

**Disposition of Peer Review Comments for
Toxicological Profile for
Trichloroethylene**

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Responses to comments that were identified by location in the pre-public draft 3 of the Toxicological Profile for Trichloroethylene that was provided to the reviewers by ATSDR.

Comments that were purely stylistic in nature were addressed at the discretion of ATSDR and do not appear in this formal disposition. Comments that warranted a formal response are listed below.

Comments provided by Reviewer #1:

COMMENT: P3 L6: It is not accurate to state that trichloroethylene (TCE) can “build up” in your body. Numerous studies show this not the case with TCE-exposed employees over a 5-day work week.

RESPONSE: *The statement was revised to indicate that when the body absorbs more trichloroethylene than it can break down quickly, some of it and its breakdown products may be stored in body fat, but once exposure ceases, these compounds quickly leave the fat.*

COMMENT: P4 L4: It should be emphasized that long-term, high-level TCE exposures are required to cause kidney cancer in humans or cancers in mice or rats.

RESPONSE: *The section was revised to note that the cancer effects in animals were observed at relatively high exposure levels.*

COMMENT: P5 L7: It should be noted that other studies of TCE in animals have shown no such effects in the various organ systems.

RESPONSE: *The requested addition was not made because the various developmental toxicity studies are difficult to compare, in part because what appear to be relatively sensitive end points in some studies were not assessed in other studies.*

COMMENT: P6 L8: Tests to detect any but a very high TCE exposure should be conducted within hours, not days of exposure.

RESPONSE: *The suggested revision was made.*

COMMENT: P8 NIOSH: The NIOSH REL of 2 ppm is intended as an occupational exposure limit, not a ceiling for its use as an anesthetic.

RESPONSE: *No change was made because the NIOSH regulation is worded exactly as stated in Appendix C of the NIOSH Pocket Guide.*

COMMENT: P11 L11, 13, 14 & 16: See suggested editorial changes.

RESPONSE: *The suggested revisions were made.*

COMMENT: P11 L25: What is “general motor restlessness”? Do you mean the stimulation that occurs in the initial phase of anesthesia?

RESPONSE: *The phrase “general motor restlessness” was deleted.*

COMMENT: P13 L8: It should also be noted that the NRC (2009) concluded “There continues to be inadequate/insufficient information to determine whether an association exists between chronic exposure to TCE and non-Hodgkin’s lymphoma. This categorization means that there are inadequate data to implicate TCE as a cause of non-Hodgkin’s lymphoma in humans. The NRC concluded “There continues to be inadequate/insufficient evidence to determine whether an association exists between exposure to TCE and hepatobiliary cancer.

RESPONSE: *The conclusions of NRC (2006, 2009) and the NTP RoC 12th edition (2012) were added to the discussion of trichloroethylene and NHL and hepatobiliary cancer.*

COMMENT: P14 L12: It should be pointed out to readers that the rodent bioassays of TCE have involved very high dose, chronic (maximally-tolerated) exposures.

RESPONSE: *The suggested statement was added.*

COMMENT: P15 L1-7: The discussion of TCE’s ability to injure the liver should be tempered. Most people exposed occupationally to TCE show little if any evidence of liver damage. Very high doses are necessary to damage the liver of laboratory animals or humans.

RESPONSE: *The following statement was added: “Where liver effects were observed, exposure levels were likely higher than present-day occupational exposure limits.”*

COMMENT: P22 L20-23: I am disappointed that ATSDR has merely adopted the chronic reference dose of the EPA (2011) as its chronic- and intermediate-duration MRL for TCE, rather than conducting its own hazard and risk assessments. It is understandable that federal agencies may want to seek consistency, but the EPA (under the influence of a long-entrenched conservative group) adopted an ultraconservative RfD and RfC that go far beyond what is necessary to protect the general populace. TCE is one of the most widely-studied and understood of all chemicals in laboratory animals and humans. Hundreds of thousands of people have been exposed to TCE and its metabolites in clinical, occupational and environmental settings for over 90 years. The preponderance of this experience reveals that TCE is simply not very toxic or carcinogenic. Klaassen and Plaa (1966), for example, had to give mice 1.6 ml TCE/kg, a near-lethal dose, to produce modest increases in serum enzyme activity (i.e., hepatocellular injury). Very high doses are required to produce adverse effects. It is astounding that EPA would arrive at a RfD as low as 0.0005 mg/kg/day for noncancer effects, in an apparent effort to match values based on their cancer risk assessments.

The NRC (2009) utilized a reasonable approach in its hazard assessment of TCE-contaminated drinking water at Camp Lejeune, NC, with which estimated human doses were compared with a range of lowest observed adverse effect levels (LOAELs) in animal studies. LOAELs of 1,000 mg/kg/day (kidney cancer in rats), 250 mg/kg/day (kidney toxicity in rats) and 22 mg/kg/day (immunosuppression in a sensitive mouse strain) provided a realistic oral dosage range for a number of effects. Upper-end estimates of child

and adult TCE exposures were typically orders of magnitude lower than the lowest LOAEL. The use of rodent data provided an additional margin of safety, as mice and rats are widely recognized to be more susceptible to TCE toxicity than humans. I would certainly prefer that ATSDR's qualified staff and contractors conduct an independent assessment, select key studies and end-points, and reach their own conclusions about MRLs that are protective, yet grounded in reality.

In contrast to NTP (2009), the EPA (2011) chose to utilize results of three studies of biological effects of unknown toxicological significance and/or relevance to humans. This is the agency's standard policy—select the study or studies that yield the lowest number—focus on the most sensitive index in the most sensitive strain of the most sensitive species of animal, irregardless of dose, dosage regime or human relevance. As noted above, 22 mg/kg/day was the lowest LOAEL considered by NRC (2009). This dosage level in drinking water produced immunosuppression in a sensitive strain of mouse (Sanders et al. 1982). As would be expected, EPA (2011) chose an even lower LOAEL (0.37 mg/kg/day) for an effect of even more uncertain toxicological significance and human relevance [i.e., developmental immunological changes in a sensitive mouse strain (Peden-Adams et al. 2006)]. Two more studies were selected that yielded similar RfD values. In the first, by the same research group (Keil et al. 2009) revealed decreased thymus weight in female B6C3F1 mice consuming TCE in their water for 30 weeks. In the second study, Johnson et al. (2003) reported heart malformations in offspring of rats exposed to TCE during pregnancy. This investigation was fraught with problems and should therefore not be used as a key study. The EPA (2011) acknowledged the study “has important limitations,” but felt “the overall weight of evidence supported an effect of TCE on cardiac development.” This is a surprising conclusion because: (a) all of the positive studies of TCE-induced cardiac anomalies in mammals were conducted in the same laboratory; (b) a much more rigorous and well-designed investigation of TCE, trichloroacetic acid and dichloroacetic acid by Fisher et al. (2001) failed to reveal cardiac malformations in rat pups; and (c) other groups of researchers (e.g., Schwetz et al. 1975, Dorfmueller et al. 1979, Carney et al. 2006) found no increase in such cardiac anomalies.

With the adoption of the 2005 Guidelines for Carcinogen Risk Assessment, toxicologists hoped that scientific judgment and weight of scientific evidence would become the key determinants in risk assessments by state and federal regulatory agencies. This has definitely not been the case with this EPA IRIS document. This is unfortunate, in view of the wealth of knowledge about TCE.”

RESPONSE: *ATSDR extensively evaluated all available human and animal data regarding health effects associated with exposure to trichloroethylene. ATSDR independently came to the same conclusions as EPA regarding adequacy of the studies and reported effect levels. The conservative approach was taken because ATSDR determined that there was sufficient information to consider immunological and developmental end points particularly sensitive targets of trichloroethylene toxicity. Human relevance was considered in the absence of convincing evidence to the contrary. Regarding the comment on the 2005 Guidelines for Carcinogen Risk Assessment, ATSDR does not conduct risk assessments for cancer end points, but relies on other experts for these assessments. EPA does not stand alone in considering trichloroethylene to be a human carcinogen, or at least a suspected or possible human carcinogen.*

COMMENT: P25 L14-19: In view of the wealth of laboratory animal and human data, why did ATSDR not derive an acute-duration oral RfD for TCE? This determination should not be limited to developmental effects, a repetitive-exposure phenomenon.

RESPONSE: *ATSDR did not derive an acute-duration oral MRL for trichloroethylene because the developmental effects in animals were observed following repeated exposure for more than 14 days, but may have resulted from exposures for 14 days or less as well, in which case the intermediate-duration oral MRL based on developmental effects is protective of acute-duration oral exposure as well.*

COMMENT: P25 L25-26 and P26 L31-33: Again, it is regrettable the ATSDR did not carry out its own, independent hazard and risk assessments of inhaled TCE. This is particularly important, in view of the conservative, old-guard regulatory policy-bound history of the group within EPA that generated the 2011 IRIS document. I find it difficult to believe that EPA would use PBPK modeling to extrapolate from the same oral data (as used for RfD calculations) to derive a RfC. There is a wealth of published information about the health effects of inhaled TCE in laboratory animals and humans. The EPA apparently found it necessary to utilize the same limited data base, in order to generate more “vanishing-low” guideline levels. EPA rationalizes its exercise by stating that it lead to a more “robust” RfD that was supported by concordance of multiple studies and effects. This outcome is not too surprising in view of “cherry picking” of end-points and studies, coupled with multiple worst case scenario assumptions to obtain the desired results.

RESPONSE: *ATSDR extensively evaluated all available human and animal data regarding health effects associated with exposure to trichloroethylene. ATSDR independently came to the same conclusions as EPA regarding adequacy of the studies and reported effect levels. The conservative approach was taken because ATSDR determined that there was sufficient information to consider immunological and developmental end points particularly sensitive targets of trichloroethylene toxicity. Human relevance was considered in the absence of convincing evidence to the contrary.*

COMMENT: P31 L25-27: The report of Sidorin et al. (1992) is not available and probably unreliable. It is very unlikely that such low TCE concentrations would adversely affect the heart.

RESPONSE: *The statement and reference were deleted from the profile.*

COMMENT: P41 L20-23: Are altered cytokine levels indicative of an altered immune system or inflammation?

RESPONSE: *The word “inflammatory” was deleted; only one of the altered cytokines is considered to be active in regulation of inflammation.*

COMMENT: P55 L31: An account of the apparent role of high-dose, recurring renal cell injury/necrosis and regenerative hyperplasia in renal cell carcinoma should be included here or other appropriate place in the document. Bruning et al. (1996, 1999) observed that every TCE-exposed kidney cancer patient in two study groups in Germany had chronic tubular toxicity. Bolt et al. (2004) reported increased urinary α 1-microglobulin in trichloroethylene-exposed renal cancer patients compared to renal cancer patients and controls without trichloroethylene exposure. These patients had been subjected for years to such high TCE exposures that they periodically had to stop working due to headache and dizziness, and go outside to breathe fresh air. Bruning and Bolt (2000) noted that reactive metabolites of the glutathione pathway are genotoxic, but concluded that development of a malignant kidney tumor required a long-term promotional event in response to ongoing destruction of tubular cells. Thus, TCE-induced kidney cancer appears to be a threshold response, as reflected by the very high and prolonged exposure required to cause tumors in male rats and humans (Goeptar et al., 1995; Dekant, 2001; Bolt, 2003).

RESPONSE: *The requested discussion was added to the profile.*

COMMENT: P57 L20-21: The incidence of Leydig cell tumors varies from just 1-5% in Sprague-Dawley rats to nearly 100% in F344 rats. Almost all of these neoplasms are benign and occur in older rats (Cook et al. 1999)."

RESPONSE: *Incidence data were added to the statement regarding Leydig cell tumors in trichloroethylene-exposed rats. However, the toxicological significance to humans is not clear and it is not considered appropriate to speculate based on results of available studies.*

COMMENT: P58 L8-10: Somewhere in the document there should be an overview of Clara cells, their susceptibility to VOC metabolites, their potential role in pulmonary tumors, and their prevalence in mice versus rats and humans.

RESPONSE: *Descriptive text regarding Clara cells was added to appropriate sections of Chapter 3.*

COMMENT: P63 L17-20: Were the "liver ailments" reported by Davis et al. (2005) self-reported or diagnosed by a clinician?

RESPONSE: *The liver ailments were clinically diagnosed; the profile was revised accordingly.*

COMMENT: P68: Were some of the reductions in body weight gain in TCE-treated animals attributed to decreased food and/or water consumption? The higher oral doses typically cause prolonged CNS depression and loss of appetite.

RESPONSE: *Water and food consumption statements were added to the profile.*

P70 L5: Does the information in line 5 pertain only to male mice?

RESPONSE: *The summary of results from Keil et al. (2009) was revised; the study included only female mice.*

COMMENT: P70 L2-16: What is the toxicological significance of the occasional TCE-induced changes in immunological parameters in the study of Keil et al. (2009), if they are not indicative of acceleration of the onset of autoimmune disease? Were any of the changes dose-dependent? What about the decreased spleen weight in females, upon which the EPA bases its RfD? Were any effects indicative of immune suppression?

RESPONSE: *The summary of this study was revised and includes explanatory information. EPA used decreased thymus weight as the basis for risk assessment; spleen weight of trichloroethylene-treated mice was not significantly different from controls.*

COMMENT: P70 L22-24: Did Griffin et al. (2000b) see significant increases in antinuclear antibodies or total serum immunoglobulins at the lower TCE concentrations (0.1 and 0.5 mg/ml)? Were the increases in these indices at the higher concentrations (2.5 and 5.0 mg/kg) (Griffin et al. 2000a) dose-dependent?

RESPONSE: *Additional information was incorporated into the summary of the study.*

COMMENT: P70 L27-32: Why are the results of the seriously-flawed studies of Dawson et al. (1993) and Johnson et al. (1999, 2003) described in 1½ pages, when those of the more robust, but negative study of Fisher et al. (2001) are described in just 5½ lines. The parameters assessed by Fisher et al. (2001) should be included, as should the fact that two potentially active metabolites (di- and trichloroacetic acid) were also evaluated.

RESPONSE: *The suggested additions to the results of Fisher et al. (2001) were made.*

COMMENT: P80 L1-13, L15-28: The document's authors, here and in the rest of the Health Effects section, are accurate and thorough in their descriptions of the experimental designs and findings of many different investigations. Seldom, however, do they mention the toxicological significance of findings, strengths, limitations, confounding factors, or relevance to humans. This need not be done for all studies, but should be included for key studies, as well as supporting and any important contradictory studies. A summary discussion of weight of evidence would be very helpful, as would be scientific interpretations and judgments relevant to the choice of key studies and derivation of MRLs. As the Health Effects section is now written, it is a comprehensive, detailed coverage of toxicological studies and data. Rationale, discussion and conclusions about major health effects of concern are lacking. There is a major disconnect between the long, detailed coverage of adverse health effects in the current document and the blanket adoption of EPA's RfD and its rationalizations. ... Again, this reader is left wondering whether any of these immunological effects, individually or collectively, is/are toxicologically significant or relevant to humans. These are very important considerations, as this is one of the key studies relied upon by EPA (2011).

RESPONSE: *Information was added to identify selected study results as a partial basis for MRLs and it was noted that the effects in animals are considered relevant to humans in the absence of data to indicate otherwise.*

COMMENT: P80 L30-33: Could reduced rearing be a merely a manifestation of CNS depression? Was the effect dose-dependent?

RESPONSE: *Text was added to indicate that the effect did not appear to be dose-dependent and that there was no effect on locomotion or total activity.*

COMMENT: P81 L9-10: Does decreased myelination match increased spatial navigation?

