Public Health is much more exhaustive than necessary given the detailed descriptions of technical data in the Health Effects Chapter. In his view, the Relevance to Public Health chapter should contain clear and concise statements of judgments related to the probable public health impacts of exposures from the general and work environments as a way of bringing the bulletized treatment of the subject in the Public Health Assessment to a summary judgment of this information. Regarding Chapter 1, Dr. Bull believes that it creates more concern about the absence of human data on a particular aspect of the toxicity data than is warranted. Somewhere, there should be a statement that there is generally some substantial confidence that animal data are largely (if not always) predictive of adverse effects in humans and that confidence is increased when the animal data are extensive and of high quality and include consideration of likely human/animal differences based on experience with other related substances.

Response: The various sections of the profile have been written in accordance with ATSDR's guidance, but Dr. Bull's suggestions will be considered for future profiles. With regard to the animal data being predictive of adverse human health effects, a statement has been added in Section 1.5, HOW CAN TRICHLOROBENZENES AFFECT MY HEALTH?, indicating that based on results from studies in animals, it is reasonable to predict that humans exposed to high amounts of trichlorobenzenes may develop liver problems. A statement was also added indicating that laboratory animals have been exposed to considerably higher amounts of trichlorobenzenes than the amounts that humans can encounter in the environment, to put the animal data in context.

Specific Comments

PR7, bottom paragraph: The comment refers to Chapter 2, RELEVANCE TO PUBLIC HEALTH. Dr. Bull states that the applicability of animal data to health concerns in humans is difficult to deal within the context of the RELEVANCE TO PUBLIC HEALTH section without reference to the information provided in Chapter 3. Dr. Bull suggests that the order of the two chapters be reversed with the Health Effects section preceding the chapter dealing with Relevance to Public Health. He states that it is very difficult to put the various effects that are observed into context without the discussions in the HEALTH EFFECTS section. Therefore, it is premature to begin discussing these results in Chapter 2. Dr. Bull further notes that an additional awkwardness of Chapter 2 is that this is where Minimal Risk Levels (MRLs) are developed, which seems to demand some experimental detail to explain points of departure, etc. The reviewer thinks that the incorporation of the experimental detail in Chapter 2 almost guarantees that it will (*not?*) be understood by the lay person, if they even read it. In other words, the sequence is extremely awkward and inefficient. Dr. Bull strongly suggests that the order of Chapters 2 and 3 be reversed and all of the detail of toxicological studies (whether human or experimental animals) be provided in the chapter now labeled as Health Effects.

Response: Chapter 2 is written in accordance to ATSDR's guidance, which states that: "The presentation in this chapter should be sufficient to provide a public health official with information that would be germane to making an initial assessment of a particular environmental scenario, but should not contain a

level of detail that goes beyond this purpose. For a more detailed discussion, the reader can refer to the other chapters of the profile." Since the chapter is intended to provide the reader an executive summary-type overview of the nature, manufacture, uses, general population exposures, and health effects, references are not deemed necessary in the final versions, although references are in place during the developmental stages of the document. Although no changes were made, the reviewer's suggestions will be considered for future profiles.

PR8, P24, second paragraph: Dr. Bull disagrees with the rationale for dismissing the hepatic carcinomas in mice for derivation of a chronic-duration oral MRL for 1,2,4-trichlorobenzene.

Response: ATSDR is not dismissing the presence of hepatic carcinoma in mice. However, ATSDR does not derive MRLs based on carcinogenicity. This is stated in the first paragraph of Section 2.3, MINIMAL RISK LEVELS (MRLs), on page 13.

PR9, P48: The comment refers to the following statements under ocular effects: "Gage (1970) reported that lacrimation occurred in rats initially during the 6-hour exposures to 70 ppm 1,2,4-trichlorobenzene but not during exposures to 20 ppm 1,2,4-trichlorobenzene. Continuous exposure of male monkeys, rats, or rabbits to up to 100 ppm 1,2,4-trichlorobenzene vapors for 26 weeks did not induce significant gross or microscopic alterations in the eyes (Coate et al. 1977)." Dr. Bull states that the first sentence is inappropriately refuted by the lack of morphological lesions mentioned in the second sentence. Dr. Bull states that lacrimation does not lead to such lesions; in fact, it probably prevents the development of such lesions. Dr. Bull notes that lacrimation is reflecting the fact that irritation is occurring and is real despite the lack of overt pathology.

Response: There is no connection between the first and second sentence. The text is not classifying lacrimation as an adverse effect; it is just reporting that it occurred. In fact, it is not listed in the Levels of Significant Exposure (LSE) Table 3-1. Perhaps eye irritation, the cause of the lacrimation, should be listed in Table 3-1. ATSDR will consider doing this in the post-public version of the profile.

