

**DISPOSITION OF PEER REVIEW COMMENTS FOR  
TOXICOLOGICAL PROFILE FOR 1,2,3-TRICHLOROPROPANE**

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

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Peer reviewers for the third pre-public comment draft of the Toxicological Profile for 1,2,3-Trichloropropane were:

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## Comments provided by Peer Reviewer #1

### ATSDR Charge Questions and Responses and General Comments

#### *Chapter 1*

**QUESTION:** Does Chapter 1 adequately summarize the published literature regarding health effects for this substance?

**COMMENT:** One important background consideration that should be shared with the reader is the analogy with other compounds with two carbon atoms in a row with halogens attached. These include ethylene dibromide and ethylene dichloride. At least in the case of ethylene dibromide, metabolism via reactions with glutathione leads to formation of a compound with a three-membered ring, where two carbon atoms are attached to a sulfur atom (an “episulfonium” compound). This compound can then react with DNA as a powerful alkylating agent, likely leading to DNA reaction and cancer. As far as I know this has not yet be documented for TCP, but it seems a possibility that should be borne in mind in light of the observed carcinogenic action of TCP.

**RESPONSE:** *This information is not relevant to Chapter 1, which is a high-level overview of the toxicological database for 1,2,3-trichloropropane. Little is known about the carcinogenic mechanisms or the causative agent. The following was added to Section 6.2:*

Although animal studies provide evidence of the carcinogenicity of 1,2,3-trichloropropane, very little information is available on the mechanisms of action for carcinogenicity and the causative agent. Mechanistic studies would provide valuable information to the understanding the carcinogenic potential in humans.

#### *Chapter 3*

**COMMENT:** The likely metabolism route via reaction with glutathione is not mentioned. It seems to me that this reaction is likely because of the analogy with ethylene dibromide, and its potential significance deserves some discussion because it could lead to primary genetic action leading to carcinogenesis. Also, according to the writeup for this compound in PubChem, “[glutathione](#) conjugation is suggested as an important metabolic route for TCP ... Abstract: [PubMed](#) Volp RF et al; *Toxicol Appl Pharmacol* 75 (1): 8-17 (1984)”

**RESPONSE:** *The results of the Volp et al. (1984) study is discussed in the profile in several toxicokinetics sections (Section 3.1). The metabolism of 1,2,3-trichloropropane via glutathione conjugation is discussed in Section 3.1.3.*

#### *Chapter 7*

**QUESTION:** We would like to know your thoughts on the regulations and guidelines that are presented and any that should be added or removed. Are you aware of any additional regulations or guidelines that we should add? Please provide citations. Are there any that should be removed? Explain.

**COMMENT:** I have no comments on the material presented in this chapter. It seems a routine compilation of numerical criteria put out by different agencies for their own purposes.

**RESPONSE:** *No response necessary.*

### ***Appendix A***

**QUESTION:** Please address the MRL worksheet based upon the questions provided above about the newly derived MRL.

**COMMENT:** I have no idea why this empirical fit of a fifth degree polynomial curve is included. There is no reasonable basis in plausible toxicological mechanisms why this kind of model is indicated. This same comment also applies to other empirical fits to arbitrary mathematical forms included elsewhere in Appendix A. Without some basis in toxicological mechanisms it seems to me they add no value to the analysis.

**RESPONSE:** *Regarding the comment on Figure A-1, the selection of the benchmark dose (BMD) model is not based on a toxicological mechanism. Rather, the model is selected based on the fit to the dose-response data. The criteria used to identify the BMD model providing the best fit is discussed in the MRL Worksheet in the “Benchmark Dose Modeling” section.*

### ***Appendix B***

**QUESTION:** Please provide comments about the process utilized in this section.

**COMMENT:** The literature search terms and procedures seem reasonable.

**RESPONSE:** *No response necessary.*

## Comments provided by Peer Reviewer #2

In addition to responding to charge questions, the Reviewer suggested a number of editorial revisions, most of the suggested revisions were made to the profile. Some stylistic changes that were purely arbitrary were not incorporated.