RESPONSE: *Possibly, according to the study authors. A statement to that effect was added to the profile.*

COMMENT: P84 L19: A paragraph summarizing some of the limitations of NCI/NTP bioassays should be added. Gavage dosing is quite different from repetitive ingestion of relatively small amounts of TCE in drinking water. Chronic administration of very high, maximally-tolerated doses that result in chronic inflammation, cell death, regenerative proliferation, and overwhelming of defense and repair mechanisms raises serious questions about the relevance of experimental findings. The relevance of

findings in B6C3F1 mice [with their high spontaneous liver tumor incidence (Haseman et al. 1999) and high rates of metabolic activation of TCE] to humans are also important topics to address.

RESPONSE: *Some of the limitations of the NCI/NTP bioassays and other studies were already presented in the toxicological profile. Additional text was added to note “high dose levels.” Gavage dosing is different from exposure via drinking water or food, but treatment-related tumor induction was noted, albeit at high doses. The high rates of metabolic activation of trichloroethylene in mice are discussed in the Mechanisms of Action section.*

COMMENT: P95 L15-18: It should be pointed out here and elsewhere that mice metabolically activate substantially more TCE than do rats (or humans), and are thus more susceptible to TCE-induced cellular injury and tumor induction.

RESPONSE: *The suggested addition was made.*

COMMENT: P97 L11-12: TCE is not rapidly absorbed through the skin. Dermal absorption of TCE is relatively slow and incomplete.

RESPONSE: *No change was made. Although the proportion of dermally-applied trichloroethylene that is absorbed is small relative to other exposure routes, the absorption that occurs is relatively rapid.*

COMMENT: P97 L14: Delete “may be.” Extensive research show that most all effects, other than CNS depression, are produced by TCE’s metabolites.

RESPONSE: *The suggested deletion was made.*

COMMENT: P98 L18: PBPK models are used to predict blood and target organ dosimetry. Pharmacodynamic models are used to predict biological/toxicological effects.

RESPONSE: *The statement was revised to indicate that the PBPK model predictions regarding target organ dosimetry have been accurate. Note: The Reviewer likely inadvertently associated the statement with page 98 of the profile, rather than page 97 where the statement was made.*

COMMENT: P102 L12-15: It should be pointed out here that the higher blood:air partition coefficients of mice and rats (versus humans) are an important determinant of systemic uptake of inhaled TCE. This, coupled with rodents’ higher alveolar ventilation rate, pulmonary (blood) perfusion rate and TCE metabolic rate, result in rodents receiving substantially greater systemic doses than do humans upon equivalent inhalation exposures.

RESPONSE: *A statement was added to indicate that trichloroethylene is more readily absorbed by the blood of rats and mice than humans.*

COMMENT: P105 L3-5: Trichloroethylene oxide (an epoxide) has not been detected in human systems. It was found only in phenobarbital-pretreated rat liver microsomes by Guengerich and his colleagues.

RESPONSE: *The section was revised to indicate that the pathway is proposed and that the oxide has been detected in rat liver microsomes.*

COMMENT: P109 L30-34: It should be recognized that Clara cells are quite common in mouse airways, unusual in rats and rare in humans.

RESPONSE: *The suggested addition was made.*

COMMENT: P110 L9: The report by NRC (2009) should also be cited. TCE metabolism, its relationship to toxicity and carcinogenicity, and factors that influence TCE metabolism are covered in Chapters 3 and 4.

RESPONSE: *The requested addition of the NRC (2009) report to the citations was made.*

COMMENT: P112 L5-6: It is important for readers to understand that N-acetylation of DCVC is a detoxification process.

RESPONSE: *The text was revised accordingly.*

COMMENT: P112 L12-14: An additional paragraph describing interspecies differences in the GSH pathway should be composed, in order to appreciate the relevance of animal studies to humans. Humans and rats are similar qualitatively, but not quantitatively in metabolic activation of TCE via this pathway. Bernauer et al. (1996) exposed rats and humans to TCE vapor levels of up to 160 ppm for 6 hours. The rats excreted 8 times more N-acetyl-DCVC than the human volunteers at each exposure level. This is attributable both to higher systemic uptake of inhaled TCE and greater extent of GSH-mediated metabolism by rats. Volkel et al. (1998) found substantially higher urinary excretion of trichloroacetic acid, N-acetyl-TCVC and dichloroacetic acid in the urine of rats than in the urine of humans subjected to identical perchloroethylene inhalation regimens.

Metabolic activation of DCVC to chlorothioketene was shown to occur 11 times more rapidly in rats than in humans (Green et al., 1997). Lash et al. (1990) and Cooper (1994) reported 10 times higher activity of cysteine β -lyase activity in rat than in human kidney. Green et al. (1990) observed that β -lyase-dependent metabolism of TCVC in kidney cytosol is more rapid and efficient than in rats than in either mice or humans. In addition, Lash et al. (2001) found cultured rat kidney cells to be more sensitive to DCVC than human kidney cells.

RESPONSE: *Text was added to appropriate sections of metabolism to indicate metabolic differences between humans and rodents. The study of Bernauer et al. (1996) was consulted; the results indicate that humans excreted more than 100 times the amount of trichloroethylene and TCA than rats and more than 30 times the amount of N-acetyl-DCVC than rats. These results indicate higher systemic uptake of inhaled trichloroethylene and greater extent of GSH-mediated metabolism in humans. A statement was added regarding relative rates of β -lyase-dependent metabolism of TCVC in kidney of rats, mice, and humans.*

COMMENT: P112 L31-32: Although the proportional flux of TCE through the P450 and GSH pathways varies from one study to another, the GSH pathway is of minor importance quantitatively.

RESPONSE: *The statement was revised to note that the GSH-dependent pathway is quantitatively minor.*

COMMENT: P149 L31-34: Undiluted or concentrated organic solvents such as TCE undoubtedly enhance their absorption by disrupting membrane lipids in skin. This is not the mechanism of absorption of the low concentrations found in most occupational and environmental settings. As TCE is a small, uncharged lipophilic molecule, it merely diffuses through membranes from an area of high to low concentration.

RESPONSE: *A statement was added to indicate diffusion is the likely mechanism of absorption from the skin at occupational and environmental exposure levels.*

COMMENT: P150 L1-7: See recommended editorial changes in text.

RESPONSE: *Suggested changes that were not purely stylistic were made.*

COMMENT: P150 L16: It is incorrectly stated here that there is no evidence for reabsorption of TCE metabolites. Stenner et al. (1997) demonstrated in rats that reabsorbed trichloroethanol (from the gut) served as a major source of trichloroacetic acid in the blood.

RESPONSE: *The statement was revised to note that there is no evidence of re-absorption from the kidney.*

COMMENT: P151 L24-34, P153 L1-6: A great deal more attention (and coverage in this Toxicological Profile) should be devoted to the large body of knowledge about interspecies differences in TCE toxicokinetics and mechanisms of action (e.g., role of PPAR α in hepatic tumors in mice versus humans). TCE metabolic activation and inactivation pathways appear to be quite similar qualitatively, but not quantitatively in rodents and humans. The Profile's authors have done a good job describing toxicokinetic differences between mice and rats. The authors also need to do so for rodents versus humans, in order to assess the relevance of findings in key and supporting animal studies to humans for the hazard and risk assessments. The authors are directed to chapters 4 and 5 of NRC (2009) for a comprehensive discussion of this important subject, as well as pertinent information on potentially sensitive subpopulations and factors (age, sex, pregnancy, genetics, lifestyle, diseases) that may impact susceptibility.

There have literally been hundreds of definitive studies of mechanisms, or modes of action of TCE and closely-related halocarbons. Thus, a great deal of pertinent information exists, from which to make reasonable, scientifically-based judgments about the weight of evidence on mechanisms. Nevertheless, the EPA (2011) chooses to invoke the use of the default assumption of unknown mechanism(s), which in turn triggers the use of the most conservative risk assessment practices. Yet again, regulatory policy and entrenched agency conservatism trump science.

For example, In lines 33 & 34, chloral hydrate's (CH's) potential mechanisms of action are said to be mutagenicity, DNA damage and micronuclei induction. In contrast, Bull (2000) concluded "there is no

evidence which clearly associates a genotoxic effect of TCE or its hepatocarcinogenic metabolites with the induction of liver cancer.” Moore and Harrington Brock (2000), in their review paper, concluded that “it is unlikely that TCE/metabolites would induce tumors in any organ through mutagenicity/genotoxicity at exposure levels relevant to humans.” CH is a sedative-hypnotic that is still widely used in medical and dental procedures, particularly in infants and children. In the report of a large epidemiological study of clinical use of CH, Haselkorn et al. (2006) concluded there was no persuasive evidence of a causal relationship between CH and cancer in humans.

The second proposed potential mechanism of action is PPAR α activation, which causes alterations in cell proliferation, apoptosis and clonal expansion of initiated cells. Male wild-type mice dosed orally with TCE exhibited hepatocyte proliferation and changes in expression of genes involved in cell growth (Laughter et al. 2004). PPAR α -null mice were refractory to those effects, which are associated with carcinogenesis. The level of PPAR α in human cells is ~10% of that in rodent liver (Lai, 2004). Mice expressing human PPAR α fail to show increases in markers of cell proliferation and are resistant to liver cancer if treated with PPAR α agonists (Yang et al., 2008). Most authorities in the field concur that it is unlikely chemicals that induce peroxisomes (and PPAR α) pose a liver cancer risk to humans (Klaunig et al., 2007). The NRC (2006) concluded that the PPAR α mode of action for liver cancer in mice is not relevant to humans.

RESPONSE: *The discussion of mechanisms of action for hepatic effects was revised to include additional proposed mode-of-action information for trichloroethylene-induced liver tumors and human relevance. Also, the reader is pointed to additional sources of mechanisms of action data. It should be noted that NTP (2012) has initiated a comprehensive evaluation of the carcinogenicity of trichloroethylene due to a lack of convincing evidence regarding mode of action and human relevance.*

COMMENT: P153 L23-32: It is implied in lines 31 & 32 that cytotoxicity and compensatory cellular proliferation is “an additional potential mode of action.” As I have discussed previously in my review, there is compelling evidence that the recurring proliferation results in clonal expansion of initiated cells. Thus, kidney cytotoxicity and mutagenicity appears to be a dual, interdependent mechanism of renal carcinogenicity operative under chronic, extreme TCE exposure conditions.

RESPONSE: *The text was revised to include the interdependent mechanism.*

COMMENT: P155 L26-27: I did not find a discussion of differences in murine and human lung morphology in Section 3.4.2.2. There are important differences that should be described.

RESPONSE: *Discussion of factors influencing the absorption of trichloroethylene from the rat, mouse, and human lung was added to Section 3.4.1.1.*

COMMENT: P155 L29-34: As I have discussed previously, a number of authorities agree that there is little risk of chloral mutagenicity at occupational or environmental exposure levels. As mentioned, Haselkorn et al. (2006) found no evidence of a causal relationship between clinical treatment with chloral hydrate and liver, lung or kidney cancer in human patients.

RESPONSE: *This section was completely re-written. It no longer includes discussion of chloral hydrate mutagenicity as previously discussed.*

COMMENT: P157 L11: It is very doubtful that TCE would be an endocrine modulator or disruptor. As TCE does not resemble sex or other hormones structurally, it is unlikely it would act as a partial agonist or antagonist.

RESPONSE: *A statement was added to make this point.*

COMMENT: P158 L5-8: Two other pertinent reviews of the relative susceptibility of adults and children to drugs and other chemicals were published by two members of the committee that wrote the 1993 NRC report. These reviews were by Bruckner and Weil (1999) and Bruckner (2000). The latter paper emphasizes age-dependent anatomical, physiological and biochemical factors that can impact the toxicokinetics of chemicals such as TCE.

RESPONSE: *Added Bruckner and Weil (1999) and Bruckner (2000) to the string of references and to Chapter 9.*

COMMENT: P159 L2-6: The discussion of the developing blood:brain barrier and its potential role in chemical toxicology is well written. It is very unlikely to play a role in neurological actions of TCE, as TCE readily diffuses across membrane barriers, irrespective of their stage of maturation. I am not aware of the involvement of any membrane transport systems in TCE movement, although it is conceivable some of its metabolites could be substrates for P-glycoprotein or other transporters.

Elbarbry et al. (2007) and de Zwart et al. (2008) described the ontogeny of hepatic cytochrome P4502E1 (CYP2E1) in rats. Johnsrud et al. (2003) described the ontogeny of hepatic CYP2E1 in humans. CYP2E1, of course, is the primary P450 isozyme responsible for metabolic activation of TCE. Neonates have relatively low levels of enzymes that metabolically activate TCE, and thus should be less susceptible to effects of TCE metabolites than children and adults, Reimche et al. (1989) determined the half-lives of chloral hydrate in premature newborns, full-term newborns and young children to be 39.8, 27.8 and 9.7 hours, respectively. Greater metabolic clearance of TCE and many other drugs in children 1-6 years old than in adults is apparently due to children's larger liver volume and higher blood flow rate (Murry et al., 2002), rather than higher CYP2E1 activity (Blanco et al., 2000). Thus, children may be more susceptible to TCE metabolite toxicity/mutagenicity than adults.

RESPONSE: *A discussion of age-related differences in trichloroethylene metabolites was added.*

COMMENT: P159 L32: Fisher et al. (1990) modeled distribution of TCE and trichloroacetic acid in the nursing mother rat and pup.

RESPONSE: *A statement was added to note the Fisher et al. (1990) modeling.*

COMMENT: P160 L7: What is the scientific basis of the statement that children have a higher concentration of lipophilic materials in their fat? Aren't triglycerides the primary lipids in fat of all ages of individuals?

RESPONSE: *The statement was revised to state that at comparable absorption levels, lipophilic substances may become more concentrated in fat of small children due to their lower amounts of fat per kg body weight (NRC 1993).*

COMMENT: P160 L17-30: A statement should be added at the end of the paragraph that many human and animal studies have not revealed evidence that TCE is a teratogen.

RESPONSE: *The suggested statement was added.*

COMMENT: P166 L24-27: The ethanol-TCE interaction described by Larson and Bull (1989) required a quite high TCE exposure level.

RESPONSE: *The lowest doses for both substances were added to the discussion.*

COMMENT: P167 L14: Induction of cardiac arrhythmias requires very high exposures to TCE, often in conjunction with stress/epinephrine and/or hypoxia.

RESPONSE: *Text was added to indicate that relatively high doses were required.*

COMMENT: P168 L12-13: It should be pointed out that inhibition of benzene metabolism by TCE would be protective from benzene myelotoxicity. Coadministration of sufficient doses of TCE and another chemical metabolized by the same P450 isozymes (e.g., CYP2E1) will result in competitive metabolic inhibition, resulting in decreased metabolic activation of one or both chemicals (i.e., be protective).

RESPONSE: *A statement was added regarding expected reduction in trichloroethylene toxicity when coexposure occurs with other substances that are metabolically activated by common cytochrome P450 isozymes.*

COMMENT: P169 L6-10: Again, Chapter 3 in the NRC (2009) report is highly recommended as a supplement to Section 3.10.

RESPONSE: *The NRC (2009) was consulted and relevant information was added.*

COMMENT: P169 L26-28: See previous comments about relative TCE metabolic activation capacity of children.

RESPONSE: *A discussion of age-related differences in trichloroethylene metabolites was added.*

COMMENT: P170 L22-24: What possible influence could testosterone have on (GI?) absorption of TCE? TCE is very readily and relatively completely absorbed in most circumstances.

RESPONSE: *The cited statement relates to dermal absorption; the statement was revised and mention of human relevance was deleted.*

COMMENT: P170 L26-30: See Chapter 3 of NRC (2009) for a more comprehensive discussion of genetic influences on TCE effects.

RESPONSE: *The NRC (2009) was added as another source of this information.*

COMMENT: P171 L32-33: Emesis may also result in aspiration of the solvent and ensuing pneumonitis.”

