

**SUMMARY REPORT  
OF THE EXTERNAL PEER REVIEW OF THE  
DRAFT TOXICOLOGICAL PROFILE FOR  
TOXAPHENE**

Submitted to:

The Agency for Toxic Substances and Disease Registry  
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## **QUALITY NARRATIVE STATEMENT**

ERG selected reviewers according to selection criteria provided by ATSDR. ATSDR confirmed that the scientific credentials of the reviewers proposed by ERG fulfilled ATSDR's selection criteria. Reviewers conducted the review according to a charge prepared by ATSDR and instructions prepared by ERG. ERG checked the reviewers' written comments to ensure that each reviewer had provided a substantial response to each charge question (or that the reviewer had indicated that any question[s] not responded to was outside the reviewer's area of expertise). Since this is an independent external review, ERG did not edit the reviewers' comments in any way, but rather transmitted them unaltered to ATSDR.

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**SECTION I**  
**PEER REVIEWERS' SUMMARY COMMENTS**



**SUMMARY COMMENTS RECEIVED FROM**

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## REVIEW OF ATSDR'S TOXICOLOGICAL PROFILES

Please answer the following questions in your review:

- ✓ Are there any data relevant to child health and developmental effects that have not been discussed in the profile and should be?

No.

- ✓ Are there any general issues relevant to child health that have not been discussed in the profile and should be?

No.

- ✓ If you answer yes to either of the above questions, please provide any relevant references.

### CHAPTER 1. PUBLIC HEALTH STATEMENT

- The tone of the chapter should be factual rather than judgmental. Does the chapter present the important information in a non-technical style suitable for the average citizen? If not, suggest alternate wording.

**Yes. The tone is factual.**

- Major headings are stated as a question. In your opinion, do the answers to the questions adequately address the concerns of the lay public? Are these summary statements consistent, and are they supported by the technical discussion in the remainder of the text? Please note sections that are weak and suggest ways to improve them.

**Yes.**

- Are scientific terms used that are too technical or that require additional explanation? Please note such terms and suggest alternate wording.

**No.**

**Detailed comments:**

1. **p.2 Drinking water – the amount of toxaphene in water is very low. Suggest adding a sentence such as “Toxaphene in water is usually 1000 times less than that found in food.”**
2. **P.3. Cancer – suggest changing the last sentence to “Toxaphene could possibly cause cancer in humans but we are not sure”.**
3. **P.4 Section 1.7, replace don’t with do not.**
4. **P.4 Section 1.8, replace “useful” with “that is meaningful to your health”.**

## CHAPTER 2. RELEVANCE TO PUBLIC HEALTH

- Do you agree with those effects known to occur in humans as reported in the text? If not, provide a copy of additional references you would cite and indicate where (in the text) these references should be included.

**Yes.**

- Are the effects only observed in animals likely to be of concern to humans? Why or why not? If you do not agree, please explain.

**Not sure.**

- Have exposure conditions been adequately described? If you do not agree, please explain.

**Yes.**

**Detailed comments:**

1. **Page 8 line 4. Suggest adding some examples of sportfish species.**
2. **Page 8. 2<sup>nd</sup> paragraph. I am not sure the conclusion that toxaphene is not teratogenic is appropriate as toxaphene can cross the placenta and developmental toxicity has been observed in a number of animal studies.**
3. **Since the general public is likely exposed to toxaphene at chronic low dose in their diet. Would it be possible to suggest using the MRL for intermediate-duration of 0.002 mg/Kg/day for risk assessment? This will be very useful for the public health professionals to do risk assessment.**

## CHAPTER 3. HEALTH EFFECTS

### Section 3.1 INTRODUCTION

This introduction is standard language (in bold). A brief substance-specific discussion may be added to explain a complex topic.

### Section 3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

#### Toxicity - Quality of Human Studies

- Were adequately designed human studies identified in the text (i.e., good exposure data, sufficiently long period of exposure to account for observed health effects, adequate control for confounding factors)? If not, were the major limitations of the studies sufficiently described in the text without providing detailed discussions. If study limitations were not adequately addressed, please suggest appropriate changes.

**Yes, limitations of human study are provided.**

- 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)? Please suggest appropriate changes.

Yes.

- Were all appropriate NOAELs and/or LOAELs identified for each study? If not, did the text provide adequate justification for excluding NOAELs/LOAELs including, but not limited to, citing study limitations? Please suggest appropriate changes.

Yes.

- Were the appropriate statistical tests used in the studies? Would other statistical tests have been more appropriate? Were statistical test results of study data evaluated properly? **NOTE:** As a rule, statistical values are not reported in the text, but proper statistical analyses contribute to the reliability of the data.

**There is very little comments on the statistics or power of the study other than statement like “This study is limited by the small numbers of cases and controls” (p.24 1<sup>st</sup> paragraph).**

- Are you aware of other studies which may be important in evaluating the toxicity of the substance? Please provide a copy of each study and indicate where in the text each study should be included.

No.

#### **Toxicity - Quality of Animal Studies**

- Were adequately designed animal studies identified in the text (i.e., adequate number of animals, good animal care, accounting for competing causes of death, sufficient number of dose groups, and sufficient magnitude of dose levels)? If not, does the inadequate design negate the utility of the study? Please explain.

Yes.

- Were the animal species appropriate for the most significant toxicological endpoint of the study? If not, which animal species would be more appropriate and why?

Yes.

- Were the conclusions drawn by the authors of the studies appropriate and accurately reflected in the text? If not, did the text provide adequate justification for including the study (e.g., citing study limitations)?

Yes.

- Were all appropriate NOAELs and LOAELs identified for each study? Were all appropriate toxicological effects identified for the studies? If not, please explain.