### ATSDR Charge Questions and Responses and General Comments

#### *Chapter 1*

**QUESTION:** Does Chapter 1 adequately summarize the published literature regarding the health effects present in Chapter 2 for this substance?

**COMMENT:** A typo has been noted on Page 5; line 28: 'bromodichloromethane' is a typo. This should be 1,2,3-trichloropropane?

**RESPONSE:** *The error was corrected.*

#### **Chapter 2**

**QUESTION:** a) First, does Chapter 2 adequately reflect the published literature regarding health effects for this substance? Are you aware of any studies that are not included that may be relevant in the derivation of MRLs for this chemical?

**COMMENT:** Health effects of 1,2,3-trichloropropane presented in original Toxicological Profile (published in 1992) has been revised by incorporating the recent literature on this chemical. This information is used together with updated methodology and guide lines to derive MRL values. The details such as dose(s), route and target organs have been adequately described including cancer endpoints. Non sensitive targets, such as body weight, lacrimation, impaired reproduction and developmental toxicity are also included. Tables and figures are adequately used to summarize the data. However, to explain the metabolism on page 54, a composite metabolic figure should be added for better understanding of the text presented.

**RESPONSE:** *An illustration of the metabolic scheme has been added to Section 3.1.3.*

**COMMENT:** Page 59; line 13--Since original manuscript (Drew et al. 1978) does not identify the isomeric form of the compounds, use of trichloro- and dichloro-propane by removal of isomeric identification is suggested.

**RESPONSE:** *The sentence in Section 3.4 was revised: Rats were exposed by inhalation to 500 ppm trichloropropane and 1,000 ppm dichloropropane alone and in combination for 4 hours (Drew et al. 1978).*

**QUESTION:** Acute-Duration Inhalation MRL: A revised acute duration inhalation MRL of 0.001 ppm was derived based on decreased thickness of the nasal olfactory epithelium of rats. This MRL is based on

a NOAEL<sub>HEC</sub> of 0.03 ppm and a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

**COMMENT:** Agree

**RESPONSE:** *No response necessary.*

**QUESTION:** Please comment on any aspect of our MRL database assessment that you feel should be addressed.

**COMMENT:** Reasoning should be presented for the use of 3 for extrapolation from animals to humans in acute duration inhalation MRL

**RESPONSE:** *As noted in the MRL Worksheet in Appendix A, a partial uncertainty factor of 3 was used to extrapolate from animals to humans because dosimetric adjustments were used. The human equivalent concentration of the NOAEL concentration was calculated using dosimetric adjustments, specifically the ratio of human to animal extrathoracic regional gas doses. The regional gas dose was calculated as the ratio of the species-specific inhalation rate to the species-specific surface area of the extrathoracic region.*

**QUESTION:** The new chronic-duration oral MRL is 0.005 mg/kg/day. Do you agree/disagree with this value? Explain. If you disagree, please specify the MRL value that you propose.

**COMMENT:** Agree

**RESPONSE:** *No response necessary.*

**QUESTION:** In deriving the chronic-duration oral MRL, a rate of 10% was used as the bench mark response. Is this response rate appropriate?

**COMMENT:** Yes based upon the current methodology

**RESPONSE:** *No response necessary.*

**QUESTION:** The point of departure used to derive this MRL was a BMDL<sub>10</sub> of 0.47 mg/kg/day for increased bile duct hyperplasia in male rats. Do you agree/disagree with the selection of this point of departure. Explain. If you disagree please specify the point of departure that you propose.

**COMMENT:** Agree

**RESPONSE:** *No response necessary.*

**QUESTION:** In deriving the chronic-duration oral MRL a total uncertainty factor of 100 was applied. The individual components which comprise the total uncertainty value are:

10 for human variability

10 for extrapolation from animals to humans

In regards to each component which contributes to the total uncertainty factor, please answer the following: Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor that you propose.