RESPONSE: *The information provided by the Reviewer was added.*

COMMENT: P172 L26-28: As mentioned in a previous comment, there is little scientific evidence of formation of TCE oxide in humans. I would think that most GSH metabolites of TCE are more likely to be a hazard than oxidation metabolites.

RESPONSE: *This statement was deleted per comment by another Reviewer.*

COMMENT: P173 L29: Reduction of stress may be helpful by reducing catecholamine release. Oxygen therapy might be useful, as hypoxia potentiates TCE-induced arrhythmias.

RESPONSE: *The information provided by the Reviewer was added.*

COMMENT: P176 L12-15: Although some investigations in animals do not reveal dose-response relationships, LOAELs, or NOAELs for all potential adverse effects, there are many studies that do. TCE is one of the most well studied and characterized of all chemicals.

RESPONSE: *Regarding the statement on P176, L12-15, the sentence regarding the lack of dose-response data was revised to state: “Although trichloroethylene toxicity has been extensively studied, quantitative dose-response data are insufficient to fully characterize effects for some of the critical targets (e.g., immunosuppression, hematologic effects, developmental effects).”*

COMMENT: P178 L20-21: Experiments by Reinhardt and others with dogs injected with epinephrine have revealed ranges of very high-level inhalation exposures necessary to induce cardiac arrhythmias.

RESPONSE: *The statement was revised to indicate that information regarding doses/concentrations resulting in cardiac effects would be beneficial, although such information is not likely due to present-day occupational exposure limits.*

COMMENT: P178 L29-33: It is not clear whether and under what exposure conditions TCE is neurotoxic (i.e., produces residual structural or functional changes, once TCE is eliminated systemically). Focused studies in animal models may be useful to learn more about the CNS as a target organ.

RESPONSE: *No change was made; trichloroethylene neurotoxicity appears to be adequately characterized.*

COMMENT: P179 L31-33: Additional studies of potential immunological and cardiac developmental effects should be given high priority. More should be learned about the human relevance and toxicological significance of the indices that are monitored.

RESPONSE: *The suggested additional points were added to the profile.*

COMMENT: P180 L8-9: Although further epi studies of persons in the proximity of hazardous waste sites are advocated, studies of occupationally-exposed populations are more likely to be fruitful, as industrial exposures are usually considerably higher and exposure levels hopefully better characterized.

RESPONSE: *The referenced statement was removed per comment by another Reviewer.*

COMMENT: P188 L6-12: High oral doses are required to produce signs of CNS dysfunction. It is unlikely that typical oral environmental exposure will elicit such effects, due to first-pass hepatic and pulmonary elimination.

RESPONSE: *The section was revised to note that large doses are required to elicit neurological effects.*

COMMENT: P189 L27: Empirical data on tissue distribution of TCE in humans is necessarily limited, but there are numerous studies of the systemic distribution of the parent compound in rats.

RESPONSE: *The text was revised to include mention that the systemic distribution of trichloroethylene has been extensively studied in animals.*

COMMENT: P191 L13-14: The accuracy of this statement should be verified. Neonates and infants have more body water and less fat than other age groups.

RESPONSE: *The statement was revised to note that lipophilic substances may become more concentrated in the fat of infants and small children due to their lower amounts of fat per kg body weight.*

COMMENT: P191 L15-16: TCE should readily cross the blood-brain barrier in all age groups.

RESPONSE: *A statement was added to the text to indicate that trichloroethylene is expected to readily cross the blood-brain barrier in all age groups.*

Comments provided by Reviewer #2:

Reviewer #2 submitted an electronic file of draft 3 of the Toxicological Profile for Trichloroethylene using tracked changes and embedded comments. Tracked changes and comments that were of sufficient nature to warrant a formal response are itemized below and identified by page (P) and line (L) on which they are found in the file submitted by Reviewer #2.

Note: Page and line numbers in this file do not correspond to the page and line numbers in the file of draft 3 of the Toxicological Profile for Trichloroethylene that was provided Reviewer #2 due to the use of tracked changes, which included suggested additions and deletions.

COMMENT: P2 L5: Reviewer #2 suggested adding that other uses of smaller amounts include dry cleaning and consumer products.

RESPONSE: *The suggested addition was made.*

COMMENT: P2 L6: Reviewer #2 suggested adding information on indoor air in the table entry for air as a possible source.

RESPONSE: *The suggested addition was made.*

COMMENT: P2 L6: Reviewer #2 stated that if exposure at facilities using trichloroethylene for metal degreasing operations is referring to air levels, the information should be moved from the section for other media to the section for air as a possible source.

RESPONSE: *The text was moved to the air section of the table.*

COMMENT: P3 L5: Reviewer #2 suggested adding a statement that you can be exposed by breathing trichloroethylene released from contaminated water into indoor air and by eating food containing trichloroethylene.

RESPONSE: *The requested additions were made.*

COMMENT: P8 L11-12: Regarding the sentence “If your doctor finds that you have been exposed to significant amounts of trichloroethylene, ask whether your children might also be exposed,” Reviewer #2 stated “This is very unclear. Does this mean someone occupationally exposed would ‘bring it home’ with them on their clothes or something like that: If it is through environmental contamination of air and water in the home, it would be obvious that children also breathe the same air and water without needing a physician to figure it out.”

RESPONSE: *This is general text for toxicological profiles. The statement may be more important for exposures to certain substances, but it appears appropriate to include it for trichloroethylene as well.*

COMMENT: P6: Regarding the first sentence, Reviewer #2 stated “At what level is drinking water considered to be ‘contaminated’? Above the MCL?”

RESPONSE: *No change was made; this is a general statement intended to inform the reader that exposure to trichloroethylene in drinking water should be limited to a reasonable extent.*

COMMENT: P6 L1: Reviewer #2 stated “In my opinion, several of the statements and advice in this section are unclear and not helpful to the public.” Referring to the statement regarding high levels of trichloroethylene in the water and soil, Reviewer #2 asked whether this means that there may be high levels at your home. Referring to the statement regarding substituting cleaner sources of water, Reviewer #2 asked whether this advice is meant for private well owners, and if so that it should be specified. Reviewer #2 noted that public water supplies are routinely monitored for trichloroethylene and that sources exceeding the MCL must be treated. Referring to the statement regarding contaminated soil, Reviewer #2 asked whether offsite soil would be contaminated.

RESPONSE: *In general, the content of this paragraph is considered adequate to address issues regarding reducing the risk of exposure. The paragraph was slightly revised to note that if you find your*

home water supply and/or soil to be contaminated with trichloroethylene, consider using a cleaner source of water. Offsite soil could become contaminated via groundwater, surface water, etc.

COMMENT: P6 L8: Regarding measurement of trichloroethylene and its metabolites in blood and urine, Reviewer #2 stated “Are these widely available clinical lab tests, or specialized analyses done in research studies? This should be made clear. If not widely available, the public reading this may incorrectly assume that they can ask their physician for these tests, when it is not the case.”

RESPONSE: *A statement was added to note that the tests require special equipment not readily available at medical facilities.*

COMMENT: P7: Reviewer #2 asked whether state guidance and standards could be included.

RESPONSE: *Inclusion of state recommendations would make the section rather lengthy, although ATSDR acknowledges that most state environmental and health information is valuable.*

COMMENT: P10 L30: Reviewer #2 noted that the statement regarding “some trichloroethylene contamination” is found yearly in 4.5–18% of tested U.S. drinking water supplies is not meaningful without information regarding detection limits. Reviewer #2 further stated that this is a recurring comment for environmental occurrence data throughout the profile.

RESPONSE: *The statement was revised to indicate that these are measurable levels, and where data were available, detection limits were added to text in other sections of the profile. However, Section 2.1 is intended as a general summary; therefore, addition of detection limits to this section is not considered necessary.*

COMMENT: P12 L21-2-31: Reviewer #2 asked whether all of the cited studies involved occupational exposures, and if so, that this should be mentioned.

RESPONSE: *The section was revised to separate occupational cohort studies from case-control studies.*

COMMENT: P13 L1: Reviewer #2 asked whether two occupational studies were cohort studies.

RESPONSE: *The text was revised to note that these were occupational cohort studies.*

COMMENT: P16 L15: Reviewer #2 asked that “intermediate duration” be defined.

RESPONSE: *A qualifying statement was added (>14 days, but <1 year).*

COMMENT: P17 L5: Reviewer #2 asked whether diffuse fasciitis is a rare disease.

RESPONSE: *Explanatory text was added to note that the condition improved after the woman started using bottled drinking water.*

COMMENT: P20 L12: Reviewer #2 asked for clarification of a statement that studies were limited by small numbers of cases in reports of developmental effects associated with trichloroethylene in the drinking water. Reviewer #2 asked whether the statement means that results were not statistically significant because of small numbers of cases.

RESPONSE: *The statement was revised to note that the studies are limited in statistical power due to small numbers of cases.*

COMMENT: P20 L14-22: Reviewer #2 stated that, as written, this section implies that the difference in results between the two sets of studies is due to different dosing regimens. However, other possible reasons for the differing results have been extensively evaluated. Reviewer #2 pointed to the IRIS Toxicological Review for Trichloroethylene as a source to be consulted and that the issues should be mentioned somewhere in the ATSDR Toxicological Profile for Trichloroethylene since cardiac malformations are important and are one of the key effects used as the basis for the MRLs.

RESPONSE: *A statement was added to indicate possible reasons for apparently conflicting results.*

COMMENT: P24 L14, P26 L16: Reviewer #2 agrees with the choice of the intermediate-duration oral and inhalation MRLs, but requested revision of the explanation of why the chronic-duration MRLs are applicable to intermediate-duration exposure.

RESPONSE: *Additional text was added to note that intermediate-duration MRLs derived in the same manner as the preferred chronic RfD and RfC would result in the same values, and that the co-critical studies used to derive the preferred chronic RfD each employed intermediate-duration oral exposure.*

COMMENT: P25 L13-20, P27 L2: Reviewer #2 stated that the rationale for not developing acute-duration MRLs is not clear. Reviewer #2 noted that several studies listed in the IRIS review found developmental effects with less than 14 days of exposure (for example Narotsky et al. 1995). Reviewer #2 stated that the possibility of developing acute-duration MRLs based on these studies should be evaluated.

RESPONSE: *An acute-duration MRL based on the results of Narotsky et al. (1995) or others might not be protective of cardiac malformations from slightly longer than 14 days of exposure, which exhibit a lower effect level.*

COMMENT: P29 L26: Reviewer #2 asked how long after exposures ended did deaths occur.

RESPONSE: *The times were variable; no change was made to the text.*

COMMENT: P31 L5&10: Reviewer #2 provided a suggestion for explanatory text for the mention of P450 activity. Reviewer #2 also asked whether cytochrome P450 in the lungs is found mainly in Clara cells.

RESPONSE: *The suggested additional text was incorporated. Text was added to describe function of Clara cells, including the release of cytochrome P450 enzymes that assist in the metabolism of xenobiotics.*

COMMENT: P35 L9-10: Reviewer #2 asked whether acute hepatitis is very rare and whether it is notable that it occurred in only one person.

RESPONSE: *This is only one report among a number of reports of hepatic effects in persons with reported exposure to trichloroethylene.*

COMMENT: P35 L20-21: Reviewer #2 asked whether anything is known about exposure level in the study report of McCarthy and Jones (1983).

RESPONSE: *No.*

COMMENT: P35 L26-27: Reviewer #2 asked whether the volunteers exposed at 200 ppm for 7 hours/day were exposed for 5 days.

RESPONSE: *Yes, this is evident from the wording of the sentence.*

COMMENT: P36 L32: Reviewer #2 asked whether exposure of the newborn rats for 10 weeks started at postnatal day 1.

RESPONSE: *They were newborn rats; additional clarification does not appear necessary.*

COMMENT: P37 L25: Reviewer #2 asked for clarification of the word “outperform” in a statement regarding use of KIM-1 as a biomarker of renal injury. Reviewer #2 asked whether the term means that it is a more sensitive indicator, a more specific indicator, or something else.

RESPONSE: *Text was added to note that it is a more sensitive indicator.*

COMMENT: P38 L14: Reviewer #2 asked whether the reported period of 1973–1999 in the study of Radican et al. (2006) refers to years during which exposure occurred.

RESPONSE: *The study report did not specify whether these were exposure years or the time period during which the study was performed.*

COMMENT: P38 L22-30: Reviewer #2 asked for information regarding the duration of exposures and exposure levels in the studies of animals exposed for intermediate periods.

RESPONSE: *Text was added to include ranges of time periods and exposure levels.*

COMMENT: P38 L30-32: Reviewer #2 asked whether the NOAELs were determined by study authors or by ATSDR authors.

RESPONSE: *The statement was deleted from the profile because it was considered unnecessary.*

COMMENT: P39 L6: Reviewer #2 asked whether dehydroepiandrosterone sulphate is a hormone or hormone metabolite.

RESPONSE: *Text was added to note that it is a metabolite of the endogenous steroid hormone dehydroepiandrosterone.*

COMMENT: P39 L24-25: Reviewer #2 asked whether generalized skin disorders from occupational exposure to trichloroethylene are via inhalation or dermal routes or both.

RESPONSE: *It was stated in the previous paragraph that dermal effects in humans are usually the consequence of direct skin contact.*

COMMENT: P46 L33: Reviewer #2 asked which study used the reported 1,568 ppm exposure level.

RESPONSE: *The text was revised to associate the exposure level with Goldberg et al. (1964b) study.*

COMMENT: P50 L15-21: Reviewer #2 asked for ranges of exposure levels in groups of workers exposed to trichloroethylene in the reports of Chia et al. (1996, 1997) and Goh et al. (1998).

RESPONSE: *Exposures were estimated based on urinary TCA levels. A statement was added for clarity.*

COMMENT: P51 L27: Reviewer #2 asked whether “spontaneous abortion” is a reproductive effect rather than a developmental effect.

RESPONSE: *It could be either.*

COMMENT: P52 L12-22: Reviewer #2 asked whether the results from the study of Yauck et al. (2004) should be presented as the comparison of exposed vs unexposed within the ≥ 38 -year-old group.

RESPONSE: *The text was revised to note that there was no significant increased risk of congenital heart defects in children from trichloroethylene-exposed mothers <38 years of age (OR 0.9; 95% CI 0.6–1.2).*

COMMENT: P52 L34, P53 L1: Reviewer #2 asked to convert units of $\mu\text{g}/\text{m}^3$ to ppm here and elsewhere in the document.

RESPONSE: *The requested conversion was made.*

COMMENT: P54 L15: Reviewer #2 asked for the proportion of the studies that reported RRs for these cancer types and, out of the ones that reported RRs, how many showed increased risk associated with trichloroethylene.

RESPONSE: *The numbers varied by cancer type. No change was made to the text.*

COMMENT: P55 L2-4: Reviewer #2 indicated that the statement is not clear to some readers not familiar with meta-analyses and needs additional explanation.

RESPONSE: *The statement was considered unnecessary and was deleted.*

COMMENT: P56 L10: Reviewer #2 asked why evidence for liver cancer is less convincing since the RRs and CIs are at least as high for liver cancer as for kidney cancer.

RESPONSE: *The sentence in question was considered unnecessary and was deleted.*

COMMENT: P56 L33 to P57 L3: Reviewer #2 asked which of the animal studies used trichloroethylene with epoxides and whether any studies used epoxide-free trichloroethylene.

RESPONSE: *The paragraph in which statements were made regarding the presence of epoxides in some trichloroethylene studies was deleted per another Reviewer's comment.*

COMMENT: P57 L15-17: Reviewer #2 asked whether the study of Maltoni et al. (1986, 1988) was performed using trichloroethylene with or without epoxide.

