

**Disposition of Peer Review Comments for
Minimal Risk Levels for Tricresyl Phosphate (TCP)**

Prepared by:

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Prepared for:

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U.S. Public Health Service
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Peer reviewers for the MRLs for tricresyl phosphate were:

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ATSDR would like to thank these scientists for their review of the document.

Comments provided by Reviewer #1

Rationale Statement

Comment: The comment refers to the appropriateness of selecting the ovarian lesions after 3 months of exposure over the adrenal cortex cytoplasmic vacuolization as basis for the intermediate-duration oral MRL for tricresyl phosphate (TCP). The Reviewer notes that although 6/10 rats showed this effect at 3 months at 7 mg/kg/day TCP (150 ppm), only 1 rat showed this effect at 9 months and no rats displayed this effect at 2 years. Hence, using ovarian lesions at 3 months constitutes a lowest-observed-adverse-effect level (LOAEL), but this becomes a no-observed-adverse-effect level (NOAEL) at 9–24 months. The Reviewer feels that the fact that this effect is, at best, minimal and disappears makes it questionable to use this parameter as an adverse effect; it appears to represent merely an adaptive change that disappears with continued chemical exposure. The comment also applies to the chronic-duration oral Minimal Risk Level (MRL).

Response: The Reviewer is correct in that the lesion appears to be reversible, but only up to doses of 7 mg/kg/day. However, there does not seem to be reversibility when the dose was increased to 15 mg/kg/day (300 ppm). The incidence in this group was 100% at the 3- and 9-month evaluations and 90% at the 15-month evaluation. All of the data sets were modeled for adrenal and ovarian lesions in female rats for the intermediate-duration oral MRL and for adrenal and ovarian lesions in female rats and liver lesions in mice for the chronic-duration oral MRL. In accordance with ATSDR's policy of selecting the most sensitive end point and lowest possible dose (or BMDL₁₀) for a specified duration, it is appropriate to base the MRLs for TCP on the ovarian lesions.

Comment: The Reviewer comments on the use of the term “sex” throughout the profile (i.e., 10/rats/sex/dose or sex-related differences); he believes that the term “gender” is more appropriate and should replace “sex”.

Response: Either word is correct and they are often used interchangeably. In the past, the word “sex” denoted males or females, whereas “gender” referred to masculine or feminine traits. No changes were made.

All other comments from Reviewer #1 were addressed as suggested.

Comments provided by Reviewer #2

Comment: The Reviewer states that the discussion of the two new MRLs is somewhat confusing and unclear. The Reviewer did not specify whether he was referring to Chapter 2 or the MRL Rationale Statement, or both. The Reviewer indicates that the major source for the confusion is that the principal study is not discussed in the text for either MRL. Therefore, the experimental design, including the dose levels and the results for adrenal and ovarian lesions in female rats on which the NOAEL, LOAEL, and BMDL₁₀ are derived, is not given in the text of either the intermediate- or chronic-duration MRLs, but are only presented in Tables 28 and 34 at the very end of the discussion. Thus, it is not possible, while reading the text, to determine that these lesions in female rats as stated in the text were the most sensitive to TCP. For example, when female rats are said to be more sensitive than male rats and the dose levels and results for the males are given, those of the female rat are not. Thus, there were no data from the female rats for comparison to the males to demonstrate that females are more sensitive. The same is true for the 600 ppm TCP dose in males that resulted in a 100% incidence of male rats with adrenal lesions. Without the dose levels and incidence in female rats, it was not possible to determine whether they too had an incidence of a 100%.

Response: A detailed summary of the National Toxicology Program (NTP 1994) study is presented in Appendix A. Section 2.3, Minimal Risk Levels, and the MRL Rationale Statement are supposed to provide enough study details so that the reader can follow the logic behind the selection of a specific end point for MRL derivation. In Chapter 2, page 34, where the NTP (1994) study is briefly summarized, the text states that TCP induced cytoplasmic vacuolization of the adrenal cortex and interstitial cell hyperplasia in the ovary in female rats and that the LOAELs were 15 and 7 mg/kg/day, respectively; the corresponding NOAELs were 7 and 4 mg/kg/day and were established at the 3-month interim evaluation in the 2-year study. The text also states that male rats dosed with 3, 6, or 13 mg TCP/kg/day (75, 150, or 300 in the diet) did not develop adrenal cortex lesions. This should be sufficient for the reader to infer that females were more sensitive than males regarding the adrenal lesions.

Comment: The Reviewer states that the document would be more logical and clear if the study used to determine the BMDL₁₀ is presented first. This should include the experimental design, including the dose levels and time points, the results (including Tables 28 and 34), and then the conclusions, including the NOAEL and LOAEL of the study. Other studies could then be presented and their results could be compared to the principal study used to calculate the BMDL₁₀. The text could then conclude, by restating the selected study and its NOAEL and LOAEL and reference, the already-presented table containing the results used to calculate the BMDL₁₀.