PR9, P48: The comment refers to endocrine effects. Dr. Bull states that it cannot be assumed that endocrine organs other than the adrenals were examined in the Sasmore et al. (1983) study just because the investigators mention that a total of 34 organs and tissues were examined.

Response: The text states that hemosiderosis was noted in the thyroid, not the adrenals; Dr. Bull probably misread the text. ATSDR believes that it is reasonable to assume that other endocrine glands were also examined even if the study was reported in 1983. For example, in the cancer bioassays in rats and mice (Moore 1994a, 1994b), 36 tissues and organs were examined and included the adrenals, thyroid/ parathyroid, and pituitary.

PR10, P49: The comment refers to metabolic effects. The text in question states that: "Intermittent exposure of rats to up to 130 ppm 1,3,5-trichlorobenzene vapors for 13 weeks did not significantly affect serum electrolyte levels or electrolyte balance (Sasmore et al. 1983)." Dr. Bull notes that it is not clear to him that the lack of effect on electrolyte levels provides assurance that there are no metabolic effects. He would label this section, Electrolyte Balance, or would simply say that no metabolic effects have been observed (or there are no data pertaining to Metabolic Effects). Dr. Bull states that there needs to be a definition of what constitutes a metabolic effect.

Response: According to ATSDR's guidance, metabolic effects include disturbances in acid-base balance. Also included are water depletion and water excess, alterations in serum electrolytes (i.e., Na^{+}, K^{+}, Cl^{-}, Ca^{2+}, Mg^{2+}, PO_4^{-3}), glucose, ketone bodies, pH, etc.

PR10, P51: Dr. Bull disagrees with the following statement: "No studies were located regarding developmental effects and cancer in humans or animals after inhalation exposure to trichlorobenzenes." He claims that it is not consistent with reports of a two-generation study (by the oral route) on page 18 or the description of hepatocellular carcinomas in mice (also administered orally) (page 24). He feels that there should be some reference to the appropriate section where the oral route is discussed.

Response: The statement in question is accurate. It does not indicate that inhalation exposure would not induce development effects or cancer. It merely states that no studies have been conducted; whether or not effects would occur is unknown. Cross-referencing to other routes of exposure for every end point that has not been examined by a specific route of exposure would add an enormous amount of text. It is assumed that the reader of Chapter 3 has read Section 3.2, DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE, which tells the reader that the information in this section is organized first by route of exposure and then by health effect.

PR10, P69: The comment refers to Figure 3-3, Levels of Significant Exposure to 1,2,4-Trichlorobenzene. Dr. Bull notes that the differences in no-observed-adverse-effect levels (NOAELs) for liver effects in rats and mice in the studies by Moore (1994a, 1994b) are trivial and do not support earlier statements in the profile indicating that the mice data would not be used for MRL derivation because liver lesions appeared at the same dose level as liver cancer.

Response: Dr. Bull is correct in that the NOAELs are similar, 19.4 mg/kg/day in rats and 21 mg/kg/day in mice. The lowest-observed-adverse-effect levels (LOAELs) were 66.5 mg/kg/day in rats and 100.6 mg/kg/day in mice; this 40% percent difference cannot be appreciated in the figure because doses are plotted in a logarithmic scale. However, as mentioned earlier, the main reason why mice were not considered for MRL derivation was that ATSDR does not derive MRLs based on neoplastic effects or precancerous lesions.

PR12, LSE figures: Dr. Bull states that the LSE figures are not clear. He indicates that he was not able to locate a definition of what the numbers represent in the designation of significant exposures.

Response: The number represents the corresponding entry in the LSE figure. This is mentioned in footnote a of the corresponding LSE table and is also explained in Appendix B, USER'S GUIDE.

PR13: The comment refers to the question of whether or not major limitations of studies are adequately and accurately discussed in the text of Chapter 3. Dr. Bull states that the text should discuss why the carcinogenicity data in mice (Moore 1994b) were not used in the development of MRLs.

Response: As previously indicated, ATSDR does not derive MRLs based on cancer. This is mentioned at the beginning of Section 2.3, MINIMAL RISK LEVELS (MRLs), "MRLs are based on noncancerous health effects only and do not consider carcinogenic effects."

PR13: The comment also refers to the question of whether or not major limitations of studies are adequately and accurately discussed in the text of Chapter 3. Dr. Bull notes that the hematological data should not be dismissed just because the changes still fall within the normal range. He states that a more

appropriate argument would be that the effects are not critical effects as they occur at much higher doses than those of studies used in the development of MRLs.