Yes.

- If appropriate, is there a discussion of the toxicities of the various forms of the substance? If not, please give examples of toxicological effects that might be important for forms of the substance.

**Yes.**

- Were the appropriate statistical tests used in the interpretation of the studies? If not, which statistical tests would have been more appropriate? Were statistical test results of study data evaluated properly? **NOTE:** As a rule, statistical values are not reported in the text, but proper statistical analyses contribute to the reliability of the data.

**There is little discussion on the statistics of study design.**

- Are you aware of other studies that may be important in evaluating the toxicity of the substance? If you are citing a new reference, please provide a copy and indicate where (in the text) it should be included.

**No.**

#### **Levels of Significant Exposure (LSE) Tables and Figures**

- Are the LSE tables and figures complete and self-explanatory? Does the "Users Guide" explain clearly how to use them? Are exposure levels (units, dose) accurately presented for the route of exposure? Please offer suggestions to improve the effectiveness of the LSE tables and figures and the "User's Guide."

**Yes.**

- Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables?

**I would consider 14% decrease in body weight (p.28) or 48% increase in liver weight (p.29) serious. I guess this is the established ASTDR classification criteria.**

- If MRLs have been derived, are the values justifiable? If no MRLs have been derived, do you agree that the data do not support such a derivation?

**Yes and yes.**

#### **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?

**Yes.**

- Has the effect, or key endpoint, been critically evaluated for its relevance in both humans and animals?

Yes.

- Have "bottom-line" statements been made regarding the relevance of the endpoint for human health?

Yes.

- 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.

**The report presented a number of studies that showed subtle effects of prenatal exposure including immune functions and neuro-performance. The conclusion that toxaphene is not teratogenic may not be justified.**

- Has adequate attention been paid to dose-response relationships for both human and animal data? Please explain.

Yes.

- Has the animal data been used to draw support for any known human effects? If so, critique the validity of the support.

No.

### **Section 3.3 GENOTOXICITY**

### **Section 3.4 TOXICOKINETICS**

- Is there adequate discussion of absorption, distribution, metabolism, and excretion of the substance? If not, suggest ways to improve the text.

Yes.

- Have the major organs, tissues, etc. in which the substance is stored been identified? If not, suggest ways to improve the text.

**Yes. However, the discussion on transfer of toxaphene (p.73) suggests that relatively little toxaphene is transferred to fetus implying little developmental toxic effect. The relative amount of toxaphene transferred to fetus is similar to that of PCB and of course the primary public health concern for PCB is developmental toxicity.**

- Have all applicable metabolic parameters been presented? Have all available pharmacokinetic/pharmacodynamic models and supporting data been presented? If not, please explain.

**Yes.**

- Is there adequate discussion of the differences in toxicokinetics between humans and animals? What other observations should be made?

**There is no discussion on interspecies comparison. Some general comparisons can be made. In fact, animal-to-human extrapolations are discussed in Section 3.5.3. I suggest moving that section here.**

- Is there an adequate discussion of the relevance of animal toxicokinetic information for humans? If not, please explain.

**No, other than one sentence stating that the rat model is not useful for humans.**

- If applicable, is there a discussion of the toxicokinetics of different forms of the substance (e.g., inorganic vs. organic mercury)?

**Not applicable.**

### **Section 3.5 MECHANISMS OF ACTION**

The propose of this section is to provide a brief overview of known mechanisms of metabolism, absorption, distribution, and excretion, and then a discussion of any substance reactions or physiological processes that may affect these mechanisms. Have all possible mechanisms of action been discussed? If not, please explain.

**Yes.**

### **Section 3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS**

### **Section 3.7 CHILDREN'S SUSCEPTIBILITY**

### **Section 3.8 BIOMARKERS OF EXPOSURE AND EFFECT**

This section begins with standard language (in bold).

- 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?

**No specific biomarker is available for toxaphene effects.**

- 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.

**No.**

- 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?

No.

- 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.

No.

### **Section 3.9 INTERACTIONS WITH OTHER CHEMICALS**

Discuss the influence of other substances on the toxicity of the substance.

- Is there adequate discussion of the interactive effects with other substances? Does the discussion concentrate on those effects that might occur at hazardous waste sites? If not, please clarify and add additional references.

Yes.

- 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.

**Yes, although many of the mechanisms are still unknown/uncertain.**

### **Section 3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE**

This section begins with standard language (in bold) and identifies known or potential unusually-susceptible populations.

- Is there a discussion of populations at higher risk because of biological differences which make them more susceptible?

Yes.

Do you agree with the choices of populations? Why or why not?

**Yes. This are the general susceptible populations to all environmental toxins.**

Are you aware of additional studies in this area?

No.

### **Section 3.11 METHODS FOR REDUCING TOXIC EFFECTS**

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.

When possible, a distinction should be made between differences in management and treatment following acute (generally high-level) vs. chronic (generally low-level) exposure. The section should not include dosages nor detailed descriptions of treatment regimens. The section should not read as though ATSDR is endorsing or recommending any particular treatment.

The first part of the section should be brief and provide a **very general** discussion regarding treatments that are known or expected to reduce peak absorption (lower initial blood levels) of the substance following exposure.

#### **There is no discussion on treatment other than listing 4 references (p.98).**

- Is the management and treatment specific for the substance, or is it general for a class of substances?
- Is there any controversy associated with the treatment? Is it a "well-accepted" treatment?
- Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)?

The second part of the section should concentrate on methods to enhance the elimination of the absorbed dose or body burden, or remove a persisting metabolite or by-product of the substance from the body. It is appropriate to discuss treatments or research regarding interference with mechanisms of distribution or retention, or alteration of the pharmacokinetics of the substance so it has less chance of reaching the target organ(s).