Response: The derivation of the MRLs follows a standard sequence used in all Toxicological Profiles. That is, presentation of all of the pertinent data first and then selection of the most sensitive end point in the best study.

Comment: The comment refers to a paragraph in the MRL Rationale Statement that discusses the adrenal lesions in rats and mice in the available intermediate-durations studies. The Reviewer states that the dose levels and results for female rats could be given and discussed here. The Reviewer notes that this would allow comparison to the adrenal results for male rats as well as the mice results that follow and would support the statement that the males are less sensitive.

Response: All of the information that the Reviewer asks for is in the paragraph in question. Further details are presented in Appendix A.

Comment: The comment refers to Table 28 in the MRL Rationale Statement. Table 28 presents the incidences of adrenal cortex and ovarian lesions in female rats at the 3- and 9-month time points in the control and 4, 7, and 15 mg/kg/day groups (0, 75, 150, and 300 ppm, respectively). The Reviewer states that the table should include the 600 ppm data at 3 months. He further notes that if the data are not used to calculate the BMDL₁₀, then the document should state why the data were not used.

Response: There was no dose calculated by NTP (1994) for the 600 ppm group; a statement was added to the text.

Comment: The comment refers to text in the MRL Rationale Statement that summarizes the chronic portion of the NTP (1994) study in rats and mice prior to modeling of the pertinent data and selecting a point of departure for MRL derivation. The Reviewer suggests that Table 34, which presents the incidences of the adrenal and ovarian lesions in female rats and the liver lesions in male mice, be referenced before the text discusses NOAELs and LOAELs. Furthermore, the Reviewer notes that the results presented in Table 34 are discussed in general terms, while the actual data are not provided in the text.

Response: Reference to Table 34 was moved up in the text as the Reviewer suggested. The actual data (i.e., incidences of lesions at specific dose levels) are presented in Table 34, so there is no need to repeat this information in the text. A detailed description of the study is presented in Appendix A.

Comment: The comment refers to the summary of the results of the NTP (1994) study presented in the worksheet in Appendix A for the intermediate-duration MRL for TCP. The Reviewer states that the paragraph should state or indicate the dose levels for the series of incidences. Also, the text should indicate why the incidences of adrenal and ovarian lesions in the 600 ppm group were not elevated beyond the 3-month period. In addition, the Reviewer questions why the 600 ppm group is not included in Table A-23.

Response: The dose levels for the series of incidences have been added to the text and statements were added that provide a possible explanation for the lack of lesions in the 600 ppm group beyond the 3-month time point. As previously mentioned, the 600 ppm group is not included in Table A-23 because NTP (1994) did not provide a dose associated with this dietary concentration of TCP.

Comment: The comment refers to the derivation of the chronic-duration MRL for tris(2-chloroethyl) phosphate (TCEP), specifically to the degenerative brain lesions in the brain from female rats in the MRL Rationale Statement and in Appendix A. The text states that *“the reporting of the data (no individual animal data) in the NTP (1991a) study does not allow the determination of whether individual animals had more than one lesion type.”* The Reviewer notes that individual animal data can be obtained from NTP and provides a link for the site. The Reviewer states that using individual animal data, the incidences of animals with at least one brain lesion for the 0, 44, and 88 mg/kg/day are 4/50 (8%), 8/50 (16%), and 37/50 (74%), respectively, which can be used to calculate a BMDL₁₀.

Response: The sentence in quotation marks above is misleading because it gives the impression that the NTP Technical Report Series typically provide individual animal data, which they do not; they provide averages in the publication's appendices. The sentence quoted above was deleted. It is beyond the scope of the profile to seek individual animal data for MRL derivation rather than the averages presented in the Technical Report Series.

Comment: The Reviewer seems to request that the models of all of the data presented in Table A-7 (intermediate and chronic data sets for urinary bladder incidence in studies in rats exposed to tri-n-butyl phosphate [TnBP]) and model fits be shown in Appendix A to assure the reader that the chosen models fit the data and that the selected BMDL₁₀ values in Table A-9 and A-10 are greater than the one chosen for the intermediate exposure.

Response: ATSDR believes that it is unnecessary to satisfy the Reviewer's request since Table A-7 lists the selected BMDL₁₀ values for the various data sets. It is clear in Table A-7 that the BMDL₁₀ values for intermediate-duration studies are lower than those for chronic-duration exposure.

All other comments from Reviewer #2 were addressed as suggested.

Comments provided by Reviewer #3

No responses were required for nearly all of the comments provided by Reviewer #3. Those comments that required a response were addressed as suggested.