**COMMENT:** Agree

**RESPONSE:** *No response necessary.*

**QUESTION:** Please comment on any aspect of our MRL database assessment that you feel should be addressed.

**COMMENT:** None.

**RESPONSE:** *No response necessary.*

### *Chapter 7\*

**QUESTION:** We would like to know your thoughts on the regulations and guidelines that are presented and any that should be added or removed. Are you aware of any additional regulations or guidelines that we should add? Please provide citations. Are there any that should be removed? Explain.

**COMMENT:** No change

**RESPONSE:** *No response necessary.*

### *Appendix A*

**QUESTION:** Please address the MRL worksheets based upon the questions provided above about the MRLs.

**COMMENT:** None

**RESPONSE:** *No response necessary.*

### *Appendix B*

**QUESTION:** Please provide comments about the process utilized in this section.

**COMMENT:** None

**RESPONSE:** *No response necessary.*

## Comments provided by Peer Reviewer #3:

### ATSDR Charge Questions and Responses and Reviewer Comments

#### *Chapter 1*

**QUESTION:** Does Chapter 1 adequately summarize the published literature regarding health effects for this substance?

**COMMENT:** Chapter 1 accurately reflects the literature review that was performed for the update of the Profile. It also summarizes the observed major health effects. Neurological effects at high doses, including discoordination and convulsions prior to death were not addressed. This could be significant regarding to possibility for neurodevelopmental/cognitive effects discussed below.

Line 28 on page 5 refers to the nematocide Bromodichloromethane, which is not the subject of this report. If the authors were referring to possible TCP contamination in preparation of the nematocide, this should be clarified and explained in Chapter 1.

**RESPONSE:** *This is an editorial mistake; the compound listed should have been 1,2,3-trichloropropane rather than bromodichloromethane. The error was corrected.*

#### *Chapter 2*

**QUESTION:** First, does Chapter 2 adequately reflect the published literature regarding health effects for this substance? Are you aware of any studies that are not included that may be relevant in the derivation of MRLs for this chemical?

**COMMENT:** The content of Chapter 2 appropriately presents the current state of knowledge regarding the health effects of TCP in exposed animals and humans, including epidemiology, occupational exposures and animal testing.

One significant omission concerns human deaths from exposure to TCP. There are at least two published reports of death and painful neuropathy and eventually death associated with exposure to a lethal dose of TCP. Although these reports are in Chinese, they could provide useful information to clinicians and toxicologist in similar cases in the USA. The articles should be obtained, translated and included in the report. The references are as follows:

1. [A death case with poisoning by accidentally oral intake of trichloropropane]. Sun S, et al. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi. 2016. Authors Sun S, Liu Y, Su L. Citation Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi. 2016 Jan;34(1):36. doi: 10.3760/cma.j.issn.1001-9391.2016.01.009.
2. [A death case with poisoning by accidentally oral intake of trichloropropane]. Sun S, et al. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi. 2016. Authors Sun S, Liu Y, Su L. Citation Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi. 2016 Jan;34(1):36. doi: 10.3760/cma.j.issn.1001-9391.2016.01.009.

Abstract No abstract available

PMID 27014815 [Indexed for MEDLINE]

Article in Chinese.

**RESPONSE:** *The citations provided by the Reviewer are for the same case report. This paper was not included in the profile because it is published in Chinese and is not likely to provide valuable information since it is based on one case of an individual ingesting a lethal dose of 1,2,3-trichloropropane. The profile discusses two other cases of neurological effects in individuals exposed to 1,2,3-trichloropropane (Han 2010; Mi et al. 2013) in Section 2.15.*

**QUESTION:** Do you agree with the revised acute-duration inhalation MRL of 0.001 ppm? Explain. If you disagree, please specify the MRL that you propose.

**COMMENT:** While I am in agreement with using decreased thickness of the nasal olfactory epithelium of rats as the most sensitive endpoint for deriving an acute-duration inhalation MRL, I am opposed to reducing the uncertainty factor for interspecies variability in this case. There are two reasons from my dissent.