- Are treatments available to prevent the specific substance from reaching the target organ(s), or are the actions general for a class of substances?

#### **General approach for all organochlorines.**

- 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?

#### **These are well accepted clinical treatment.**

- Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)?

#### **Not known.**

- 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])?



**No.**

The last part of the section should focus on clinical or experimental methods that are known or expected to block the mechanism of toxic action at any point from initial interaction with body processes, to the actual physical damage or functional change.

**Same as above.**

- 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?
- 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?
- Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)?

### **Section 3.12 ADEQUACY OF THE DATABASE**

This section begins with standard ATSDR language (in bold). "Data needs" are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized and a substance-specific research agenda will be proposed.

#### **Existing Information on Health Effects of [Substance X]**

Figure 2-X "Existing Information on Health Effects of [Substance X]" is provided to illustrate that positive and negative data exist. There is standard language (in bold) in the text. The dots in the figure do not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information.

- Do you know of other studies that may fill a data gap? If so, please provide the reference.

**No.**

#### **Identification of Data Needs**

Carefully consider the data needs because they will serve as the basis for establishing a substance-specific research agenda. Data needs are discussed in Sections 6.8.1, 6.8.2 and 7.3.1 as well. The following questions also pertain to both of those sections.

- Are the data needs presented in a neutral, non-judgmental fashion? Please note where the text shows bias.

**Yes.**

- Do you agree with the identified data needs? If not, please explain your response and support your conclusions with appropriate references.

**Yes.**

- Does the text indicate whether any information on the data need exists?

**Yes.**

- 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.

**Yes.**

#### **CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION**

This chapter should contain very little text. Most of the information should be presented in tabular form.

- Are you aware of any information or values that are wrong or missing in the chemical and physical properties tables? Please provide appropriate references for your additions or changes.

**No.**

- Is information provided on the various forms of the substance?

**Yes. However, some discussion on the evolution of the nomenclature will be useful for public health professionals to follow the literature. Some of this presented in Table 6-3 but it will help to give some context here.**

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

The level of detail in this chapter should be appropriate to an overview.

- Are you aware of any information that is wrong or missing? If so, please provide copies of the references and indicate where (in the text) the references should be included.

**No.**

#### **CHAPTER 6. POTENTIAL FOR HUMAN EXPOSURE**

This chapter includes general statements describing the ways in which substance releases are modified by time and environmental fate processes and the potential for human exposure to the substance via the different pathways.

- Has the text appropriately traced the substance from its point of release to the environment until it reaches the receptor population?

**Yes.**

Does the text provide sufficient and technically sound information regarding the extent of occurrence at NPL sites?

**Yes.**

Do you know of other relevant information? Please provide references for added information.

No.

- Does the text cover pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media?

Yes.

Do you know of other relevant information? Please provide references for added information.

No.

- Does the text provide information on levels monitored or estimated in the environment, including background levels?

**There are a lot of studies on Toxaphene in Alaska and the Canadian Arctic because of the atmospheric transfer to the Arctic. I suggest adding some discussion in the Arctic Ecosystems.**

Are proper units used for each medium?

Yes.

Does the information include the form of the substance measured?

Yes.

Is there an adequate discussion of the quality of the information?

Yes.

Do you know of other relevant information? Please provide references for added information.

- 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?

Yes.

Do you agree with the selection of these populations? If not, why? Which additional populations should be included in this section?

Yes.

- 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.

**Same answers as in Section 3.**

## CHAPTER 7. ANALYTICAL METHODS

This chapter begins with standard language (in bold). Most information should be presented in tabular form.

- Are you aware of additional methods that can be added to the tables? If so, please provide copies of appropriate references.

**No.**

- Have methods been included for measuring key metabolites mentioned previously in the text?

**Yes.**

- If unique issues related to sampling for the substance exist, have they been adequately addressed in the text?

**Yes.**

What other discussion should be provided?

**No really.**

- For Section 7.3.1, Identification of Data Needs, answer the same questions presented in Section 3.12.2, Identification of Data Needs.

**Same.**

## CHAPTER 8. REGULATIONS AND ADVISORIES

This chapter should present most information in tabular form. Information that is relevant but does not fit conveniently into the tabular format may be described in a brief paragraph. **NOTE:** In the table, only IARC and WHO recommendations are to be included under "International."

- Are you aware of other regulations or guidelines that may be appropriate for the table? If so, please provide a copy of the reference.

**No.**

## CHAPTER 9. REFERENCES

The intent of this section is to provide a reasonably complete list of references, whether cited in the text or not. Every reference cited in the text should appear with an asterisk in the bibliography.

- 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.

**No.**

## UNPUBLISHED STUDIES (IF APPLICABLE TO REVIEW)

See previously stated criteria for evaluating the quality of human and animal studies.

- For each of the unpublished studies included with the profile, prepare a brief evaluation that includes your assessment of the:
  - ✓ Adequacy of design, methodology, and reporting;
  - ✓ Validity of results and author's conclusions; and
  - ✓ Study inadequacies or confounding factors.
- Provide a summary of your conclusions?

**The draft profile is well written and is at the same high caliber as all the TP published by ATSDR.**

- Do you agree or disagree with those of the author? If not please explain why.

**The only major disagreement that I have with the author is that toxaphene is not teratogenic. I agree that it is not a potent teratogen but enough animal evidences suggest subtle physiological and developmental effects after prenatal exposure.**



**SUMMARY COMMENTS RECEIVED FROM**

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## REVIEW OF “DRAFT TOXICOLOGICAL PROFILE FOR TOXAPHENE”

This document summarizes all available information on the characteristics, exposure, and health effects of toxaphene. It is prepared in the standard format for the ATSDR Toxicological Profiles, which discuss health effects in relationship to route of exposure (oral, inhalation, dermal).