RESPONSE: *Statements regarding epoxide were removed per another Reviewer's comments.*

COMMENT: P57 L17-18: Reviewer #2 asked whether the statement regarding increases in Leydig cell tumors and slight increases in tubular renal adenocarcinoma that EPA and other groups regard such increases as indicative of a hazard potential unless there are reasons to rule this out refers to testicular, renal, or both types of cancer and questioned why they would not be indicative of hazard potential.

RESPONSE: *The statement was deleted per another Reviewer's comments.*

COMMENT: P57 L18-19: Regarding the statement "However, other authorities believe that testicular tumors are common in rats that are not exposed to toxic substances," Reviewer #2 stated that this is not a meaningful comment, needs revision, and that even if there is a high background incidence of a certain tumor, it may still be relevant and indicative of carcinogenicity if the incidence is higher in the treated groups. Reviewer #2 noted that there are no citations for this statement.

RESPONSE: *The statement was deleted per another Reviewer's comments.*

COMMENT: P58 L5-8: Reviewer #2 questioned the relevance and implications of the content of this sentence to cancer risk.

RESPONSE: *The sentence was deleted.*

COMMENT: P58 L9-12: Reviewer #2 stated that the Laib et al. (1979) study should not be discussed as a carcinogenicity study. Reviewer #2 noted it is a study of possible mechanisms that could be related to liver carcinogenicity.

RESPONSE: *The study summary was removed from this section.*

COMMENT: P58 L22-23: Reviewer #2 asked for identification of the animal studies that were the basis for IARC's conclusion that trichloroethylene is probably carcinogenic to humans, based on sufficient evidence in experimental animals and limited evidence in humans.

RESPONSE: *This section is intended to inform the reader of determinations made by selected authorities regarding cancer hazard. The reader should refer to the documents produced by these authorities for more detailed information.*

COMMENT: P59 L9-10: Reviewer #2 noted that the cancer risk levels are not in Figure 3-1.

RESPONSE: *The cancer risk levels were inadvertently left out of the figure; they have been reinserted.*

COMMENT: P60 L23-25: Regarding the statement "Histopathological changes in the lungs have not been observed in other intermediate- and chronic-duration studies of rats or mice orally exposed to trichloroethylene," Reviewer #2 asked whether the sentence should read "non-neoplastic histological changes" because neoplastic lung tumors are a histopathological change.

RESPONSE: *The word "non-neoplastic" was added.*

COMMENT: P61 L7-8: Reviewer #2 asked whether the parental symptoms could have been stress related by having a child with leukemia. Reviewer #2 asked whether comparisons were made to other adults with exposure to the same contaminated drinking water source and who did not have a sick child.

RESPONSE: *The cardiological effects might have been stress related. However, the study report did not include such information and did not make the comparison.*

COMMENT: P63 L26-29: Regarding the results of the Stott et al. (1982) study, Reviewer #2 stated that a lower dose was used in the rats compared to the mice and asked whether the differences in reported hepatic effects might be attributable to metabolic differences.

RESPONSE: *The differences could be dose related and/or related to differences in metabolism.*

COMMENT: P63 L31 to P64 L5: Reviewer #2 stated that this section is very confusing, that it needs to be stated that peroxisomal beta oxidation and palmitoyl CoA oxidation are markers of peroxisome proliferation, and that the rat/mouse differences may be due to differences in metabolism.

RESPONSE: *The following addition was made: "Peroxisomal beta oxidation and palmitoyl CoA oxidation are markers of peroxisome proliferation. The differences in responses between the rats and*

mice may reflect species differences in trichloroethylene metabolism.” The sentence: “The study authors suggest that trichloroethylene induces mitosis and DNA proliferation in mature hepatocytes” was deleted.

COMMENT: P64 L6-7: Reviewer #2 asked what “no change in hepatocyte DNA content, but increased incorporation of radiolabelled thymidine” indicate.

RESPONSE: *The text was revised to indicate that these results are responses suggestive of cellular proliferation.*

COMMENT: P64 L24-34: Reviewer #2 stated that the statement about differences in absorption efficiencies from corn oil and water is not supported by the results of Henschler et al. (1984), NCI (1976), and NTP (1990) all of whom used corn oil and showed minimal or no hepatic effects, and that this point should be made.

RESPONSE: *The statement regarding differences in absorption efficiencies from corn oil and water was deleted.*

COMMENT: P65 L4-12: Reviewer #2 stated that the studies cited in this paragraph indicate that rats are less sensitive than mice and that this should be stated.

RESPONSE: *The following statement was added to the beginning of the paragraph: “Rats appear to be less sensitive than mice to trichloroethylene hepatotoxicity.”*

COMMENT: P69 L1: Reviewer #2 stated that the total number of adults tested should be added.

RESPONSE: *The requested addition was made.*

COMMENT: P69 L22: Reviewer #2 asked at what doses depression of delayed-type hypersensitivity occurred and noted a discrepancy in what was stated as the highest dose tested.

RESPONSE: *The section was revised after consulting the study report. Changes included revision of the reported effects (which included deletion of the reference to depression of delayed-type hypersensitivity) and correction of the highest dose tested.*

COMMENT: P69 L24-25: Reviewer #2 asked for the basis/citations for the statement “Overall, females were more sensitive and the effects on the immune system were consistent with those of other chlorinated hydrocarbons.”

RESPONSE: *The statement in question does not appear to necessitate addition of citations.*

COMMENT: P70 L5: Reviewer #2 stated that the statement regarding the lack of effect on thymus weight is in contradiction to the statement in the previous sentence that thymus weight was decreased by 30%.

RESPONSE: Reference to the lack of effect on thymus weight was deleted.

COMMENT: P70 L11-13: Reviewer #2 asked whether the significant changes in serum anti-glomerular antigen antibody levels occurred at both exposure levels.

RESPONSE: *The exposure data were added to the summary.*

COMMENT: P70 L20-22: Reviewer #2 asked whether the significant increases in antinuclear antibodies and total serum immunoglobulins occurred at both exposure levels.

RESPONSE: *A statement was added to note that the effects were dose related.*

COMMENT: P70 L22-24: Reviewer #2 asked whether trichloroethylene caused an effect in the study of Griffin et al. (2000b), and at what dose levels.

RESPONSE: *Effects were added and doses included where relevant.*

COMMENT: P71 L1-10: Reviewer #2 indicated that the reported doses appear to be in error.

RESPONSE: *The errors were corrected.*

COMMENT: P71 L8-10: Reviewer #2 asked whether the statement is still supported by the corrected dose information.

RESPONSE: *Yes.*

COMMENT: P71 L31: Reviewer #2 asked whether the lack of neurological complaints was based on reported symptoms as opposed to tests of neurological function.

RESPONSE: *Yes.*

COMMENT: P72 L6-9: Reviewer #2 asked for information regarding the comparison group in the study of Kilburn and Warshaw (1993) and noted that the statement "However, efforts were made..." should read "However, no efforts were made..."

RESPONSE: *Information regarding the comparison group was added and the word "no" was added.*

COMMENT: P73 L1-2: Reviewer #2 asked whether dichloroacetylene caused effects at lower doses than trichloroethylene and/or more serious effects.

RESPONSE: *The study employed a single dose level.*

COMMENT: P73 L17: Reviewer #2 stated that, in general, the section on animal studies in Section 3.2.2.5 could be better organized.

RESPONSE: *No change was made; the organization appears adequate.*

COMMENT: P73 L31 to P74 L2: Reviewer #2 asked whether testis/epididymal weights were affected in the study of NTP (1985).

RESPONSE: *Yes, the organ weight information was added.*

COMMENT: P74 L17-19: Reviewer #2 stated that results from the NTP (1985) study had been presented in a previous paragraph.

RESPONSE: *The repetitious text was deleted.*

COMMENT: P74 L31-32: Reviewer #2 stated that the sentence “There is some evidence that exposure to trichloroethylene in drinking water may cause certain types of birth defects” is vague.

RESPONSE: *The sentence was deleted.*

COMMENT: P75 L1-5: Regarding the study of Bove et al. (1995), Reviewer #2 asked about exposure to other chemicals.

RESPONSE: *The presence of other chemicals was added as a study limitation.*

COMMENT: P76 L7-22: Reviewer #2 asked for description of the “other substances in the water” from the study of Goldberg et al. (1990).

RESPONSE: *The substances included dichloroethylene and chromium; this information was added.*

COMMENT: P77 L26-29: Reviewer #2 stated that the reported ocular effects occurred at doses below the threshold of maternal toxicity and that these effects occurred with less than 14 days of exposure and could therefore be used as basis for an acute-duration MRL.

RESPONSE: *A statement was added to inform the reader of the threshold of maternal toxicity. The results are not considered adequate for deriving an acute-duration MRL because slightly longer than 14-day exposures resulted in developmental effects at much lower exposure levels.*

COMMENT: P80 L20-22: Reviewer #2 asked whether autoantibodies to double-stranded DNA and delayed type hypersensitivity responses were affected in the pups from the Peden-Adams et al. (2006) and whether SRBC was defined.

RESPONSE: *Text was added to discuss the effects on double-stranded DNA and delayed type hypersensitivity responses; SRBC was defined earlier in the profile.*

COMMENT: P82 L17-19: Regarding leukemia among residents of Woburn, Massachusetts and the presence of trichloroethylene and other chlorinated organic compounds in wells, Reviewer #2 stated that the statement “etiologic factors for the leukemia were not identified...” is unclear. Reviewer #2 asked whether the statement means that the solvents were not associated with leukemia.

RESPONSE: *Leukemia could not be specifically linked to the substances in the wells. A statement to that effect was added.*

COMMENT: P82 L22-23: Reviewer #2 asked whether the incidences were compared in children using contaminated wells versus those not using contaminated wells.

RESPONSE: *No.*

COMMENT: P82 L28-31: Reviewer #2 stated that the statement “Geophysical modeling has suggested that the contamination had probably been present earlier than the initial measurements that had identified the problem. This possibility makes the analyses of period-specific rates of effects incomplete since no time can be specified for the initiation of exposures” needs a citation.

RESPONSE: *No citation was found; the statement was deleted.*

COMMENT: P82 L34 to P83 L1: Reviewer #2 asked whether the statement “water consumed from other sources...” was contaminated or uncontaminated.

RESPONSE: *A qualifying statement was added to note that the quality of the water consumed from other sources.*

COMMENT: P84 L13-16: Reviewer #2 asked whether there were epoxides in the trichloroethylene used in the NTP (1988) study.

RESPONSE: *The following statement was added: “The test material contained an amine stabilizer at a concentration of 8 ppm, but no epichlorohydrin or 1,2-epoxybutane.”*

COMMENT: P85 L23: Reviewer #2 suggested adding a statement that occupational exposure may involve inhalation and dermal exposure routes.

RESPONSE: *The suggested addition was made to the beginning of Section 3.2.3.*

COMMENT: P96 L1-2: Reviewer #2 stated that the phrase “trichloroethylene may be carcinogenic without necessarily being genotoxic” is confusing and asked whether rate of DNA synthesis is a sign of carcinogenicity.

RESPONSE: *The statement was revised and the confusing text was deleted.*

COMMENT: P102 L23-26: Reviewer #2 asked how sex differences in uptake and metabolism of trichloroethylene vary.

RESPONSE: *The statement in question was revised; it was noted that dermal absorption of trichloroethylene in control female rats was twice that of control males and that deprivation of testosterone to males resulted in increased dermal absorption and administration of testosterone to females resulted in decreased dermal absorption.*

COMMENT: P103 L12-13: Reviewer #2 stated that the intended meaning of the sentence “Solubility in blood is a major factor determining the trichloroethylene concentration in blood leaving the lungs during inhalation exposure, as indicated by the blood:air partition coefficient” is unclear and needs to be clarified.

RESPONSE: *The statement was moved to absorption Section 3.4.1.1. The subsequent sentence explains how the blood:air partition coefficient factors into the extent of transfer of a substance from air to blood in the lungs.*

COMMENT: P103 L13-15: Reviewer #2 asked whether the studies that determined the blood coefficients are discussed in subsequent text.

RESPONSE: *No.*

COMMENT: P103 L17-18: Reviewer #2 asked whether the humans in the studies of tissue distribution were volunteers or occupationally-exposed individuals and requested the general range of exposure levels.

RESPONSE: *They were volunteers and the exposure data were added to the profile.*

COMMENT: P103 L30-32: Reviewer #2 questioned the use of the word “increase” when referring to binding of trichloroethylene to proteins in the blood and asked whether the statement should be moved to the oral section because it employed gavage administration.

RESPONSE: *The word “increase” was replaced with “likely influences.” The statement remains in the inhalation section because the information from the gavage study is relevant to the subsequent text in the inhalation section.*

COMMENT: P104 L22-23: Reviewer #2 is not sure about the statement regarding orally-absorbed trichloroethylene bypassing the liver.

RESPONSE: *The Pfaffenberger et al. (1980) study was consulted and the statement was revised to note that a portion of an absorbed dose may exceed the capacity of the liver to metabolize it during the initial pass through the liver and that trichloroethylene and its breakdown products that leave or bypass the liver are taken up by other tissues to some extent, particularly fat.*

COMMENT: P104 L23: Reviewer #2 asked whether the dose presented as mg/day was given as mg/kg/day in the study.

RESPONSE: *No.*

COMMENT: P104 L26-28: Reviewer #2 asked for the time points when adipose tissue levels of trichloroethylene were measured in the study of Pfaffenberger et al. (1980) and asked what the result shows.

RESPONSE: *Mention of the specific time points of adipose tissue level measurements does not appear necessary; additional quantitative data were added. It should be clear from the revised text that adipose tissue levels dropped rapidly following the cessation of treatment.*

COMMENT: P105 L13-14: Reviewer #2 asked for dose/exposure level information for the statement that none of the cited human studies provide evidence of saturation of trichloroethylene metabolism.

RESPONSE: *The range of highest exposure levels was added to the profile.*

COMMENT: P106 L19-21: Reviewer #2 questioned the statement “The evidence for DCA formation is equivocal...” because a previous statement indicates that MCA was found in human urine after trichloroethylene exposure. Reviewer #2 asked how MCA would form if not from DCA.

RESPONSE: *The statement in question was revised to state “Quantification of the amount of DCA formed is difficult....”*

COMMENT: P109 L27: Reviewer #2 asked whether studies discussed in this section are also discussed in the oral absorption section.

RESPONSE: *Discussion of these studies was added to the oral absorption section.*

COMMENT: P110 L8-10: Reviewer 2# asked for the percent (or range of percents) of total metabolism that occurs through the GSH pathway in reference to the statement “quantitatively minor.”

RESPONSE: *It varies as discussed in a previous paragraph, and more precise quantitation is not possible.*

COMMENT: P110 L12: Regarding the statement “Phenobarbital, an inducer of some forms of cytochrome P450...”, Reviewer #2 asked for specification of the forms.

RESPONSE: *The qualification “(e.g., CYP2E1, CYP2B6, CYP2C9, CYP2C19)” was added.*

COMMENT: P110 L15-17: Reviewer #2 stated that the statement needs to be better explained and asked whether ethanol and/or phenobarbital induce CYP2E1.

RESPONSE: *The statement was revised to note that CYP2E1 is the most prominent isozyme involved in metabolizing trichloroethylene to chloral hydrate in rat liver and human liver microsomes. The mention of methods used by Nakajima et al. (1992a) in elucidating CYP2E1 as the most prominent isozyme was deleted to eliminate confusion.*

COMMENT: P110 L27-29: Reviewer #2 asked for the duration of exposure in the study of Stott et al. (1982).