Response: ATSDR did not intend to dismiss the hematological data. The issue is whether the mean values that result after exposure to the chemical should be considered NOAELs or LOAELs given that they are within the normal range established for unexposed male or female animals from the same age and strain.

PR15, P125: The comment refers to Section 3.5.1, Pharmacokinetic Mechanisms. Dr. Bull states that the discussion of pharmacokinetic mechanisms is a waste of paper. He adds that there are not sufficient data to speak meaningfully to this point. Dr. Bull has the same comment for Section 3.4.5, Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models. Dr. Bull also notes that the discussion of changes in drug metabolism enzymes in this section is probably more relevant to mechanisms of toxicity than pharmacokinetics. Dr. Bull also states that there are no data provided that indicate that changes in P450 or glucuronyltransferase have substantive effects of the pharmacokinetics of trichlorobenzenes.

Response: The text in Section 3.4.5, Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models is boilerplate text that appears in all Toxicological Profiles; it is not specific to trichlorobenzenes. If there had been models for trichlorobenzenes, they would have been discussed following the boilerplate text. ATSDR agrees with the reviewer in that there are limited data regarding pharmacokinetic mechanisms for trichlorobenzenes. However, that does not mean that the limited data should not be discussed. The discussion of the role of metabolism in the toxicity of trichlorobenzenes could be discussed in either section, but ATSDR will consider moving this information to Section 3.5.2, Mechanisms of Toxicity, in the post-public version of the profile.

PR16, P135: The comment refers to Section 3.11.3, Interfering with the Mechanism of Action for Toxic Effects. Dr. Bull specifically refers to the following sentence: “Since 2,3,5-trichlorophenyl methyl sulfone results from the conjugation of glutathione with a 1,2,4-trichlorobenzene hydroxyl derivative, theoretically, reducing glutathione levels would prevent, at least in part, the effects of 1,2,4-trichlorobenzene.” The reviewer states that the suggestion of reducing systemic glutathione concentrations is a very dangerous intervention. Dr. Bull suggests that this not be included in the profile because somebody may get the idea that this is a benign intervention.

Response: The sentence in question was not removed, but text was added indicating that reducing glutathione levels is not an established procedure that may have unintended health consequences.

PR16, P135: The comment refers to Section 3.12, ADEQUACY OF THE DATABASE. Dr. Bull states that it is unlikely that all of the data needs identified in this section will be addressed with new data. He further notes that conducting many of the identified studies would be a waste of time considering what is already known about these compounds.

Response: Pertinent information can be found in the introduction to Section 3.12 and in Section 3.12.1. As indicated in Section 3.12.1, ATSDR defines a data gap as any substance-specific information missing from the scientific literature. At the same time, ATSDR notes that not all data needs discussed in this section must be filled. The identified data need will be evaluated and prioritized, and a substance-specific agenda will be proposed. Specifically, lack of MRLs for a particular route (inhalation or oral) and exposure durations constitute an automatic data need for studies aimed at obtaining appropriate information. Dr. Bull should note that there is no call for additional studies on trichlorobenzenes for which MRLs are available. Even for trichlorobenzenes for which MRLs are not available (i.e., acute-,

intermediate-, and chronic-duration inhalation exposure), the text suggests that factors need to be considered before a decision recommending additional studies is made.

All other comments provided by Dr. Bull were addressed as suggested.

Review comments provided by Ralph L. Kodell, Ph.D.

PR33, P112: The comment refers to Section 3.4.5, Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models. Dr. Kodell states the he could not find a discussion of PBPK models for trichlorobenzenes. The reviewer notes that he does not know that this is because no such models exist, or if it means that the text containing such discussion has been inadvertently left out.

Response: Page 125 clearly states that no PBPK/PD models have been developed for trichlorobenzenes.

PR34, P133: The comment refers to Section 3.8.2, Biomarkers Used to Characterize Effects Caused by Trichlorobenzenes and specifically to the following sentence: "Based on the existing information regarding the effects of trichlorobenzenes in animals, it is difficult to envision a health condition that could be attributed solely to exposure to trichlorobenzenes." Dr. Kodell thinks that it would be better to simply state that no specific biomarker was found because there is limited information.

Response: ATSDR disagrees; the sentence in question is accurate. Trichlorobenzenes affected mainly the liver in animal studies and the specific effects observed could be induced by many different chemicals.

All other comments provided by Dr. Kodell were addressed as suggested.

Review comments provided by James E. Klaunig, Ph.D.

Dr. Klaunig's comments did not necessitate responses.