Overall, the document is well written, in a clear style, and well documented. Most Tables and Figures are good comprehensive compilations of information, and are useful for comparison of data and values. In contrast to other similar document, the present one is not particularly repetitious or redundant. Some issues may need additional clarifications, as suggested in the specific comments below. Furthermore, some sections (e.g. genotoxicity) would benefit of an overall conclusion statement, as some data can be subject to different interpretations.

Specific comments are listed below; they are divided by chapters, with indications of the page number and line.

### CHAPTER 1. PUBLIC HEALTH STATEMENT

This initial Chapter summarizes all information on toxaphene in a simple and clear manner. However, in Subsection 1.3 (How I might be exposed to toxaphene) it may also be stated that drinking water is an unlikely source of exposure due to toxaphene's low water solubility (see Section 6.4.2, p. 144).

### CHAPTER 2. RELEVANCE TO PUBLIC HEALTH

- p. 7, line 22: The term Parlar is introduced to indicate toxaphene congeners (after Dr. Harum Parlar), but there is no explanation of this term, nor is the term listed in the Glossary (Section 10). In this regard it is of note that the number of isomers of technical toxaphene is indicated in the document as 670 (p. 7), while a limited review of some literature provided the following range: 177 (Chu et al. 1986), 500 (Lamb et al. 2008), 800 (Simon and Manning, 2006), and 13,000 (Tryphonas et al. 2001). Perhaps some additional information to orient the reader would be useful.
- p. 11, line 8: An MRL was derived for acute-duration oral exposure (14 days or less). The study chosen to derive the acute MRL is that by Chu et al. (1986). This study is a 13 week study in dogs, in which neurological symptoms were found in the first two days only, at the highest dose tested (10 mg/kg). These effects were seen in 1/6 male dogs and 2/6

female dogs, and were reported as “brief convulsions, salivation, and vomiting” (Chu et al. 1986). Because of these signs, the dose was decreased to 5 mg/kg after two days. There were no other clinical signs in the following days and weeks at any of the tested dose levels. Because of all this issues, this study would seem as less-than ideal to determine an acute NOAEL. It should also be stated here why a BMD approach was not used in this case (possibly for the none-or all-response found in the study).

p. 15, line 1: MRL for intermediate duration. The study of Tryphonas et al (2001) provided a NOAEL of 0.1 mg/kg/day. This should be stated here. This study is also 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). The 13-week study of Chu et al. (1986) in dogs provided a NOAEL of 0.2 mg/kg/day, as stated by the authors (though it is indicated in the Supplemental Document for Toxaphene - p. 50 - as 2.0 mg/kg), and this study may be used for derivation of a BMD. It may be useful discussing why the Tryphonas et al. (2001) study in primates was chosen over the Chu et al. (1986) study in dogs, as they provide similar NOAEL values. In the Tryphonas et al. (2001) study, a total standard UF of 100X was applied to the BMD, 10X for interspecies differences and 10X for intraspecies differences. Is the 10X for interspecies differences fully justified, given that the BMD was derived from a study in non-human primates, where the end-point of relevance is considered less serious, and in which the NOAEL is one or more orders of magnitude lower than in other studies in rodent species?

### **CHAPTER 3. HEALTH EFFECTS**

#### **Section 3.1 INTRODUCTION**

p. 17, line 15: Define Parlars

#### **Section 3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE**

p. 19, line 11: Can this concentration (3-4,000 mg/m<sup>3</sup>) be considered an LC<sub>50</sub>?

p. 21, p.22: Table 3.1 and Figure 3.1 are not very useful, though they appear consistent with the format of Table 3.2 and Figure 3.2. The latter two have more substantial and useful content.

- p. 47, line 26: The statement that increased liver weight indicates an adaptive response rather than an adverse effect, needs to be referenced. This appears to be relevant, as Goodman et al. (2000) suggest that the mode of action of toxaphene carcinogenicity may be similar to that of phenobarbital, and may involve liver enlargement and induction of microsomal enzymes.
- p. 47, line 27: In the study of Chandra and Durairaj (1982) the dose of 300 mg/kg is indicated as an acute oral NOAEL for hepatic effects, yet a follow-up study by the same investigators (Chandra and Duraijai, 1985) seems to contradict this. The statement on NOAEL may be removed.
- p. 53, line 4: In the discussion of the Triphonas et al. (2001) study, which forms the basis for the derivation of the MRL for intermediate duration, it should be clearly stated that 0.1 mg/kg/day was a NOAEL. It would also be helpful to indicate here why the observed adverse effect (depressed humoral immunity) is considered less serious than other effects. Indeed, it is somewhat unclear how ATSDR arrives at the conclusion that an effect is serious or less serious (see also discussion on p. 18). A 22% decrease in body weight is considered serious, and so are neurological effects, yet the observed immunological effects were considered less serious.
- p. 56, line 5: Some of the information in this section on Reproductive Effects overlaps with Developmental Effects.
- p. 59, line 1: It would be useful to indicate the incidence of thyroid tumors at each dose level. The same would be true for the hepatocellular adenomas/carcinomas.
- p. 59, line 16: The reference to IRIS, 2010 is unclear and may be misleading. The web address provided indicates that an EPA IRIS for toxaphene is dated 1991, not 2010.