First, TCP is a possible human carcinogen and is certainly carcinogenic in rodents. I am opposed to increasing the MRL for any suspected carcinogen, despite the ATSDR's practice of not using the cancer endpoint in its calculation of MRLs. It should still be considered when proposing to decreasing the MRL. Second, it is not clear that any of the studies evaluated effects on neurodevelopment or cognitive function in exposed individuals, especially children or the unborn embryo or fetus. In the absence of such data, it is in my opinion unwise to increase the MRL based on a histological endpoint that may occur at doses that are much higher than those that might affect brain development or function. A lack of histological changes does not justify ignoring the possibility of significant functional effects. Rather than decrease the 1992 MRL, in my opinion it should be increased by a factor of 10 to account for unknown effects on the developing fetus/embryo.

**RESPONSE:** *MRLs are designed to be protective of noncancer health effects and carcinogenicity is not factored into MRL derivations. ATSDR uses uncertainty factors to account for several specific classes of uncertainty: using a LOAEL for a point of departure, extrapolation from animals to humans, and intrahuman variability. Modifying factors are sometimes used when data gaps have been identified that may impact the MRL value, such as incomplete data for a potentially sensitive target. Although potential neurodevelopmental effects have not been evaluated for 1,2,3-trichloropropane, there are no data to suggest that this would be a sensitive endpoint. The use an uncertainty factor of 10 for human variability is likely protective of increased susceptibility of infants and children, as well as developing organisms.*

**QUESTION:** Please comment on any aspect of our MRL database assessment that you feel should be addressed.

**COMMENT:** The assessment should include more discussion of the limitations of using only histological changes as endpoints in the assessment. There is a real and urgent need for biomarkers of effect that are more sensitive than histological changes, which indicate significant cellular damage or loss of function.

**RESPONSE:** *ATSDR agrees with the Reviewer that there is a need for studies identifying biomarkers of effects. The following statement was added to the discussion of data needs in Section 6.2:*

Additional animal studies or examination of humans with known exposure to 1,2,3-trichloropropane are needed to identify potential biomarkers of exposure, especially biomarkers that would be indicative of subclinical alterations.

**QUESTION:** The new chronic-duration oral MRL is 0.005 mg/kg/day. Do you agree/disagree with this value? Explain. If you disagree, please specify the MRL value that you propose.

**COMMENT:** The availability of new data provides an opportunity to calculate an MRL for chronic-duration oral exposures. In my opinion, the MRL for oral chronic exposure should be reduced 100-fold, to 0.00005 mg/kg/day.

**RESPONSE:** *See Response to the Comment in which the Reviewer provides a rationale for lowering the MRL.*

**QUESTION:** In deriving the chronic-duration oral MRL, a rate of 10% was used as the bench mark response. Is this response rate appropriate? The point of departure used to derive this MRL was a BMDL10 of 0.47 mg/kg/day for increased bile duct hyperplasia in male rats. Do you agree/disagree with the selection of this point of departure. Explain. If you disagree please specify the point of departure that you propose.

**COMMENT:** Yes, I agree with use of a BMDL10 0.47 mg/kg/day for bile duct hyperplasia in male rats. The approach used to arrive at this benchmark was appropriate.

**RESPONSE:** *No response necessary.*

**QUESTION:** In deriving the chronic-duration oral MRL a total uncertainty factor of 100 was applied. The individual components which comprise the total uncertainty value are:

- 10 for human variability
- 10 for extrapolation from animals to humans

**COMMENT:** I agree with an factor of 10 for human variability. I agree with an factor extrapolation from animals to human.

**RESPONSE:** *No response necessary.*

**QUESTION:** In regards to each component which contributes to the total uncertainty factor, please answer the following: Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor that you propose.

**COMMENT:** While I agree with both of uncertainty factors used in calculating the chronic-duration MRL for oral TCP exposure, I **disagree** with the total factor used in deriving the MRL. I believe it would inadequately protect at risk individuals and communities from potential harm in a chronic exposure setting.