RESPONSE: *Exposure duration (6 hours) was added.*

COMMENT: P111 L7: Reviewer #2 asked for the dose or range of doses associated with the statement “At high gavage doses...”:

RESPONSE: *The dose range was added.*

COMMENT: P111 L9-10: Reviewer #2 asked whether the statement “The net metabolism of trichloroethylene to TCA and trichloroethanol was similar in rats and mice given single gavage doses of 1.5–23 mmol/kg (197–3,022 mg/kg) (Larson and Bull 1992a)” contradicts an earlier statement that metabolism was saturated in rats at 100 mg/kg. Reviewer #2 asked whether the “excess” trichloroethylene would be excreted unchanged at 3,022 mg/kg.

RESPONSE: *Text was added to note that the residence time of trichloroethylene and its metabolites was longer in rats than mice and that the original statement is not contradictory based on the observations of faster metabolism in mice and longer residence time in rats.*

COMMENT: P111 L15-18: Reviewer #2 questioned the statement indicating that direct exposure to selected trichloroethylene metabolites resulted in greater liver tumor induction in rats and mice. Reviewer #2 asked for clarification of the statement “greater tumor induction” and asked whether the results mean that rats and mice are equally susceptible to liver tumors if exposed to equal amounts of the metabolites.

RESPONSE: *The text was revised to indicate that administration of the trichloroethylene metabolites resulted in liver tumors in mice, but comparative quantification of tumor incidences is not possible based on available data.*

COMMENT: P111 L33 to P112 L1: Reviewer #2 asked for identification of the enzymes in the statement “non-P450-mediated...”.

RESPONSE: *The statement was revised as follows: Results of assays using isolated rabbit pulmonary cells (Clara, Type II, and alveolar macrophages) indicate that some type of non-P450-mediated bioactivation of trichloroethylene is involved in cytotoxicity because addition of 1-aminobenzotriazole (a suicide substrate inhibitor of cytochrome P450) is not necessary to cause cytotoxicity because it failed to decrease the non-selective cytotoxicity of trichloroethylene in all three cell types (Nichols et al. 1992).”*

COMMENT: P112 L1-4: Reviewer #2 stated that the statement “Trichloroethylene metabolism also appears to be important in trichloroethylene-induced nephrotoxicity, although the GSH-dependent

pathway is the pathway that produces the principal nephrotoxic metabolites” is unclear. Reviewer #2 asked whether it is intended to mean that trichloroethylene is metabolized in the kidney or that metabolites produced elsewhere reach the kidney and cause toxicity.

RESPONSE: *The statement was revised to note that the GSH-dependent pathway includes the liver and kidney. More precise information is not available.*

COMMENT: P114: Reviewer #2 asked for the meaning of the brackets around selected metabolites.

RESPONSE: *The brackets were removed because their meaning was not explained in the available sources for the metabolic scheme.*

COMMENT: P116 L22-28: Reviewer #2 asked whether the individual reporting of various reported half-lives could be synthesized into a single statement and an explanation given for different values from different studies.

RESPONSE: *It appears appropriate to present the results separately. Differences could be the result of many factors in study design. It does not appear appropriate to speculate on differences across studies.*

COMMENT: P117 L6: Reviewer #2 asked for definition of the term “trichloro compounds.”

RESPONSE: *The term was considered unnecessary and was deleted.*

COMMENT: P117 L13-14: Reviewer #2 asked for the proportion of radioactivity that was excreted in the feces of the mice and the percentages of radioactivity found in the urine, breath, and feces of the rats.

RESPONSE: *The requested quantitative information was added.*

COMMENT: P117 L18-20: Reviewer #2 asked whether TCA is a metabolite of tetrachloroethylene as well as trichloroethylene and noted that it is unclear in the statement.

RESPONSE: *Yes, explanatory text was added.*

COMMENT: P117 L31 to P118 L1: Regarding the statement “The percentage of radioactivity excreted in the urine was 40%, while 10.9% was in expired air as carbon dioxide, and 34.6% was in the feces, carcass, and cage wash,” Reviewer #2 asked where the other 15% went and how the 14.5% excreted unchanged in air contributes to the reported percentages.

RESPONSE: *The other 15% (reported as 14.5%) was excreted unchanged in expired air as described in the text.*

COMMENT: P120 L5-7: Reviewer #2 stated that boilerplate statements “A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.” are unclear. Reviewer

#2 asked “Can reduce the magnitude of cumulative uncertainty as compare to what?” Reviewer #2 also asked whether the word “adequacy” means the ability of the model to accurately predict reality.

RESPONSE: *This is boilerplate text. ATSDR will consider the comments and incorporate changes in future drafts of toxicological profiles if deemed appropriate.*

COMMENT: P120 L9-11: Regarding the boilerplate text “PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances,” Reviewer #2 stated that the language in this text should be consistent with the definitions of MRLs, RfDs, and cancer risk assessments.

RESPONSE: *This is boilerplate text. ATSDR will consider the comments and incorporate changes in future drafts of toxicological profiles if deemed appropriate.*

COMMENT: P121 L2: Reviewer #2 stated that it should be mentioned that the GSH metabolic pathway is not included in these models if that is the case.

RESPONSE: *Text was added to state that models focus on trichloroethylene and its oxidative metabolites.*

COMMENT: P123 L6-8: Reviewer #2 asked which species are included in the models of Fisher and colleagues.

RESPONSE: *The species were identified in the previous paragraph.*

COMMENT: P123 L12-14: Reviewer #2 stated that the metabolites discussed are GSH pathway metabolites. Reviewer #2 suggested to clearly state which models include this pathway and which do not.

RESPONSE: *This is explained in a subsequent paragraph.*

COMMENT: P123 L14-16: Reviewer #2 asked whether the GSH pathway that produces the DCVC metabolite in the liver, which can travel from the liver to the kidney, as stated in the metabolism section of Section 3.4, is included in the Clewell et al. (2000) model.

RESPONSE: *Explanatory text was added to note that the model assumes that all GSH conjugation of trichloroethylene in the liver or kidney leads to the appearance of DCVC in the kidney.*

COMMENT: P123 L27-29: Reviewer #2 asked what priority data needs would be satisfied by extrapolating the results of inhalation toxicity studies to oral exposure through the use of existing PBPK modeling.

RESPONSE: *The statement in question was removed from the profile per a comment by another Reviewer.*

COMMENT: P124 L12: Reviewer #2 requested adding a few sentences to explain Bayesian probabilistic approaches to parameter value estimation.

RESPONSE: *An explanation would be rather lengthy and would not likely benefit most intended readers of the profile.*

COMMENT: P126: Reviewer #2 stated that Figure 3-6 needs to include definitions for all of the numerous abbreviations. Reviewer #2 also stated that if the conjunctive metabolism box applies to rats and humans only, to which species do the other boxes apply.

RESPONSE: *The text makes it clear that the model applies to rats, mice, and humans.*

COMMENT: P128: Reviewer #2 suggested considering moving Tables 3-5 to 3-7 to an appendix.

RESPONSE: *The tables are appropriate in Section 3.4.5.*

COMMENT: P157 L21-25: Reviewer #2 asked for explanation for why the dose metrics were total oxidative metabolism for heart defects, but total amount of trichloroethylene metabolized for immunological effects.

RESPONSE: *The dose metric for heart defects was selected because several studies have demonstrated that oxidative metabolites also induce cardiac malformations. Total amount of trichloroethylene metabolized was selected as the dose metric for immunological effects due to the lack of information on the role of metabolites or mode of action for trichloroethylene-induced immunological effects.*

COMMENT: P159 L15-18: Reviewer #2 stated that the word “detoxification” is not appropriate for the context in which it was used and suggested using the phrase “well characterized pathways of xenobiotic metabolism.”

RESPONSE: *The suggested change was made.*

COMMENT: P159 L18: Reviewer #2 asked for explanation of where reabsorption occurs.

RESPONSE: *In the kidney, as indicated by Reviewer #2. Text was added.*

COMMENT: P159 L24-29: Reviewer #2 asked for the dose range for the linearity of dose-response for trichloroethylene, asked which are the detoxification pathways and which pathways produce toxic metabolites. Reviewer #2 further asked to what the statement “threshold effect” refers.

RESPONSE: *The section in question was deleted.*

COMMENT: P160 L7+: Reviewer #2 stated that information in this section indicates that oxidation and GSH metabolic pathways both produce toxic metabolites, whereas the previous section implies that

there are detoxification pathways. Reviewer #2 asked whether the detoxification pathways are conjugation to glucuronides. Reviewer #2 asked for clarification.

RESPONSE: *The statement in the previous section regarding detoxification pathways was deleted. As stated in previous sections of the profile, oxidation and GSH-conjugation can result in toxic metabolites, which can be detoxified via further metabolism and glutathione conjugation.*

COMMENT: P160 L14-17: Reviewer #2 asked which trichloroethylene metabolites exhibit longer residence times in rats than mice.

RESPONSE: *The specific metabolites were added.*

COMMENT: P160 L29-31: Reviewer #2 asked which gender has more body fat.

RESPONSE: *The statement was revised to note that women exhibit a generally higher body fat content.*

COMMENT: P162 L8-10: Reviewer #2 asked whether all of the listed modes of action for liver cancer are really possible modes, even if they are occurring.

RESPONSE: *The text was revised to more completely discuss possible modes of action for trichloroethylene-induced liver tumors in animals.*

COMMENT: P164 L18: Reviewer #2 questioned the statement that plausible mechanisms for cardiac defects are under investigation.

RESPONSE: *The statement was deleted.*

COMMENT: P164 L22 to P165 L20: Reviewer #2 made several comments regarding the information in Section 3.5.3.

RESPONSE: *The section was completely re-written; the comments of Reviewer #2 are no longer applicable to the revised section.*

COMMENT: P166 L1-3: Boilerplate statements “Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife.” Reviewer #2 suggested consulting statements of WHO, the Endocrine Society, and the Pediatric Endocrine Society at specified web links because they contain information relevant to the statements in the boilerplate.

RESPONSE: *ATSDR will review the information and consider making appropriate changes to the boilerplate text in future drafts of toxicological profiles.*

COMMENT: P166 L3-5: Boilerplate statement “However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the

natural environment.” Reviewer #2 stated that this statement should be removed or revised because it implies that endocrine active chemicals in general do not pose a significant risk without acknowledging specific instances where this is not the case. Reviewer #2 also noted the lack of a citation for the statement.

RESPONSE: *ATSDR will review the information and consider making appropriate changes to the boilerplate text in future drafts of toxicological profiles.*

COMMENT: P169 L33 to P169 L11: Reviewer #2 suggested that the EPA Child-Specific Exposure Factors Handbook be consulted and cited for information in this section.

RESPONSE: *The cited EPA (2008) reference is the same as that described by Reviewer #2. This handbook was consulted for information contained in the paragraph.*

COMMENT: P169 L5: Reviewer #2 suggested providing data and citations on trichloroethylene levels in breast milk after exposure of mothers.

RESPONSE: *The statement regarding exposure via breast milk was deleted.*

COMMENT: P169 L5-6: Reviewer #2 asked whether there are data and citations showing trichloroethylene in house dust and dirt.

RESPONSE: *No such sources were found.*

COMMENT: P169 L7-11: Reviewer #2 suggested that these statements be synthesized and discussed with selected statements in the subsequent paragraph.

RESPONSE: *This section was revised to more clearly present information regarding age-related susceptibility to internalized trichloroethylene.*

COMMENT: P169 L25+: Reviewer #2 asked whether all of the information in this section was discussed in more detail in the health effects section, and that it should be so stated if true.

RESPONSE: *Reference was made to the fact that this information was discussed in detail in Section 3.2.*

COMMENT: P171 L22-25: Reviewer #2 suggested moving the following statements to a subsequent paragraph: “There are two biological exposure indices (BEIs) for exposure to trichloroethylene at the ACGIH threshold limit value (TLV-TWA) of 10 ppm (ACGIH 2012). When measured at the end of an 8-hour shift at the end of a 40-hour workweek, the BEI for TCA in urine is 15 mg/g creatinine and the BEI for trichloroethanol in the blood is 0.5 mg/L.”

RESPONSE: *The requested move was made.*

COMMENT: P172 L11-14: Reviewer #2 stated that these sentences should be moved to the section on Biomarkers of Effects.

RESPONSE: *The requested move was made.*

COMMENT: P172 L22-25: Reviewer #2 asked why total adducts of trichloroethylene and its metabolites could be used as a measure of exposure based on the information in this sentence.

RESPONSE: *This sentence was deleted because protein adducts formed following exposure to trichloroethylene were not identified and selected trichloroethylene metabolites (which may also be produced from other xenobiotics) can also result in protein adducts.*

COMMENT: P173 L4-6: Regarding the statement concerning the use of urinary NAG as an indicator of renal damage and the caveat that part of such an effect may include an age-dependent component, Reviewer #2 asked whether age can be controlled for when evaluating the data.

RESPONSE: *The statement was revised and reference to the age-dependent component was deleted.*

COMMENT: P173 L20-25: Reviewer #2 indicated that the statements in this portion contradict earlier statements. Reviewer #2 asked for data or citations to support the statement that urine levels of trichloroethanol may give a better indication of recent exposure.

RESPONSE: *The statements on L20-25 were deleted.*

COMMENT: P173 L34 to P174 L2: Reviewer #2 asked for trichloroethylene levels to be reported from the study of Feldman et al. (1988).

RESPONSE: *The levels were added.*

COMMENT: P174 L2-4: Reviewer #2 asked whether the neurological effect reported by Feldman et al. (1988) is an effect specific to trichloroethylene. The comment was in reference to a statement in the profile that refinement of the technique used to elucidate group differences might make it a useful tool in the future.

RESPONSE: *The statement regarding the usefulness of the neurological test used by Feldman et al. (1988) as a future tool was deleted.*

COMMENT: P174 L23-25: Reviewer #2 assumes that changes in serum protein levels having been used to assess exposure to trichloroethylene would not be specific to trichloroethylene.

RESPONSE: *Yes, a statement to that effect was added.*

COMMENT: P174 L32 to P173 L4: Reviewer #2 suggested moving this section to a previous location.

RESPONSE: *The requested move was made.*

COMMENT: P175 L7-11: Reviewer #2 suggested slight revision of the statement regarding the usefulness of glutathione transferase alpha urinary levels as a biomarker of effect for trichloroethylene to note that the level of this enzyme is not an accurate indicator of trichloroethylene exposure because these increases are not unique to trichloroethylene exposure.

RESPONSE: *The text was slightly revised to note that effects on levels of this enzyme are not unique to trichloroethylene because they are affected by numerous other xenobiotics.*

COMMENT: P175 L22-27: Reviewer #2 suggested moving this information to the end of the subsequent paragraph and asked whether the effects reported in animals and humans are due to ethanol, trichloroethylene, or both.

RESPONSE: *The requested move was not made. However, the first paragraph of this section was revised to note that in a controlled human study, consumption of alcohol following exposure to trichloroethylene resulted in 2-fold higher mean trichloroethylene levels in expired air than levels measured without consumption of alcohol. Furthermore, the text regarding the results in rats was revised to make clear that ethanol exacerbated trichloroethylene-induced depressant effects.*

COMMENT: P176 L27-28: Reviewer #2 asked for identification of “these compounds.”

RESPONSE: *The requested addition was made; the compounds are disulfiram, isopropanol, pyrazole, and tetrachloroethylene.*

COMMENT: P177 L1-3: Reviewer #2 suggested adding the following sentence: “By enhancing the metabolism of trichloroethylene to its cytotoxic metabolites, compounds that induce the hepatic monooxygenase system can potentiate the hepatotoxicity of trichloroethylene.”

RESPONSE: *The suggested addition was made.*

COMMENT: P177 L8-10: Reviewer #2 asked how “selected pharmaceutical drugs” in the study of Cheikh Rouhou et al. (2013) alter metabolism of trichloroethylene.