### **Section 3.3 GENOTOXICITY**

This section would benefit of an overall conclusion. Most often, results from genotoxicity studies provide contrasting results, with both positive and negative findings, and an overall conclusion related to the potential genotoxicity of a compound must rely on a weight-of-evidence approach. In the case of toxaphene, the majority of in vitro studies seem to suggest that it is a genotoxic compound, and genotoxicity appears to be due to the parent compound, rather than to metabolites. The in vivo studies that should substantiate or confute such conclusion are weak and unclear. The human study (Samosh, 1974) is indicated as negative in Table 3.4, but it is stated in the text (p. 64, line 8-10) that there was a higher incidence of chromosomal aberration in toxaphene-exposed women. This would leave only the two negative animal studies (Epstein et al. 1972; Hedli et al. 1998). It would appear that congeners in

toxaphene may be mutagens, but they are rapidly metabolized to non mutagenic compounds. Thus, the relevance of in vitro genotoxicity assays in the overall evaluation of toxaphene genotoxicity in vivo may be limited. The interpretation of the results should be clarified in the document.

### **Section 3.4 TOXICOKINETICS**

- p. 68, line 2: The statement that dermal absorption of toxaphene is low is contradicted by statements in other location of the document. For example, on p. 69, last paragraph, it is stated that “toxaphene appears to be well absorbed following dermal exposure in animals..” and that “absorption in humans may also be substantial following dermal exposure”. Yet on p. 103, line 16, it is indicated that “absorption through the skin is much less efficient”. There is a need for more consistent statements.
- p. 70, line 24: Change “The highest concentration of activity” to “The highest levels of radioactivity”.
- p. 81, line 25: Starting from here to page 83, there is a section on toxaphene excretion in breast milk, both in animals and in humans. As exposure through milk may represent an important route for certain populations, this section could be highlighted, perhaps by marking it as a separate subsection.
- p. 84: The section on PBPK/PD modeling could be shortened, since the only available model for toxaphene (Wen and Chan, 2000) appears to be of limited or no use, as it dose not take into account metabolism, an important component in toxaphene toxicokinetics. Is the generic text on p. 84-85 and Figure 3.4 necessary?

### **Section 3.5 MECHANISMS OF ACTION**

- p. 87: Is section 3.5.1 necessary? What specific pharmacokinetic mechanisms are described here? Is this just a summary of the previous sections on toxicokinetics? Should the term used be toxicokinetics instead of pharmacokinetics?
- p.88, line 6: Wording should be changed in the following sentence: “..these enzymes may have become disoriented”.
- p. 88, line 14: Specify that it is GABA-A receptors.
- p. 88, line 17: Clarify that GABA is an inhibitory neurotransmitter and that inhibition of an inhibition will lead to excitation of the CNS.
- p. 89, line 4: Goodman et al. (2000) is not in the Reference list.

p. 89, line 4: There should be a better discussion on possible mode of action for toxaphene carcinogenicity. Goodman et al. (2000), Simon and Manning (2006), and Lamb et al. (2008) provide their interpretation of data, but what is the interpretation put forward in the document?

p. 89, line 5: There should be a better discussion on weight-of-evidence of genotoxicity.

### **Section 3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS**

p. 90-91: Is this generic introduction necessary?

p. 91, line 10: Is it possible to quantify the “weak estrogenic” effect, perhaps indicating concentrations of toxaphene and compare them with those of an estrogen?

### **Section 3.7 CHILDREN’S SUSCEPTIBILITY**

p. 91-92: Is this general section necessary?

### **Section 3.8 BIOMARKERS OF EXPOSURE AND EFFECT**

p. 93-94: Is this general discussion of biomarkers necessary?

p. 94, line 12: It should be stated here whether or not there are known biomarkers of susceptibility to toxaphene toxicity. An additional subsection (3.8.2) could be added. Susceptible populations would be another, though strictly related, issue.

### **Section 3.9 INTERACTIONS WITH OTHER CHEMICALS**

No specific comments.

### **Section 3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE**

Title: It may be changed to “population that may be unusually susceptible”, as there is no strong evidence of particular susceptibility, though all issues raised are potentially relevant.

p. 96, line 27: The effects during development need to be quantified. Do they occur at dose levels that are lower than those capable of eliciting the same effects in adults?

### **Section 3.11 METHODS FOR REDUCING TOXIC EFFECTS**

p. 100, line 12: It should be clarified that the toxicity category may be the same for all indicated organochlorine insecticides, but the mechanism of action (with regard to neurotoxicity) is different for some of them (DDT, kepone, mirex).

### **Section 3.12 ADEQUACY OF THE DATABASE**

p. 103, line 10: Chu et al. (1980) should be Chu et al. (1986)

p. 103, line 16: Here it is stated that dermal absorption is less efficient (see comment to p. 68, line 2).

p. 104-105: Genotoxicity. One should consider weight-of-evidence of genotoxicity data. It would appear that sufficient data are available with regard to in vitro genotoxicity assays. Perhaps more in vivo data would be useful.

p. 105-106: Neurotoxicity. It may be mentioned here that developmental neurotoxicity data would be useful, given a single study which identified potential adverse effects (Olson et al. 1980).

p. 106, line 26: What would this “alternate biomarker of exposure” be?

## **CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION**

No specific comments.

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

Toxaphene was banned as a pesticide in the USA in 1990, and was added to the “dirty dozen” list of the Stockholm convention on persistent organic pollutants in 2001. It is unclear from this section whether toxaphene is still produced in the USA, and if so, what is it used for. Elsewhere in the document it is stated that toxaphene is still used as a pesticide in Mexico, some parts of Asia and Eastern Europe. Is it produced in the USA and exported to these countries for this purpose?