First, as already stated in the answer to Question 1, TCP is a rodent **carcinogen** and a suspected human carcinogen. While the ATSDR does not use cancer endpoints in driving an MRL, I do not feel this is wise. Carcinogens and non-carcinogens should not be treated as equal. Animal carcinogenesis data are often limited by the number of animals used in assessing carcinogenesis. The classical “hockey stick” dose-response curve can simply reflect the statistical threshold for detecting cancer. If ten times the number of animals are treated with a lower dose, would cancer be detected? There is no simple answer to

this question. There were no epidemiology studies that looked at the effect of TCP on the incidence of human cancer. Therefore, I think we should include an additional safety factor of 10 for carcinogens such as TCP.

Second, even if we ignore the fact that it is a carcinogen, TCP is also a **mutagen**. The literature reviewed did not include any studies of how TCP exposures affects mutation rates in the exposed embryo or fetus. Some rodent studies did observe effects on litter size, but the mechanisms were not evaluated. It is therefore unclear if mutations induced by TCP, especially after chronic exposure reduced embryo development and/or contributed abnormal development in subsequent generations. An increase in germline mutation rates would not necessarily lead to histopathological mutations in testes or ovaries, and hence would not be detected until subsequent generations.

There were no studies evaluating the epigenetic effects of development exposure to TCP. However, at least one study suggested that F1 progeny of exposed P0 rodents had reduced numbers of offspring. Such observations are consistent with epigenetic effects due to in utero exposure of nascent germ cells in the F1 fetus.

Therefore, studies performed to date have not eliminated the potential for mutagenic and/or epigenetic effects during development. As such, it seems appropriate to include a safety factor of 10 for uncertainty on developmental processes.

In summary, while I agree with the safety factors that were applied, in my opinion, the data are inadequate to ignore a safety factor of 10 for carcinogenesis and another factor of 10 for uncertainty of effects during developmental exposure. My opinion is based on guidelines from the European Medicine Agency that address the use of additional safety factors for risk identification in the manufacture of different medicinal products (see comments for Chapter 7 below). It is my opinion that the MRL for acute-duration oral TCP exposure should be lowered to **0.00005 mg/kg/day**.

**RESPONSE:** *The MRL is not designed to be protect against carcinogenic effects. Cancer-specific screening values (such as EPA's cancer slope factors) are utilized to assess a population's cancer risk. Based on a comparison of the NOAEL and LOAEL values from available data, bile duct hyperplasia appears to be a more sensitive endpoint than the developmental effects. After 15 months of exposure, the NOAEL and LOAEL values for bile duct hyperplasia in male rats were 3 and 10 mg/kg (5 days/week). The NTP (1990) continuous breeding study reported a NOAEL of 30 mg/kg/day and LOAEL of 60 mg/kg/day for decreases in litter size. These data suggest that the MRL based on bile duct effects should be protective of the developmental effects. The uncertainty factor for intrahuman variability is intended to account for differences in development-related sensitivity.*

### **Chapter 3**

**COMMENT:** Chapter 3 reviewed several factors, including the use of biomarkers of exposure and effect. The chapter rightly concluded that there was a dearth of studies using biomarkers of effect. Relying primarily on histological changes remains a limitation. For example, one study cited saw swelling of kidneys. This was deemed as being insignificant. However, this conclusion was not based on emerging sensitive and specific markers of effects such as Kim1 in the kidneys. Future studies should include such biomarkers of toxicity and or incipient disease.

**RESPONSE:** *The following statement was added to the discussion of biomarker data needs in Section 6.2:*

Additional animal studies or examination of humans with known exposure to 1,2,3-trichloropropane are needed to identify potential biomarkers of exposure, especially biomarkers that would be indicative of subclinical alterations.

### *Chapter 5*

**COMMENT:** Little is known about the persistence of TCP in ground water, a major source of potential human exposure. The report states that “may persist in groundwater for a relatively long time”. What this means needs to be defined. The chemical half-life of TCP was given as ~ 44 years with little evidence for its metabolism by soil biota. Thus, there is significant opportunity for its accumulation in the environment, and hence for increasing human exposure.