RESPONSE: *The subsequent two sentences discuss specific pharmaceuticals and their effects on levels of trichloroethylene metabolites. The first sentence of the study summary was slightly revised to make clear that the subsequent sentences were referring to the Cheikh Rouhou et al. (2013) study.*

COMMENT: P177 L21-23: Reviewer #2 asked how caffeine increases the incidence of epinephrine-induced arrhythmias in rabbits exposed to trichloroethylene.

RESPONSE: *Speculation by the study authors was added to indicate possible involvement by stimulating the release of catecholamines from the adrenal medulla and thus elevating circulating levels of epinephrine or by stimulating the release of norepinephrine from adrenergic nerve endings.*

COMMENT: P177 L33 to P178 L3: Reviewer #2 asked which serum enzyme levels declined in the study of Steup et al. (1993) and whether this is a known effect of trichloroethylene or carbon tetrachloride.

RESPONSE: *Serum enzymes were ALT and SDH; these were added to the statement.*

COMMENT: P178 L22-24: Reviewer #2 asked whether the observation of decrease conjugated phenol excretion in rats directly after coexposure to benzene and trichloroethylene, but higher conjugated phenol excretion than in rats exposed to benzene alone 2 days after exposure is due to competition early on and enzyme induction later.

RESPONSE: *The original study reports were consulted and the text was revised to state the following: "Rats injected with mixtures of benzene and trichloroethylene generally exhibited lower rates of excretion of conjugated phenol than that observed from rats receiving benzene alone, indicating that coexposure resulted in inhibition of benzene metabolism (Starek 1991). At higher doses of trichloroethylene (5 mmol/kg), conjugated phenol excretion was decreased by coexposure to benzene directly following trichloroethylene exposure, but higher than in the rat exposed to benzene alone 2 days after trichloroethylene exposure. Co-exposure to trichloroethylene and other chemicals that are metabolized by common cytochrome P450 isozymes to reactive metabolites would be expected to result in decreased trichloroethylene toxicity due to competitive metabolic inhibition and resulting decreased metabolic activation."*

COMMENT: P178 L33: Reviewer #2 asked for reference for the word "first" in the statement "The NIOSH report concluded that the first employee illness reports..."

RESPONSE: *The entire paragraph was deleted per another Reviewer's comment.*

COMMENT: P179 L28-30: Reviewer #2 stated that the statement regarding increased absorption of trichloroethylene in children exposed by inhalation is contradictory to a previous statement.

RESPONSE: *The statements were revised to note that inhaled trichloroethylene may be absorbed in greater concentrations in children exposed by inhalation due to increased ventilation rates (e.g., inspired volume per minute per kg body weight per unit alveolar surface area) and increased cardiac output per kg body weight compared to adults (EPA 2008; NRC 2009; Snodgrass 1992).*

COMMENT: P179 L32-33: Reviewer #2 stated that the statement regarding exposure via breast milk needs quantitative data and a citation.

RESPONSE: *A citation was added, but quantitative data were not located.*

COMMENT: P179 L33-34: Reviewer #2 asked whether trichloroethylene has been found in household dust.

RESPONSE: *No; a statement was added to note that no information was located regarding trichloroethylene levels in household dust or dirt.*

COMMENT: P181 L14-15: Reviewer #2 asked whether there are any useful websites for information.

RESPONSE: *ATSDR is not aware of any.*

COMMENT: P182 L15: reviewer #2 stated that Section 3.11.2 is confusing, that much of the text appears speculative, and that the title is misleading because the section discusses other topics.

RESPONSE: *ATSDR separated various statements into appropriate sections.*

COMMENT: P182 L19-20: Reviewer #2 asked for clarification as to whether the advice in Section 3.11.2 is intended for emergency exposure to high levels or for exposures from environmental contamination.

RESPONSE: *The statement was revised to note that the potential methods for reducing the body burden are intended to address acute exposure to trichloroethylene.*

COMMENT: P183 L1-4: Reviewer #2 stated that the statement is confusing because the GSH pathway leads to formation of toxic metabolites.

RESPONSE: *The entire paragraph was deleted. It was speculative and inaccurate. It would appear that reducing trichloroethylene metabolism would be appropriate as stated in the subsequent paragraph.*

COMMENT: P183 L10-13 and P183 L33 to P184 L2: Reviewer #2 asked why one would be given catecholamines for trichloroethylene poisoning.

RESPONSE: *Text was added to note that catecholamines might be indicated only in cases of seizures.*

COMMENT: P184 L5-6: Reviewer #2 asked for explanation of the “consequences.”

RESPONSE: *Explanatory text was added.*

COMMENT: P188 L2-8: Reviewer #2 suggested adding EPA (IRIS) conclusions to this section. Regarding the statement that “A few reports of acute oral and inhalation exposures have indicated that adverse hepatic and renal effects occur in humans, but exposure/dose data are not available,” Reviewer #2 asked about data on increased cancer in workers and noted that the EPA cancer classification of trichloroethylene as a human carcinogen is based on human data which should be mentioned.

RESPONSE: *EPA conclusions were added.*

COMMENT: P188 L15-17: Reviewer #2 asked whether the statement “there is a paucity of data for effects resulting from acute and chronic exposures” is really true. Reviewer #2 asked how the

completeness of the database on acute and chronic animal studies for trichloroethylene compares to the database for other environmental contaminants.

RESPONSE: *The statement in question was deleted.*

P189 L2-3: Reviewer #2 asked whether LC₅₀ values have been identified in animals.

RESPONSE: *An acute lethality statement was added.*

COMMENT: P190 L23-24: Reviewer #2 stated that the statement “Further information gained from accidental human exposures could be utilized in defining the lowest air level that affects humans” is confusing and asked whether it means “Further analysis of the data from accidental human exposures.”

RESPONSE: *No, it means ongoing accidental exposures. The text was revised to state “When accidental human exposures occur, investigations to determine trichloroethylene exposure levels might add valuable information regarding exposure-response relationships.”*

COMMENT: P191 L20-27: Reviewer #2 asked why developmental effects were not included in this paragraph.

RESPONSE: *Developmental effects were added.*

COMMENT: P193 L1: Reviewer #2 asked whether decreased thymic cellularity is considered a sensitive end point.

RESPONSE: *It is a relatively sensitive end point.*

COMMENT: P193 L3-4: Reviewer #2 asked which end points should be evaluated.

RESPONSE: *A statement was added to indicate end points such as developmental toxicity and immunotoxicity.*

COMMENT: P193 L12+: Reviewer #2 stated that this section should be better integrated with the discussion of chronic human effects in the previous paragraph.

RESPONSE: *The section is designed to present noncancer data first, followed by cancer data. No change was made.*

COMMENT: P193 L16-19: Reviewer #2 asked whether the 15 cohort and case-control studies used in EPA’s meta-analysis are occupational studies.

RESPONSE: *No.*

COMMENT: P194 L2-4: Reviewer #2 asked whether it is true that animal studies “do not point to a particular target organ for increased tumor incidence.”

RESPONSE: *The phrase was deleted.*

COMMENT: P200 L13-14: Reviewer #2 asked whether “humans” refers to volunteers or accidentally-exposed individuals.

RESPONSE: *The statement was revised as follows: “Neurological testing of humans with documented oral exposure to trichloroethylene could provide valuable insight as well.”*

COMMENT: P200 L16-19: Reviewer #2 asked whether the referenced studies include the ones used in the meta-analysis for cancer.

RESPONSE: *Yes.*

COMMENT: P203 L9-11: Reviewer #2 asked for citations for statements regarding exposure via breast milk and household dust.

RESPONSE: *See response to comments on P169.*

COMMENT: P274 L13-14: Reviewer #2 asked whether state regulations could be added.

RESPONSE: *Inclusion of state standards would result in lengthy tables for selected substances.*

COMMENT: P273 L26-28: Reviewer #2 stated that cancer slope factors should be included in this statement.

RESPONSE: *The cancer risk values are presented in Table 8-1.*

Comments provided by Reviewer #3:

Reviewer #3 submitted a file that contained specific comments that were identified by location in pre-public draft 3 of the Toxicological Profile for Trichloroethylene that was provided to the reviewer by ATSDR. The comments and responses are presented below and when possible are identified by page (P) and line (L) on which they are found in pre-public draft 3 of the Toxicological Profile for Trichloroethylene.

COMMENT: P2 L6 (Where is trichloroethylene found? Water:): The Reviewer indicated that trichloroethylene could be deposited at the bottom of aquifers, from which it is slowly released into the ground water.

RESPONSE: *A statement was added to note that trichloroethylene can slowly enter groundwater from contaminated surface water.*

COMMENT: P10 L7-8: One of the reasons why trichloroethylene has been used so much was its non-inflammability, which had led to careless use in the past.

RESPONSE: *The first sentence was revised to note that trichloroethylene is nonflammable.*

COMMENT: P11 (Neurological Effects): The neurotoxicity of the decomposition product dichloroacetylene could be mentioned here (for instance, see Reichert et al 1976).

RESPONSE: *No change was made. This section is not intended to include discussion of the source of neurotoxicity following exposure to trichloroethylene.*

COMMENT: P14 (Cancer): It could be mentioned that kidney cancer was primarily seen in studies that included higher human exposures to trichloroethylene.

RESPONSE: *No change was made. Most of the human studies used in EPA's meta-analysis did not include meaningful estimates of actual exposure levels, although the few in which exposure levels were estimated reported levels ranging from 4 ppm to as high as 100–200 ppm.*

COMMENT: P31 L5-8: In this Toxicological Profile, cytochrome(s) P-450 are called “P-450” throughout. This has a taste of lab slang. Either say “cytochrome P-450” or include the term “P-450” in the glossary and explain it.

RESPONSE: *The term Cytochrome P-450 was added to the glossary. The text was revised to consistently state “cytochrome p-450”.*

COMMENT: P31-32 (Cardiovascular Effects): I find the case described by Konietzko and Elster (1973) particularly noteworthy, where ventricular extrasystoles associated with trichloroethylene occurred only at the workplace upon exposure, not elsewhere.

RESPONSE: *The results of Konietzko and Elster (1973) were added to the profile.*

COMMENT: P43-44: The almost classical case (dehydrochlorination of trichloroethylene to dichloroacetylene by alkaline CO₂ absorbers and subsequent symptoms, upon Mercury spacecraft testing), as described by Saunders (1967, see references) may be mentioned here.

RESPONSE: *A statement was added to Section 3.2.1.4 to note that effects on the trigeminal nerve may be more prominent following exposure to dichloroacetylene (a decomposition product of trichloroethylene) than to trichloroethylene itself. A similar statement was already present in Section 3.2.1.4 (Neurological Effects) for oral exposure, which was the exposure route used in the animal studies.*

COMMENT: P54 L28: What does “up to 15 studies” mean? Is it 15 or less? Which number?

RESPONSE: *The phrase “up to 15 studies” is correct. The main meta-analysis included all 15 studies. However, as described in the text, meta-analysis of 10 of the 15 studies (the 10 studies reported risks for what were considered higher exposure groups) was performed as well.*

COMMENT: P102-103: The impact of the compound’s lipophilicity on its distribution/accumulation behavior could be better addressed.

RESPONSE: *A statement was added to the summary at the beginning of Section 3.4 to indicate that trichloroethylene can accumulate in fat because it is lipophilic.*

COMMENT: P104 L14: The statement of non-saturability reads quite apodictic. I would add: ...in humans, although there is evidence of saturation of the oxidative pathway in experimental animals.

RESPONSE: *The suggested addition was made.*

COMMENT: P106 (Figure 3-3): There is no legend for this figure. Without further explanation, the non-standard abbreviation/expression “TCE-O-P450” makes odd reading. What is this? Also, the appearance of the metabolite N-(hydroxyacetyl)-aminoethanol needs additional explanation, because one wonders where the nitrogen comes from. [It most likely arises from reaction of trichloroethylene oxide with aminoethanol moieties in phospholipids.]

RESPONSE: *Explanatory text was added to the figure. Two possible explanations were added to the text in Section 3.4.3.*

COMMENT: P114 L6: “urinary levels of trichloro compounds” – What is this? [Probably, the long outdated Fujiwara colorimetric reaction had been used. In this case, I would delete “trichloro compounds”, as most of this material is trichloroethanol anyway.]

RESPONSE: *The suggested deletion was made.*

COMMENT: P149 L31: What is a “generalized disruption of the cellular phospholipid membrane”

RESPONSE: *The statement was revised to eliminate the uncertainty regarding the term “generalized”.*

COMMENT: P150 L4-6: This is a wrong interpretation of the paper of Stevens et al (1992). This paper actually shows irreversible (covalent) binding of metabolites of ¹⁴C-labeled trichloroethylene to hemoglobin and albumin of rodents, and metabolic incorporation of the radioactive label as well. This irreversible attachment does not “facilitate their distribution”!

RESPONSE: *The statement regarding adduct formation facilitating distribution was removed.*

COMMENT: P152 L24-25: This statement refers to neurotoxicity upon repeated dosing [not to the acute (pre-)narcotic neurotoxic effects].

RESPONSE: *An explanatory statement was added to indicate that the postulated modulation of neurotrophin gene expression in the hippocampus refers to repeated trichloroethylene exposure.*

COMMENT: P163 L22: Under which practical conditions is “increased renal function” observed? This is nebulous. I think that the last sentence of this paragraph could be deleted.

RESPONSE: *The phrase “increased renal function” was changed to “increased renal output”.*

COMMENT: P166 L26-27: What is a “reduced state in the hepatocyte”? I would delete this sentence.

RESPONSE: *The sentence was revised to read: “consistent with the hypothesis of a more reduced state in the hepatocyte caused by generation of excessive reducing agents by ethanol metabolism.”*

COMMENT: P167 L5: Avoid the old-fashioned and outdated term “mixed-function oxidase”! Call it “monooxygenase”.

RESPONSE: *The suggested change was made.*

COMMENT: P168 L20-25: I do not understand this paragraph. How can propane be the source of CO? Was there possibility of involvement of methylene chloride, which is metabolized to CO?

RESPONSE: *The paragraph was removed because it really is not pertinent to interactions.*

COMMENT: P178 L20-21: It appears to me that this is theoretical wishful thinking. In humans, at the trichloroethylene concentrations observed today, it will not be possible to get such information anymore.

RESPONSE: *The sentence was revised to indicate that although such information would be useful, it is not likely that such information will be available based on present-day occupational exposure limits.*

COMMENT: P179 L33-34: Are studies on dermal exposure to determine targets differing from those upon inhalation or oral dosage really a priority issue? My very personal opinion is that, given the excellent existing toxicokinetic database, this might be a waste of animals and resources.

RESPONSE: *The sentence was revised to indicate that such studies might be useful.*

COMMENT: P182 L7-8: I do not support this vague statement. In my view, the nephrocarcinogenicity of trichloroethylene is clearly established. Research focus should be on elucidation of the other potential endpoints of human carcinogenicity, namely leukemia and non-Hodgkin’s lymphoma (as discussed in 3.2.2.7).

RESPONSE: *The paragraph was revised to indicate that additional studies should focus on cancer sites other than the kidney.*

COMMENT: P188 L11-12: I would prefer a phrasing: “Application of a complete battery of neurological and neurobehavioral tests...is needed”.

RESPONSE: *The suggested change was made.*

COMMENT: P192 (Table 3-10): Ongoing studies: The compilation in Table 3-10 (p. 192) is very helpful. I think that this in fact represents the most important topics to be studied. 2nd entry of this table: Should MGST1 be GSTM1?

RESPONSE: *MGST1 was spelled out (microsomal glutathione transferase-1).*

COMMENT: P202 (Figure 6-1): As there is no legend to this figure – what do the different colors mean?