## **CHAPTER 6. POTENTIAL FOR HUMAN EXPOSURE**

p. 123, line 2: There should be a better description of the differences between technical toxaphene, and “weathered” toxaphene. Various papers underline the fact that there may be important differences with toxicological implications (e.g. Simon and Manning, 2006; Lamb et al. 2008).

- Table 6.1: Is the release of toxaphene only due to disposal activities of old stock, or to new production?
- p. 135, line 1: The biomagnification of toxaphene should be compared with that of other organochlorine compounds (e.g. DDT). This may possibly show that biomagnifications is somewhat lower in case of toxaphene.
- p. 149: Section 6.4.4, Other Environmental Media. This section is important as it deals with potential food contamination with toxaphene. Diet may indeed be the most significant route of exposure to toxaphene. To bring attention to this issue, the title should be modified to indicate food or diet.
- p. 159, line 9: Where does the “reported guideline of 0.001 mg/kg/day for intermediate exposure” come from?
- p. 159, line 17: Data on levels of toxaphene in breast milk in Canada may be added here.
- p. 162, line 8: If toxaphene is not produced for use as a pesticide in the USA, but it is still produced in Idaho and Texas, what is it produced for?
- p. 163, line 2: Again, here is indicated that “export of toxaphene to foreign nations for use as a pesticide is not expected since nations around the globe have adopted similar bans under the Stockholm convention”. The overall issue of current or recent toxaphene production and use in the USA (and elsewhere) needs to be clarified.
- p. 166, bottom  
line: The sentence may be rephrased as “No ongoing studies regarding the potential for human exposure to toxaphene were located”.

## **CHAPTER 7. ANALYTICAL METHODS**

- p. 184, line 12: Biomarkers of effects do not belong in this section, which seems to be devoted to analytical methods to measure toxaphene (and/or its congeners and metabolites).

## **CHAPTER 8. REGULATIONS AND ADVISORIES**

- p. 187, line 16: The reference IRIS (2010) is misleading. EPA’s IRIS document is dated 1991, and should be listed under EPA rather than IRIS.

## **CHAPTER 9. REFERENCES**

## **CHAPTER 10. GLOSSARY**

Add the term Parlar, with explanation.

## **APPENDIX C**

Add the following acronyms: BMF, CCC, CMC, PCB, PCC, as they are present in the text of the document.



**SUMMARY COMMENTS RECEIVED FROM**

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**Peer Review Comments for Toxicological Profile for Toxaphene**

Mark Gregory Robson, PhD, MPH, DrPH  
October 2, 2010

**GENERAL**

This is a well written and comprehensive document that will be a useful resource for the lay public as well as health and environmental professionals. I use the ATSDR Profiles in the teaching of two of my graduate courses in public health, Introduction to Environmental Health and Environmental Risk Assessment.

I am especially pleased to see the 2010 version has the Pediatric section added as noted on vii. This is a very important addition from the 1996 version.

Toxaphene is such an interesting chemical and it is quite remarkable that this profile covers published literature from 1949 (Lackey) to 2010 (US EPA).

**CHAPTER 1. Public Health Statement**

The chapter is written at the correct level and the tone is at the correct level, the concepts are conveyed clearly and thoughtfully.

For 1.2 p2: I think it would be useful to add a time frame in years to the comment on “it can last for years....” Perhaps one could say “it can last from xx years to xx years”

For 1.4 p3: I think you may wish to include the contribution of washing and bathing, if it is or if it is not an important exposure pathway then indicate that. Washing and bathing are part of what the lay public associates with dermal exposure and water, especially when the ingestion pathway of drinking water is also discussed.

For 1.5 p3: In the discussion of kidneys, the bullet lists swollen kidneys, this is also what appears in the body of the document and the report, perhaps a better description of what that means, or why a condition of swollen kidneys might be of concern would be helpful.

For 1.6 p4: I think there needs to be a better explanation of “through their mothers’. Perhaps simply “through their mothers via.....”

For 1.7 p4: Avoid using **don't**, it is the only time this level of informality appears in this document. Change to **do not**.

For 1.9 p5: A more detail explanation of MCL is needed. MCL is an important concept; a thoughtful discussion of MRL is included in 2.3 p10 and in the Glossary. MCL does not appear in the Glossary p239, it should appear there, too.

## **CHAPTER 2. Relevance to Public Health**

The information cited for the occurrence of effects in human health is extensive, I agree with the assessments made in this section.

The discussion on animal effects v. human effects is reasonable and the associations made are appropriate.

Exposure conditions have been adequately described.

## **CHAPTER 3. Health Effects**

The literature spans more than six decades for toxaphene. The profile describes the limitations, especially for the older studies where the protocols were not as rigorous. Conclusions, including limitations are listed and covered in sufficient detail LOAEL and NOAEL values were cited and justified.

I am not aware of additional studies that should be included.

For 3.4.5 p84: This is a very well written and thoughtful explanation of PBPK/PD models. This should be useful to readers at many levels.

For 3.12 p100: The animal studies described are basically those available from the literature may of these studies date back to the 1970s and 1980s. They represent the protocols and approaches taken for that time, the data are useful and the information is included with the limitations and caveats that should be included when citing this work. Figure 3.5 p102 provides a reasonable summary.

An MRL for intermediate duration oral is set at 0.002 mg/kg/day.

A chronic-duration oral MRL was **not** derived and the explanation given was reasonable and justifiable.

The text is extensive, comprehensive, and covers the wide range of studies and relevant toxicities adequately. Proper and adequate attention has been paid to the dose response relationships and other relevant factors.

Biomarkers as listed here are for the compound of concern, toxaphene. Because of the length of time this chemical was in production and because of its wide use there are numerous studies that have measured the compound in a number of matrices, breast milk, urine, blood, fat, etc.