**RESPONSE:** *The statement in Section 5.1–It may persist in groundwater for a relatively long time–was deleted from the profile.*

### *Chapter 6*

**COMMENT:** The adequacy of the database used in developing the upgraded profile is extremely limited. As indicated, there are only three informative human studies and one epidemiology study that examined the effects on development. The latter did not find any significant association and could not be used to assess causality. Future amendments to the profile will require additional information on human health effects.

There is also a significant need for more studies examining biomarkers of exposure and effect. All studies used to date have relied heavily on histological endpoints or general endpoints such as litter size. Over the past two decades there have been significant advances in the use of toxicogenomics and high throughput assays in cell lines and alternative species. There has also been increased development of specific toxicity biomarkers (e.g. Kim1) and identification of adverse effects (toxicity pathways) that are more sensitive markers of toxicity and incipient disease. Future studies of TCP should include the evaluation of such biomarkers of effect. Such endpoints may provide a superior basis for setting points of departure in the derivation of MCLs, especially in the areas of development and epigenetic effects. Future studies should also include sensitive neurological and cognitive endpoints, since pregnant women and unborn children may be at elevated risk.

**RESPONSE:** *As noted in previous Responses, a data need for biomarkers of effect was added to Section 6.2. The Developmental toxicity data need was expanded to include the need for neurological endpoints: Single and 2-generation studies examining a wide range of endpoints are needed; the developmental studies should also include neurological and cognitive endpoints.*

### *Chapter 7*

**COMMENT:** The European Medicine Agency has developed guidelines that require safety factors of 10 each for compounds that are carcinogens and for which developmental toxicity has not been fully evaluated (see reference below). I have used these guidelines in rendering my opinion.

The state of new Jersey has recently reevaluated risk associated with exposure to TCP in drinking water (see references below). A panel of experts used available data and their best judgement to propose a new drinking water standard at 0.00003 mg/l (30 ng/L, or 30 ppt). For a 60 kg person, who consumes 2 liters

of water per day, this translates into **0.001 mg/kg/day**. This is five-fold lower than the MRL for chronic acute-duration being proposed by the ATSDR in the current update. This legislation has been introduced to the NJ State legislature and is currently under consideration. The ATSDR should take note of this new standard in setting a new MRL for chronic-duration oral exposure and consider lower the proposed MRL to at least this level. However, give the concerns I raised regarding the use of safety factors. It should in my opinion be even lower than the level proposed via the NJ water standard.

- European Medicines Agency- EMA/CHMP/ CVMP/ SWP/169430/201. Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities.  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2014/11/WC500177735.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/11/WC500177735.pdf)
- NJ DEP – Drinking Water Institute “recommends that the Department propose and adopt an MCL of 0.03 µg/L (30 ng/L; 30 ppt) for 1,2,3-TCP in drinking water”.  
<http://www.nj.gov/dep/watersupply/pdf/123-tcp-recommend.pdf>  
[ftp://www.njleg.state.nj.us/20182019/S0500/74\\_I1.PDF](ftp://www.njleg.state.nj.us/20182019/S0500/74_I1.PDF)  
[http://www.nj.gov/dep/watersupply/g\\_boards\\_dwqi.html](http://www.nj.gov/dep/watersupply/g_boards_dwqi.html)

**RESPONSE:** *The MRL is a screening value designed to be protective for noncancer health effects and thus, an uncertainty factor to account for carcinogenicity is not relevant. The New Jersey health-based MCL is based on cancer effects and would not be comparable to the MRL which is based on noncancer effects.*

#### **Appendix A**

**QUESTION:** Please address the MRL worksheet based upon the questions provided above about the newly derived MRL.

**COMMENT:** The worksheets are appropriate. I have no concerns.

**RESPONSE:** *No response necessary.*

#### **Appendix B**

**QUESTION:** Please provide comments about the process utilized in this section.

**COMMENT:** The process used in this section are appropriate. My concerns are limited to the value and types of safety factors used.

**RESPONSE:** *No response necessary.*