RESPONSE: *The figure shows the frequency of NPL sites (by state) with trichloroethylene contamination (as noted in the figure legend above the map). The frequency is presented by state. Within the figure is a color-coded description of the frequency (e.g., a red state means that trichloroethylene was detected in 1-7 NPL sites for that state).*

General comments and comments on charge questions and statements from the Guidelines for Peer Review of ATSDR’s Toxicological Profiles

Comments provided by Reviewer #1:

Reviewer #1 provided no comments on the charge questions and statements.

Comments provided by Reviewer #2:

COMMENT: Reviewer #2 stated “A general comment that applies to some sections of the document relates to the way that the findings of some the cited studies. In some cases, the findings of the studies are presented without adequate context or explanation of their significance. Also, the results of multiple studies related to the same question are often not integrated to provide an overall conclusion on the topic. An overall statement about what conclusions can be made from the total body of information from the various studies in each section would greatly improve the usefulness of the document.”

RESPONSE: *ATSDR has made an effort to provide information regarding the significance of particular findings and to provide overall conclusions to results for a particular health effect. In addition, Chapter 2 contains general conclusions and summaries for particular health effects that are presented in greater detail in Chapter 3.*

Charge Question Comments by Reviewer #2

COMMENT: Regarding the charge questions “Are there any data relevant to child health and developmental effects that have not been discussed in the profile and should be? Are there any general

issues relevant to child health that have not been discussed in the profile and should be?”, Reviewer #2 stated “I am not aware of any studies relevant to the above issues that were not included in the profile. However, I believe that the discussion of the basis Intermediate Duration Oral and Inhalation MRLs presented in Appendix A should be expanded to better explain why the Chronic MRLs are also appropriate for Intermediate Duration. The draft does not discuss the important point that developmental effects (cardiac defects), which are one of the key endpoints for the MRLs, can occur over a shorter than chronic timeframe during the critical developmental time period for the effect.”

RESPONSE: *Responses to this comment are made in response to specific comments in the annotated pages file that are relevant to this comment. The profile does note that the developmental effects in animals occurred at intermediate-duration exposure periods.*

CHAPTER 1. PUBLIC HEALTH STATEMENT

COMMENT: Charge question “Does the chapter present the important information in a non-technical style suitable for the average citizen?” Reviewer #2 stated “Yes, for the most part. The few instances where improvements in wording are suggested are marked in the text.”

RESPONSE: *See the next section for responses to suggestions on annotated pages.*

COMMENT: Charge questions “Do the answers to the questions adequately address the concerns of the lay public? Are these summary sections consistent, and are they supported by the technical discussion in the remainder of the text?” Reviewer #2 stated “For the most part, yes. An important comment is that inhalation of TCE released from contaminated drinking water in the home (e.g., during showering and bathing; laundry; dishwashing) is an important exposure source from contaminated drinking water, in addition to ingestion. This is important because the public may not be aware that using contaminated water for non-potable purposes in the home can lead to exposure. These and other comments are provided in the text.”

RESPONSE: *See the section titled Responses to Comments on Annotated Pages.*

COMMENT: Charge question “Are the scientific terms that are used too technical or require additional explanation?” Reviewer #2 stated “For the most part, the level of wording is appropriate. A few comments are marked in the text.”

RESPONSE: *See the section titled Responses to Comments on Annotated Pages.*

CHAPTER 2. RELEVANCE TO PUBLIC HEALTH

COMMENT: Charge question “Do you agree with those effects known to occur in humans as reported in the text?” Reviewer #2 stated “Yes. A few comments are noted in the text.”

RESPONSE: *See the section titled Responses to Comments on Annotated Pages.*

COMMENT: Charge question “Are the effects only observed in animals likely to be of concern to humans?” Reviewer #2 stated “The effects reported from animal studies are generally consistent with human data. A few specific effects seen in animal studies that were not reported in humans were

mentioned such as immune and neurobehavioral effects after developmental exposures. However, these types of effects are difficult to assess in human populations and are consistent with other effects reported in humans (neurological and immune toxicity in adults). Therefore, these effects would also reasonably be expected to occur in humans exposed to sufficient doses.

RESPONSE: *No change was suggested.*

COMMENT: Charge question “Have exposure conditions been adequately described?” Reviewer #2 stated “It is suggested that indoor air exposure be mentioned along with ambient air and drinking water ingestion as one of the most important exposure routes (p. 10, 3rd paragraph). In subsequent chapters, it is mentioned that indoor air levels are usually higher than outdoor air levels, and that inhalation of TCE released from contaminated drinking water results in exposures equal to or greater than from ingestion of the water.”

RESPONSE: *Chapter 2 was revised to include the following statement: “The most important routes of exposure to trichloroethylene for most members of the general population appear to be inhalation of the compound in ambient air and ingestion of drinking water. Trichloroethylene may evaporate from contaminated groundwater and soil and migrate into air spaces beneath buildings to enter the indoor air, a process termed vapor intrusion (EPA 2002).”*

COMMENT: Charge for comments on MRLs (Section 2.3). Reviewer #2 stated “I agree with the use of the EPA IRIS RfDs and RfCs as chronic and intermediate duration oral and inhalation MRLs. However, the explanation of why the chronic RfD and RfC were used for the intermediate duration MRL is extremely confusing and is not understandable to me. This should be clarified. These sections are marked in the text. Also, the ATSDR-defined exposure durations for acute, intermediate, and chronic MRLs should be provided in Section 2.3, not just in the Appendix A. Additionally, a key point about the reason that the chronic RfD/RfC is applicable to shorter durations is not mentioned in the draft and should be added. One of the critical endpoints for the RfD/RfC is heart malformations in the rat. This effect occurs within the shorter-than-chronic timeframe that is the critical period for development of the heart. For this reason, the RfD/RfC is applicable to an intermediate duration timeframe, as well as a chronic timeframe. Finally, the explanation for the decision not to develop acute MRLs is not clear. Was any consideration given to whether or not the developmental effect could occur within the 14 day time window for acute MRLs? More importantly, several studies listed in Table 4-98 of the IRIS Toxicological Review found developmental effects with less than 14 days of exposure. For example, the developmental effects reported by Narotsky et al. (1995) from exposures to rats on GD 6-15 should be evaluated, and the possibility of developing acute MRLs based on these studies should be considered. Both oral and inhalation studies can be considered for use as the basis of inhalation or oral MRLs, since PBPK models are available to extrapolate between routes of exposure.”

RESPONSE: *The suggested addition of durations for acute-, intermediate-, and chronic-duration exposures was made to boilerplate in chapter 2. The point regarding cardiac malformations that occur within shorter-than-chronic timeframes and its applicability to an intermediate duration timeframe as well as chronic, was made in the profile. The question of whether consideration was given to whether cardiac malformations could occur within the 14-day timeframe for an acute-duration exposure and its possible use for developing an acute-duration MRL had already been addressed in the profile and it was noted that an acute-duration MRL was not derived due to uncertainty as to the duration of exposure required to cause the critical effects such as cardiac malformations. Regarding the possibility of developing an acute-duration MRL based on developmental effects reported by Narotsky et al. (1995) following acute-duration exposure, an acute-duration MRL based on the results of Narotsky et al. (1995)*

might not be protective of cardiac malformations from slightly longer than 14 days of exposure, which exhibit a lower effect level than that from the study of Narotsky et al. (1995). Specific responses to other comments made on annotated pages are addressed below.

CHAPTER 3. HEALTH EFFECTS

COMMENT: Charge question “*Were adequately designed human studies identified in the text? If not, were the major limitations of the studies sufficiently described without providing detailed discussions?*” Reviewer #2 stated “Most of the human studies described in the text involved unintentional occupational or environmental exposures. For this reason, the actual exposures/doses received are often uncertain or unknown. These limitations are appropriately described in the text.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question “*Were the conclusions drawn by the authors of the studies appropriate and accurately reflected in the profile? If not, did the text provide adequate justification for including the study (e.g. citing study limitations)?*” Reviewer #2 stated “In general, the answer to these questions is yes. Comments on this topic are shown in the text.”

RESPONSE: *See the section titled Responses to Comments on Annotated Pages.*

COMMENT: Charge question “*Were all appropriate NOAELs and LOAELs identified for each study? If not, did the text provide adequate justification for excluding NOAELs/LOAELs?*” Reviewer #2 stated “As above, most of the human studies involve unintentional exposures. For most of these studies, there is insufficient quantitative exposure data to identify LOAELs/NOAELs.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question “*Were the appropriate statistical tests used in the studies?*” Reviewer #2 stated “The text does not discuss which statistical tests were used, and does not specifically state that the effects mentioned were statistically significant. To clarify, perhaps it could be stated that the effects were considered statistically significant by the tests and significance level used by the study authors unless otherwise noted.”

RESPONSE: *Report of specific statistical tests employed by the study authors does not appear necessary.*

COMMENT: Charge question “*Are you aware of other relevant studies?*” Reviewer #2 stated “No, I am not.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question “*Quality of Animal Studies: Were adequately designed animal studies identified in the text? If not, does the inadequate design negate the utility of the study?*” Reviewer #2 stated “Yes, adequately designed animal studies were identified.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question “*Were the animal species appropriate for the most significant toxicological endpoint of the study?*” Reviewer #2 stated “The meaning of this question is somewhat unclear. All relevant studies are reported in the text, regardless of which species was used. Differences among species related to pharmacokinetics are discussed in another section of the report.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question “*Were the conclusions drawn by the authors of the studies appropriate and accurately reflected in the profile? If not, did the text provide adequate justification for including the study (e.g. citing study limitations)?*” Reviewer #2 stated “In general, the answer to these questions is yes. Comments on this topic are shown in the text.”

RESPONSE: *See the section titled Responses to Comments on Annotated Pages.*

COMMENT: Charge question “*Were all appropriate NOAELs and LOAELs identified for each study? If not, did the text provide adequate justification for excluding NOAELs/LOAELs?*” Reviewer #2 stated “In general, yes. Any comments or suggestions are shown in the text”

RESPONSE: *See the section titled Responses to Comments on Annotated Pages.*

COMMENT: Charge question “*If appropriate, is there a discussion of the toxicities of the various forms of the substance?*” Reviewer #2 stated “TCE does not exist in more than one form. However, in some of the carcinogenicity studies, the TCE tested contained stabilizers which are known to be carcinogenic. This issue is appropriately discussed in the text.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question “*Were the appropriate statistical tests used in the studies?*” Reviewer #2 stated “The text does not discuss which statistical tests were used, and does not specifically state that the effects mentioned were statistically significant. To clarify, perhaps it could be stated that the effects were considered statistically significant by the tests and significance level used by the study authors unless otherwise noted.”

RESPONSE: *Report of specific statistical tests employed by the study authors does not appear necessary.*

COMMENT: Charge question “*Are you aware of other relevant studies?*” Reviewer #2 stated “No, I am not.”

RESPONSE: *No revisions were suggested.*

COMMENT: LSE charge question “*Are the LSE tables and figures complete and self-explanatory?*” Reviewer #2 stated “For the most part, yes. However, the 10^{-4} – 10^{-7} cancer risk levels are not shown in the figures.

RESPONSE: *The cancer risk levels were added to the LSE table.*

COMMENT: Charge question “Does the “Users Guide” explain clearly how to use them?” Reviewer #2 stated “Yes.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question “Are exposure levels (units, dose) accurately presented for the route of exposure?” Reviewer #2 stated “Yes.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge statement “Please offer suggestions to improve the effectiveness of the LSE tables and figures and the “User’s Guide.” Reviewer #2 stated “I think that the tables, figures, and User’s Guide are clearly written and provide the needed information for the most part. My main suggestion is that the criteria for defining effects as “Less Serious” and “Serious” should be provided.”

RESPONSE: *Definitions and general criteria are provided in the Introduction to Section 3.2.*

COMMENT: Charge question “Do you agree with the categorization of “less serious” or “serious” for the effects cited in the LSE tables?” Reviewer #2 stated “The criteria used to decide if an effect is “less serious” or “serious” are unclear, and it is difficult to determine if the categorization was done consistently and appropriately from the information provided. I recommend that more information on this be provided. Some specific examples are how it was decided that #30, 31, 46, and 47 in Table 3-1 are “less serious” and #45 was “serious”. Also, is there a specific % cutoff for decreased weight gain to be considered “less serious” versus “serious”? For example, #11 in Table 3-2 is “serious” while other studies with decreased weight gain close to the same percent are “less serious”. In addition to these examples, the basis for categorization of quite a few other LOAELs is also unclear.”

RESPONSE: *Definitions and general criteria are provided in the intro to Section 3.2.*

COMMENT: Charge question “If MRLs have been derived, are the values justifiable?” Reviewer #2 stated “The intermediate and chronic MRLs are based on the IRIS chronic RfD and are well justified. It is appropriate to use the same value for the intermediate and chronic duration MRLs based on the data available for TCE.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question “If no MRLs have been derived, do you agree that the data do not support such a derivation?” Reviewer #2 stated “The rationale for not developing acute MRLs is not clear, and it seems important to provide some guidance for short exposures, if possible. Numerous studies with acute exposure durations are listed in Tables 1 and 2. Were these studies not used because the LOAELs were so much higher than the LOAELs for developmental effects in slightly longer studies (slightly >14 days)? In the text, it is acknowledged that the developmental effects used for the

intermediate and chronic studies that occurred in slightly more than 14 days (e.g., Johnson et al, 2003, 21 day duration) might occur in 14 days.”

RESPONSE: *This point was made in the profile and it was noted that an acute-duration MRL was not derived due to uncertainty as to the duration of exposure required to cause the critical effects such as cardiac malformations.*

COMMENT: Charge questions regarding Evaluation of Text “*Have the major limitations of the studies been adequately and accurately discussed? How might discussions be changed to improve or more accurately reflect the proper interpretation of the studies?*” Reviewer #2 stated “For some studies, the results are summarized with no mention of whether or not there are any major limitations.” “*Has the effect, or key endpoint, been critically evaluated for its relevance in both humans and animals?*” Reviewer #2 stated “For some studies, the results are summarized without discussion of relevance.” “*Have 'bottom-line' statements been made regarding the relevance of the endpoint for human health?*” Reviewer #2 stated “The relevance for human health of endpoints observed in humans is fairly obvious. It does not appear that “bottom line” statements about relevance to human health were included for many or most of the animal studies.” “*Are the conclusions appropriate given the overall database? If not, please discuss your own conclusions based on the data provided and other data provided to you but not presented in the text.*” Reviewer #2 stated “I do not see general conclusions based on the overall database. The section consists of descriptions of studies related to various endpoints, with separate sections for each route of exposure. There is no section where the information in the overall database has been integrated to develop conclusions.”

RESPONSE: *Overall conclusions are presented in the first paragraph of Chapter 2, some of which were added in response to Reviewer #2’s comment. Limitations of the major studies that provide a basis for MRL derivation are presented in the profile. Statements regarding human relevance of results from key animal studies are presented in the profile.*

COMMENT: Charge question “*Has adequate attention been paid to dose-response relationships for both human and animal data? Please explain.*” Reviewer #2 stated “Dose-response is adequately discussed for most of the studies. I have commented in the texts in any instances where more discussion is needed.”

RESPONSE: *See the section titled Responses to Comments on Annotated Pages.*

COMMENT: Charge question “*Has the animal data been used to draw support for any known human effects? If so, critique the validity of the support.*” Reviewer #2 stated “In many instances, the human and animal studies are summarized, but the information is not integrated. In many instances, it is not discussed whether or not the animal data supports the human effects.”

RESPONSE: *Selected statements were added to the profile, particularly regarding the human relevance of the animal data.*

Section 3.3 GENOTOXICITY

COMMENT: Reviewer #2 stated “A few comments are noted in the text.”