There is a reasonable level of information provided for susceptible populations.

The section for reducing toxic effects is brief but provides the relevant information for this compound. The compound has not been permitted for use for 20 years; direct exposure by application is not likely. The four major works cited for treatment are some of the standard texts for this information. Given the chemical properties of toxaphene the concern is convulsions and seizures, traditional treatments of Diazepam, Phenobarbital, etc., have been shown to be effective in counteracting the effects associated with toxaphene exposure. As indicated given the age of this compound and the number of years since it is banned there are no on-going studies on toxaphene.

#### **CHAPTER 4. Chemical and Physical Information**

The section on Chemical and Physical Properties is adequate.

#### **CHAPTER 5. Production, Import/Export, Use, and Disposal**

The section on Production, Import/Export, Use, and Disposal is adequate.

#### **CHAPTER 6. Potential for Human Exposure**

I have some concerns about the use of the word “release”. For a toxic where we measure emissions, spills, etc., we should use the word “release”. Where this is problematic, at least to me, is the word release when it is used to describe the application of a pesticide. Pesticides are economic poisons intentionally designed to be toxic and intentionally applied to crops for the control of an insect pest. We should distinguish the accidental emissions spills, leaks, etc., from the amount applied in agriculture and indicate that amount of toxaphene applied, usually as active ingredient (AI). Formulated product

reporting is a challenge as it can range from low concentrations 20% active to much higher. The reader needs to understand that the acreage treated had the chemical applied to it, usually in a fairly uniform manner over a long period of time; in this case cotton and other labeled crops were treated for decades. An analogy is when we look at metals. Metals that were released by spills or leaks or dumped versus when we see elevated metals in soils that are a result of being a contaminant in fertilizer or for land applications of sludge material used as plant nutrients.

I think the distinction should be made for TRI type releases of toxaphene and the amount applied directly to crops for agricultural purposes.

There is adequate and in fact very extensive information provided for transport and partitioning. It is covered adequately.

There is also considerable amount of monitoring data provided for air, soil and sediment. Since this is a pesticide registered for agricultural purposes there is also data for food crops and food residues. There is also a considerable body of literature for toxaphene concentrations in fish.

#### **CHAPTER 7. Analytical Methods**

The information for analytical methods is extensive for toxaphene; covering biological samples and environmental samples this includes citations from 1949 to 2010.

#### **CHAPTER 8. Regulations and Advisories and Guidelines**

The section on Regulations and Advisories and Guidelines is adequate.

#### **CHAPTER 9. References**

This is a very large body of literature that spans a 61 year period; it is very extensive and complete.

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**SECTION II**

**ADDITIONAL REFERENCES AND DATA  
SUBMITTED BY THE PEER REVIEWERS**



There were no additional references and data submitted by reviewers for this review.



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**SECTION III**

**ANNOTATED PAGES FROM  
THE DRAFT PROFILE DOCUMENT**





**ANNOTATED PAGES FROM  
THE DRAFT PROFILE DOCUMENT  
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1. PUBLIC HEALTH STATEMENT

<b>Form</b>	Toxaphene is usually found as a solid or gas. In its original form, toxaphene is a yellow to amber waxy solid that has a piney odor.
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1.2 WHAT HAPPENS TO TOXAPHENE WHEN IT ENTERS THE ENVIRONMENT?

<b>Movement between air, water, soil, and sediment</b>	When toxaphene is released to the environment, it can enter the air (by evaporation), the soil (by sticking to soil particles), and the water (from runoff after rains). Toxaphene does not dissolve well in water, so it is more likely to be found in air, soil, or the sediment at the bottom of lakes and streams.
<b>Breaks down slowly</b>	Once toxaphene is in the environment, it can last for years because it breaks down very slowly. ←
<b>Transported by air over long distances</b>	Toxaphene has been found in water, soil, sediment, air, and animals in places far from where it has been used. This shows that toxaphene can be carried long distances by the air.
<b>Bioaccumulates</b>	Toxaphene levels may be high in some predatory fish and mammals because toxaphene accumulates in fatty tissues. Even when levels are low or confined to a certain area, they could be high in individual animals.

Provide a range

1.3 HOW MIGHT I BE EXPOSED TO TOXAPHENE?

<b>Hazardous waste sites</b>	People living near a location with heavy toxaphene contamination, such as a hazardous waste sites, may be exposed to higher levels through breathing contaminated air or through direct skin contact with contaminated soil or water.
<b>Eating contaminated soil</b>	Infants and toddlers, who are likely to put things in their mouth, may be exposed to toxaphene by eating contaminated soil.
<b>Eating fish, shellfish, and wild game</b>	People who eat large quantities of fish, shellfish, or wild game animals from areas contaminated by toxaphene may have higher exposure to this substance since these animals tend concentrate toxaphene in their fatty tissues.
<b>Drinking water</b>	Individuals may be exposed to toxaphene through drinking water contaminated with toxaphene runoff from contaminated soils.

1. PUBLIC HEALTH STATEMENT

1.4 HOW CAN TOXAPHENE ENTER AND LEAVE MY BODY?

<b>May enter your body through food, drinking water, breathing, and skin contact</b>	Toxaphene can enter your body if you eat food contaminated with toxaphene, such as fish caught from water where toxaphene is present. Toxaphene in drinking water can similarly enter your body. Toxaphene could enter your body if it were to come into contact with your skin or if you were to breathe air containing toxaphene.
<b>Leaves through bodily fluids</b>	Toxaphene is quickly broken down into other substances in your body. Toxaphene and its breakdown products leave your body mostly in urine and feces. Small amounts may leave through breast milk and exhaled air.

