

**DISPOSITION OF PEER REVIEW COMMENTS FOR
TOXICOLOGICAL PROFILE FOR
TOXAPHENE**

**Agency for Toxic Substances and Disease Registry
U.S. Public Health Service
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Peer reviewers for the third draft of the Toxicological Profile for Toxaphene were:

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

Review comments provided by Laurie Chan, Ph.D.

PR6, P16, first paragraph: Dr. Chan suggested using the intermediate-duration oral Minimal Risk Level (MRL) for toxaphene for risk assessment since the general public is likely exposed to toxaphene at a chronic low dose in the diet.

Response: The hazards of chronic oral exposure to toxaphene have not been adequately characterized. Therefore, the intermediate-duration oral MRL is not intended to be used to assess the risk of chronic oral exposure.

PR10, P68-84: Dr. Chan states that there is no discussion on interspecies toxicokinetic comparisons in Section 3.4. Dr. Chan further states that there is inadequate discussion of the relevance of animal toxicokinetic information for humans.

Response: Available information (or the lack thereof) regarding interspecies toxicokinetic comparisons is presented in Section 3.5.3 (Animal-to-Human Extrapolations). ATSDR considers this section to be the appropriate location for comparing toxicokinetics among species.

PR15, Chapter 6: Dr. Chan suggests adding a discussion of Arctic ecosystems to Chapter 6 because many studies on toxaphene in Alaska and the Canadian Arctic have been performed following atmospheric transfer of toxaphene to the Arctic.

Response: The suggested additional information is considered beyond the scope of the Toxicological Profile for Toxaphene and was not added.

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

Review comments provided by Lucio Costa, Ph.D.

PR21-22, P11, L8: Dr. Costa questioned the use of clinical signs of neurological symptoms in toxaphene-treated dogs as the critical effect for deriving an acute-duration oral MRL for toxaphene. Dr. Costa also suggested adding a statement to clarify why a benchmark dose (BMD) approach was not taken to derive the MRL.

Response: The end point is considered justified because it was observed in some dogs at the 10 mg/kg/day dose level during 2 days of treatment, but not in dogs receiving toxaphene at 5 mg/kg/day for as long as 13 weeks. This effect was selected as the critical effect because it identified the highest no-observed-adverse-effect level (NOAEL) associated with the lowest lowest-observed-adverse-effect level (LOAEL) among those identified in the available animal studies. A BMD approach was not taken because the numbers of animals exhibiting the effect were low, thus precluding the use of statistical approaches. However, a statement to this effect was not added to the Toxicological Profile for Toxaphene because it is considered beyond the scope of the document to include a rationale for not using a BMD approach in this section.

PR22, P15, L1: Dr. Costa indicated that the study of Tryphonas et al. (2001) is “less-than ideal” as it considers effects that were seen at <365 days of treatment in a 75 week study, and the effects eventually change (i.e. are later seen only at higher dosages).” Dr. Costa stated that the dog study reported by Chu et

al. (1986) identified a NOAEL of 0.2 mg/kg/day, which is similar to the NOAEL of 0.1 mg/kg/day identified in the monkey study of Tryphonas et al. (2001) and requested an explanation as to why the monkey study was selected over the dog study to serve as basis for the intermediate-duration oral MRL. Dr. Costa noted that ATSDR used a NOAEL of 2.0 mg/kg/day in its supplemental document rather than the NOAEL of 0.2 mg/kg/day reported by Chu et al. (1986).

Response: ATSDR performed a statistical analysis of the incidence data for histopathologic liver lesions in the dogs from the study of Chu et al. (1986) and determined that significantly increased incidences of liver lesions occurred only at the highest dose tested (5.0 mg/kg/day) and not at 0.2 or 2.0 mg/kg/day. Reported liver weight increases (20% higher than controls) in the female dogs dosed at 2.0 mg/kg/day were not considered to represent an adverse effect in the absence of significantly increased incidences of liver lesions. Furthermore, incidences of thyroid lesions in toxaphene-treated male and female dogs of the Chu et al. (1986) study did not exhibit dose-response characteristics. Therefore, ATSDR considers the identification of the 2.0 mg/kg/day dose level as a NOAEL to be justified.

PR23, P53, L4: Dr. Costa stated that it would be useful to indicate why depressed humoral immunity is considered less serious than other effects such as a 22% decrease in body weight and clinical signs of neurological effects.

Response: Definitions of less serious and serious effects are found at the beginning of Section 3.2. ATSDR has historically considered altered humoral or cell-mediated immune responses to sheep blood cells to represent a less serious effect and convulsions to represent a serious neurological effect. It is beyond the scope of the toxicological profile to provide explanations for the serious or less serious nature of each health effect.

PR23, P59, L16; PR27, P187, L16: Dr. Costa stated that the reference to IRIS (2010) may be misleading because the provided web address indicates that the entry for toxaphene is dated 1991, not 2010.

Response: Although the assessment was last revised on 1/1/1991, the assessment is considered valid to date. ATSDR uses the search date to indicate that the valid assessment was reviewed at that time.

PR25, P91, L10: Dr. Costa asked if it is possible to quantify the “weak estrogenic” effect of toxaphene and compare the effects to those of estrogen.

Response: The magnitude of the effect varies by study and the authors typically described the response as only “weakly estrogenic”. No change was made.

PR25, P94, L12: Dr. Costa suggested that an additional subsection (3.8.2) could be added to discuss whether there are known biomarkers of susceptibility to toxaphene toxicity.

Response: Susceptibility to toxaphene toxicity is discussed in Section 3.10 (Populations that are Unusually Susceptible). This follows ATSDR convention. The suggested change was not made.

PR26, P105-106: Dr. Costa suggested indicating that additional developmental neurotoxicity data would be useful, given the findings of Olson et al. (1980).

Response: The data need for additional information to support the developmental neurotoxicity data reported by Olson et al. (1980) is identified in the section of data needs titled “Developmental Toxicity”. Mention of this data need in the neurotoxicity section is not considered necessary.

PR26, Chapter 5; PR27 Table 6.1; PR27, P162, L8; PR27; P163, L2: Dr. Costa asked whether toxaphene is still produced in the United States and exported to countries where it is still used as a pesticide because some statements in Chapter 5 indicate continued U.S. production of toxaphene.

Response: According to the Toxics Release Inventory (TRI 2010), there were reports of toxaphene production in 2008 in Texas and Idaho. Attempts by ATSDR to uncover additional information regarding U.S. production of toxaphene since the ban in 1990 have not been successful.

PR27, 135, L1: Dr. Costa stated that the biomagnifications of toxaphene should be compared with that of other organochlorine compounds and that such comparisons might show that biomagnification of toxaphene is somewhat lower than that of other organochlorine compounds.

Response: This section was not modified because comparisons with DDT and PCBs had already been made.

PR27, P184, L12: Dr. Costa stated that biomarkers of effects do not belong in Section 7.3.1.

Response: The information regarding biomarkers of effects in this section refers to analytical methods for determining biomarkers of effect, not the biomarkers of effect. No change was made.

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

Review comments provided by Mark Robson, Ph.D.

PR31, P3, Section 1.5: Dr. Robson asked for a better description of “swollen kidneys” or why a condition of swollen kidneys might be of concern.

Response: The study report did not provide additional description of the observation of swollen kidneys at autopsy. No additional information was available for inclusion.

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