RESPONSE: *See the section titled Responses to Comments on Annotated Pages.*

Section 3.4 TOXICOKINETICS

COMMENT: Charge question “*Is there adequate discussion of absorption, distribution, metabolism, and excretion of the substance? If not, suggest ways to improve the text.*” Reviewer #2 stated “I made numerous comments on the sections discussing these issues, shown in tracked changes in the text.”

RESPONSE: *See the section titled Responses to Comments on Annotated Pages.*

COMMENT: Charge question “*Have the major organs, tissues, etc. in which the substance is stored been identified? If not, suggest ways to improve the text.*” Reviewer #2 stated “This information is discussed. Any comments have been made in the text.”

RESPONSE: *See the section titled Responses to Comments on Annotated Pages.*

COMMENT: Charge question “*Have all applicable metabolic parameters been presented? Have all available pharmacokinetic/pharmacodynamic models and supporting data been presented? If not, please explain.*” Reviewer #2 stated “These topics are discussed in detail. Instances where the discussion is unclear are noted in the text.”

RESPONSE: *See the section titled Responses to Comments on Annotated Pages.*

COMMENT: Charge question “*Is there adequate discussion of the differences in toxicokinetics between humans and animals? What other observations should be made?*” Reviewer #2 stated “This topic is discussed. Instances where the discussion is unclear or should be expanded are noted in the text.”

RESPONSE: *See the section titled Responses to Comments on Annotated Pages.*

COMMENT: Charge question “*Is there an adequate discussion of the relevance of animal toxicokinetic information for humans? If not, please explain.*” Reviewer #2 stated “This topic is discussed. Instances where the discussion is unclear or should be expanded are noted in the text.”

RESPONSE: *See the section titled Responses to Comments on Annotated Pages.*

COMMENT: Charge question “*If applicable, is there a discussion of the toxicokinetics of different forms of the substance (e.g., inorganic vs. organic mercury)?*” Reviewer #2 stated “This issue is not relevant to TCE, as there is only one form.”

RESPONSE: *No revisions were suggested.*

Section 3.5 MECHANISMS OF ACTION

COMMENT: Charge question “*Have all possible mechanisms of action been discussed? If not, please explain.*” Reviewer #2 stated “The mechanisms of action are discussed. I had numerous comments on this section which are shown in the text.”

RESPONSE: See the section titled Responses to Comments on Annotated Pages.

Section 3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

COMMENT: Reviewer #2 stated “I had substantial comments on the general language at the beginning of this section (shown in the text). I suggest that more recent information sources about the general topic of endocrine disruption by environmental contaminants be discussed and provided citations for some suggested sources.”

RESPONSE: See the section titled Responses to Comments on Annotated Pages.

Section 3.7 CHILDREN’S SUSCEPTIBILITY

COMMENT: Reviewer #2 stated “My comments on this section are shown in the text.”

RESPONSE: See the section titled Responses to Comments on Annotated Pages.

Section 3.8 BIOMARKERS OF EXPOSURE AND EFFECT

COMMENT: Charge question “*Are the biomarkers of exposure specific for the substance or are they for a class of substances? If they are not specific, how would you change the text?*” Reviewer #2 stated “The issue of specificity is generally discussed appropriately. Comments in text indicate any parts that need improvement.”

RESPONSE: See the section titled Responses to Comments on Annotated Pages.

COMMENT: Charge question “*Are there valid tests to measure the biomarker of exposure? Is this consistent with statements made in other sections of the text? If not, please indicate where inconsistencies exist.*” Reviewer #2 stated “Biomarkers for exposure are appropriately discussed, in general. Comments are shown in text.”

RESPONSE: See the section titled Responses to Comments on Annotated Pages.

COMMENT: Charge question “*Are the biomarkers of effect specific for the substance or are they for a class of substances? If they are not specific, how would you change the text?*” Reviewer #2 stated “This question is discussed in the text. Any comments are shown in the text.”

RESPONSE: See the section titled Responses to Comments on Annotated Pages.

COMMENT: Charge question “*Are there valid tests to measure the biomarker of effect? Is this consistent with statements made in other sections of the text? If not, please indicate where inconsistencies exist.*” Reviewer #2 stated “Biomarkers of effects are appropriately discussed, in general. Comments are shown in text.”

RESPONSE: See the section titled Responses to Comments on Annotated Pages.

Section 3.9 INTERACTIONS WITH OTHER CHEMICALS

COMMENT: Charge question “*Is there adequate discussion of the interactive effects with other substances?*” Reviewer #2 stated “This is adequately discussed. Any comments are shown in the text.”

RESPONSE: See the section titled *Responses to Comments on Annotated Pages*.

COMMENT: Charge question “*Does the discussion concentrate on those effects that might occur at hazardous waste sites? If not, please clarify and add additional references.*” Reviewer #2 stated “Interactions with alcohol, pharmaceuticals, and industrial chemicals which might be found at hazardous waste sites are discussed. In general, the levels of exposure at which interactions occurred for industrial chemicals are much higher than the exposure levels expected near hazardous waste sites.”

RESPONSE: No revisions were suggested.

COMMENT: Charge question “*If interactive effects with other substances are known, does the text discuss the mechanisms of these interactions? If not, please clarify and provide any appropriate references.*” Reviewer #2 stated “When known, the mechanisms are discussed. Any comments are shown in the text.”

RESPONSE: See the section titled *Responses to Comments on Annotated Pages*.

Section 3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

COMMENT: Charge question “*Is there a discussion of populations at higher risk because of biological differences which make them more susceptible? Do you agree with the choices of populations? Why or why not? Are you aware of additional studies in this area?*” Reviewer #2 stated “In general, this topic is discussed appropriately. However, there are some general statements which are not supported by citations specific to TCE. These and other comments are shown in the text.”

RESPONSE: See the section titled *Responses to Comments on Annotated Pages*.

Section 3.11 METHODS FOR REDUCING TOXIC EFFECTS

COMMENT: Charge question “*Where data or reasonable conjecture permit, this section describes directions of clinical practice and research that may help develop new methods for reducing toxic effects in individuals or populations exposed to a substance. It is intended to inform the public of existing clinical practice(s) and the status of research concerning such methods. It is not intended as a guide to treatment for poisoning.*” Reviewer #2 stated “I have added a few works to emphasize the point above (see text).”

RESPONSE: See the section titled *Responses to Comments on Annotated Pages*.

COMMENT: Charge question “*When possible, a distinction should be made between differences in management and treatment following acute (generally high-level) vs. chronic (generally low level) exposure.*” Reviewer #2 stated “I have added comments in the text where this was not sufficiently clear.”

RESPONSE: See the section titled *Responses to Comments on Annotated Pages*.

COMMENT: Charge question “*Is the management and treatment specific for the substance, or is it general for a class of substances?*” Reviewer #2 stated “For the most part, it is general rather than specific to TCE.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question “*Is there any controversy associated with the treatment? Is it a "well accepted" treatment?*” Reviewer #2 stated “Section 3.11.2 describes well accepted approaches.”

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, Reviewer #2 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: Charge question “*Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)?*” Reviewer #2 stated “I am not aware of any such hazards.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question “*Are treatments available to prevent the specific substance from reaching the target organ(s), or are the actions general for a class of substances?*” Reviewer #2 stated “Some methods are rather general, and others (e.g., administering compounds with SH group) are specific to TCE or other chemicals for which GSH is involved in metabolism.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question “*Is there any controversy associated with the treatment? Is it a "well-accepted" treatment? If the discussion concerns an experimental method, do you agree with the conceptual approach of the method?*” Some of the methods are general and well accepted, such as hydration. I am not sure of the feasibility or usefulness of other suggested approaches including administration of compounds with SH groups, particularly since the GSH pathway forms toxic metabolites of TCE. Also, compounds with SH groups, mixed function oxidase inhibitors, and competitive inhibitors of TCE metabolism/cytochrome P-450 inhibitors which might be used are not specified. These might also have their own toxicities or toxic interactions with TCE, as is the case for ethanol.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question “*Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)?*” Reviewer #2 stated “As

above, compounds with SH groups, mixed function oxidase inhibitors, and competitive inhibitors of TCE metabolism/cytochrome P-450 inhibitors which might be used are not specified. These might also have their own toxicities or toxic interactions with TCE, and children may be particularly susceptible to these effects.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question “*Are there treatments to prevent adverse effects as the substance is being eliminated from the major organs/tissues where it has been stored (e.g., as a substance is eliminated from adipose tissue, can we prevent adverse effects from occurring in the target organ[s])?*” Reviewer #2 stated “This is not specifically discussed. Approaches which affect metabolism of TCE would be relevant to TCE released from tissues where it is stored.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question “*Are treatments available to prevent the specific substance from reaching the target organ(s), or are the treatment's actions general for a class of substances?*” Reviewer #2 stated “Such treatments are not discussed.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question “*Is there any controversy associated with the treatment? Is it a "well accepted" treatment? If the discussion concerns an experimental method, do you agree with the conceptual approach of the method?*” Reviewer #2 stated “The use of beta blockers appears to have a valid conceptual basis. The basis for the other approaches discussed in subsequent paragraphs of this section appear to be extremely speculative.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question “*Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)?*” Reviewer #2 stated “I am not sure if children are susceptible to cardiac arrhythmias from TCE, and, if so, if there are any particular risks of beta blockers in children. If so, this should be taken into consideration when deciding whether to use beta blockers in children.”

RESPONSE: *No revisions were suggested.*

Section 3.12 ADEQUACY OF THE DATABASE

Existing Information on Health Effects of [Substance X]

COMMENT: Charge question “*Do you know of other studies that may fill a data gap? If so, please provide the reference.*” Reviewer #2 stated “I am not aware of any additional information to fill data gaps. However, I suggest that it be acknowledged that the risk of cancer from oral exposure has been estimated from inhalation data by USEPA IRIS, using PBPK modeling for route to route extrapolation.

RESPONSE: *This explanation has been added to the text.*

Identification of Data Needs

COMMENT: Charge question “*Are the data needs presented in a neutral, non-judgmental fashion? Please note where the text shows bias.*” Reviewer #2 stated “In general, this has been done. Any comments are noted in text.”

RESPONSE: *See the section titled Responses to Comments on Annotated Pages.*

COMMENT: Charge question “*Do you agree with the identified data needs? If not, please explain your response and support your conclusions with appropriate references.*” Reviewer #2 stated “In general, I agree.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question “*Does the text indicate whether any information on the data need exists?*” Reviewer #2 stated “The text indicates what information is currently available.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question “*Does the text adequately justify why further development of the data need would be desirable; or, conversely, justify the "inappropriateness" of developing the data need at present? If not, how can this justification be improved.*” Reviewer #2 stated “The reasons that additional information is needed are mentioned where relevant.”

RESPONSE: *No revisions were suggested.*

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

COMMENT: Charge question “*Are you aware of any information or values that are wrong or missing in the chemical and physical properties tables?*” Reviewer #2 stated “I am not aware of any additional or incorrect information.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question “*Is information provided on the various forms of the substance? If not, please explain.*” Reviewer #2 stated “This issue is not relevant to TCE as it does not exist in more than one form.”

RESPONSE: *No revisions were suggested.*

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

COMMENT: Charge question “*Are you aware of any information that is wrong or missing?*” Reviewer #2 stated “I am not aware of any additional or incorrect information.”

RESPONSE: *No revisions were suggested.*

CHAPTER 6. POTENTIAL FOR HUMAN EXPOSURE

COMMENT: Charge questions “*Has the text appropriately traced the substance from its point of release to the environment until it reaches the receptor population? Does the text provide sufficient and technically sound information regarding the extent of occurrence at NPL sites? Do you know of other relevant information? Please provide references for added information.*” Reviewer #2 stated “In general, these topics are adequately covered. Comments are provided in the text. I believe that the information about New Jersey in the map (Figure 6-1) is incorrect, although I do not have a citation for the correct information.”

RESPONSE: *See the section titled Responses to Comments on Annotated Pages. The map was corrected; there are 107 sites according to the latest information from the HazDat database (2007).*

COMMENT: Charge question “*Does the text cover pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media? Do you know of other relevant information? Please provide references for added information.*” Reviewer #2 stated “In general, these topics are adequately covered. Comments are provided in the text.”

RESPONSE: *See the section titled Responses to Comments on Annotated Pages.*

COMMENT: Charge questions “*Does the text provide information on levels monitored or estimated in the environment, including background levels? Are proper units used for each medium? Does the information include the form of the substance measured? Is there an adequate discussion of the quality of the information? Do you know of other relevant information? Please provide references for added information.*” Reviewer #2 stated “Comments are provided in the text. In general, the units used to present information on environmental concentrations are not consistent, and this makes it difficult to read and interpret the information. It appears that the information may be presented using the units used by the authors of the cited study, and I recommend converting to consistent units. Additionally, the reporting levels or detection levels are not presented for quite a few of the studies. Occurrence frequencies, such as for water or other media, are not meaningful without including the reporting/detection level. Other comments are shown in the text.”

RESPONSE: *See the section titled Responses to Comments on Annotated Pages. Units were presented as per study author. When units were reported in mg/m³, for example, they were converted to ppm and portrayed in parentheses. In lengthy Table 6-5, air concentrations were not converted.*

COMMENT: Charge questions “*Does the text describe sources and pathways of exposure for the general population and occupations involved in the handling of the substance, as well as populations with potentially high exposures? Do you agree with the selection of these populations? If not, why? Which additional populations should be included in this section?*” Reviewer #2 stated “Specific comments, particularly as related to exposure from drinking water, are shown in the text.”

RESPONSE: *See the section titled Responses to Comments on Annotated Pages.*

COMMENT: Charge statement “*For Sections 6.8.1, Identification of Data Needs and 6.8.2, Ongoing Studies, answer the same questions presented in Section 3.12.2, Identification of Data Needs and*

3.12.3, *Ongoing Studies*.” Reviewer #2 stated “In general, this section is adequate. It would be helpful to include more information on the exposures at Camp Lejeune and Camp Pendleton, if it is possible to do so.”

RESPONSE: *A statement was added to direct the reader to an ATSDR URL for additional information regarding Camp Lejeune.*

CHAPTER 7. ANALYTICAL METHODS

COMMENT: Charge question “*Are you aware of additional methods that can be added to the tables? If so, please provide copies of appropriate references.*” Reviewer #2 stated “I am not aware of additional methods.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question “*Have methods been included for measuring key metabolites mentioned previously in the text?*” Reviewer #2 stated “Yes.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge questions “*If unique issues related to sampling for the substance exist, have they been adequately addressed in the text? What other discussion should be provided?*” Reviewer #2 stated “In general, there are no major unique issues for sampling for TCE.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge statement “*For Section 7.3.1, Identification of Data Needs, answer the same questions presented in Section 3.12.2, Identification of Data Needs.*” Reviewer #2 stated “In general, this section is adequate. A few comments are shown in the text.”

RESPONSE: *See the section titled Responses to Comments on Annotated Pages.*

CHAPTER 8. REGULATIONS AND ADVISORIES

COMMENT: Charge question “*Are you aware of other regulations or guidelines that may be appropriate for the table? If so, please provide a copy of the reference.*” Reviewer #2 stated “Can guidelines or standards developed by states that are different or in addition to Federal be included? If so, I can provide some of this information later.”

RESPONSE: *State guidelines and standards were formerly included in ATSDR toxicological profiles. However, their inclusion made the table bulky and less focused. Therefore, state guidelines and standards are no longer included. The reader is advised to contact state agencies for this information.*

CHAPTER 9. REFERENCES

COMMENT: Charge question “*Are there additional references that provide new data or are there better studies than those already in the text? If so, please provide a copy of each additional reference.*” Reviewer #2 stated “I am not aware of newer or better references.”

RESPONSE: *No revisions were suggested.*

Comments provided by Reviewer #3:

Reviewer #3 provided no comments on the charge questions and statements.