Include contribution from bathing and washing

1.5 HOW CAN TOXAPHENE AFFECT MY HEALTH?

This section looks at studies concerning potential health effects in animal and human studies.

<b>Nervous system</b>	Convulsions were experienced by some people who accidentally or intentionally swallowed large amounts of toxaphene, including three women who ate collard greens contaminated with toxaphene. However, since toxaphene is no longer used as a pesticide, you would not likely eat enough toxaphene-contaminated food to affect your nervous system in this way.
<b>Immune system</b>	Effects on the immune system have been observed in laboratory studies of animals that were given toxaphene by mouth in amounts that you would not likely get by eating food or drinking water containing toxaphene.
<b>Liver</b>	Toxaphene temporarily damaged the liver of a man who attempted suicide by drinking a large amount of an insecticide that contained toxaphene. Liver damage was seen in laboratory studies of animals that were given toxaphene by mouth in amounts that you would not likely get by eating food or drinking water containing toxaphene.
<b>Kidneys</b>	Toxaphene temporarily damaged the kidneys of a man who attempted suicide by drinking a large amount of an insecticide that contained toxaphene. Swollen kidneys were seen in a small boy who died after drinking a large amount of toxaphene. Kidney damage was seen in laboratory studies of animals that were given toxaphene by mouth in amounts that you would not likely get by eating food or drinking water containing toxaphene.
<b>Cancer</b>	Toxaphene caused liver cancer in mice and possibly thyroid cancer in rats that were given toxaphene by mouth in large amounts that you would not likely get by eating food or drinking water containing toxaphene. We do not know whether toxaphene would cause cancer in humans.

Explanation of swollen kidneys

1. PUBLIC HEALTH STATEMENT

1.6 HOW CAN TOXAPHENE AFFECT CHILDREN?

This section discusses potential health effects in humans from exposures during the period from conception to maturity at 18 years of age.

<b>Effects in children</b>	Toxaphene would be expected to affect children in the same manner as adults. It is not known whether children are more susceptible than adults to the effects of toxaphene.
<b>Developmental effects</b>	In one laboratory study, young rats that had been exposed to toxaphene through their mothers took longer to learn a swimming behavior than young rats from mothers that were not exposed to toxaphene. We do not know if toxaphene would cause delayed development of the nervous system in humans.

Explanation of "through their mothers"



1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO TOXAPHENE?

<b>Reduce consumption of foods and drinking water that contain toxaphene</b>	For people who live in areas where surface waters (lakes) have been contaminated with toxaphene, consumption of toxaphene-contaminated foods such as fish may need to be reduced. Also, don't drink water that has been contaminated with toxaphene.
--	--

Avoid don't use do not



1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO TOXAPHENE?

<b>Can be measured in blood and urine</b>	Toxaphene and some of its breakdown products can be measured in blood and urine. However, it is not likely that you would be exposed to enough toxaphene to make such measurements useful.
---	--

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. The EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that develop regulations for toxic substances. Recommendations provide valuable guidelines to protect public health, but cannot be enforced by law. The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) are two federal organizations that develop recommendations for toxic substances.

1. PUBLIC HEALTH STATEMENT

Regulations and recommendations can be expressed as “not-to-exceed” levels. These are levels of a toxic substance in air, water, soil, or food that do not exceed a critical value. This critical value is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that provides it.

Some regulations and recommendations for toxaphene include the following:

<b>Levels in drinking water set by EPA</b>	<p>The EPA has determined that exposure to toxaphene in drinking water at concentrations of 0.004 mg/L for one day or 0.004 mg/L for 10 days is not expected to cause any adverse effects in a child.</p> <p>The EPA has determined that lifetime exposure to 0.01 mg/L toxaphene in the drinking water is not expected to cause any adverse noncancer effects if the only source of exposure to toxaphene is the drinking water.</p> <p>EPA established a maximum contaminant level (MCL) of 0.003 mg/L for toxaphene in drinking water.</p>
<b>Bottled water</b>	<p>The FDA has determined that the toxaphene concentration in bottled drinking water should not exceed 0.003 mg/L.</p>
<b>Levels in workplace air set by OSHA</b>	<p>OSHA set a legal limit of 0.5 mg/m<sup>3</sup> for toxaphene in air averaged over an 8-hour work day.</p>

provide explanation



1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

### 3. HEALTH EFFECTS

absorption, distribution, and excretion of toxaphene were evident from these studies, but insufficient information regarding the dose of toxaphene precludes any estimation of the extent and rate of excretion.

#### 3.4.4.4 Other Routes of Exposure

Mohammed et al. (1983) reported that  $^{14}\text{C}$ -toxaphene was rapidly distributed to most tissues and organs following intravenous administration in mice. Between 20 minutes and 4 hours after injection, there was a significant increase in the radioactivity observed in the intestinal contents. The presence of radioactivity in the intestine probably represented the biliary excretion of  $^{14}\text{C}$ -toxaphene and its metabolites. Sixteen days after administration, the tissue showing the highest concentration of  $^{14}\text{C}$  toxaphene was abdominal fat, which had concentrations about 10% of those found 4 hours after administration.

Based on the rapid and extensive metabolism seen in all animals, the fate of toxaphene in humans is probably similar. The negligible quantities of parent compound in the excreta and the lack of persistence of metabolites in the tissues indicate that toxaphene and its components are readily removed from the body. Low-level exposure is not expected to cause significant harm to humans. Theoretically, however, acute high-level exposure may saturate metabolic pathways and consequently allow toxaphene to accumulate in the tissues for a longer period of time (>16 days).

#### 3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from

well written section  
←