DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR ENDRIN

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 Endrin were:

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ATSDR would like to thank these scientists for their review of the toxicological profile for endrin. Depending on the nature of the comment, each Reviewer's comments have been divided into sections which could include General Comments, Specific Comments, ATSDR Charge Questions and Responses, and Annotated Comments. The Reviewer's exact comment is presented in plain text in the **COMMENT** field. ATSDR's response to each comment is presented in italics in the ***RESPONSE*** field. If the response included revised text from the toxicological profile, this appears indented under the response in plain text.

Comments provided by Reviewer #1

General Comments

COMMENT: Overall this updated profile on endrin covers the salient scientific literature and experimental findings on endrin toxicity. The information in the text is in general thoroughly presented and well documented. However in selected portions of the text the choice of words or phrases are awkward. This reviewer has added both comments as well as provided wording suggestions in the text using the track changes application in word.

RESPONSE: *Responses to individual comments can be found in the Annotated Comments section at the end of the formal disposition to comments provided by Reviewer #1.*

ATSDR Charge Questions and Responses

Chapter 1

QUESTION: 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.

COMMENT: The effects reported in the text for humans' covers those available references on this topic. The authors do good job in bringing forth the effects of endrin on humans.

RESPONSE: *No response is necessary.*

QUESTION: 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.

COMMENT: The authors correctly noted the major effects of endrin in both animals and humans to be the neurotoxic effects. Those results only seen in animals are adequately described and their potential importance to human risk are well noted.

RESPONSE: *No response is necessary.*

QUESTION: Have exposure conditions been adequately described? If you disagree, please explain.

COMMENT: The exposure conditions are adequately described. No additional comments.

RESPONSE: *No response is necessary.*

QUESTION: Do you believe the derived acute oral MRL value is justifiable? If you disagree, please explain. (see also Appendix A)

COMMENT: The acute oral MRL is justified.

RESPONSE: *No response is necessary.*

QUESTION: Do you believe the derived acute oral MRL is also protective of intermediate exposure durations?

COMMENT: Yes

RESPONSE: *No response is necessary.*

QUESTION: Do you agree that the data do not support derivation of acute, intermediate, and chronic inhalation MRLs?

COMMENT: Yes

RESPONSE: *No response is necessary.*

Chapter 2

QUESTION: Do the health effect conclusions made in Chapter 2 adequately reflect the findings in the published literature for endrin?

COMMENT: Yes, the text reflects the current state of the literature for endrin.

RESPONSE: *No response is necessary.*

QUESTION: 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)? Were the major study limitations sufficiently described in the text without going into lengthy discussions? If study limitations were not adequately addressed, please suggest appropriate changes.

COMMENT: The authors did an excellent job in defining and describing the human studies and in particular pointing out the strengths and weakness of the human studies.

RESPONSE: *No response is necessary.*

QUESTION: 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.

COMMENT: The animal studies on endrin appear to be complete and are well defined. The authors, as with the human studies point out and problems with the animal studies that would impact on the incorporation of these studies into the risk evaluation.

RESPONSE: *No response is necessary.*

QUESTION: 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?

COMMENT: Yes, no changes needed.

RESPONSE: *No response is necessary.*

QUESTION: Are you aware of any studies that are not included in the profile that may be important in evaluating the toxicity of endrin? Please provide a copy of each study and indicate where in the text each study should be included.

COMMENT: I am not aware of any additional studies on endrin that should be included in the text.

RESPONSE: *No response is necessary.*

QUESTION: Are you aware of any studies that are not included in the profile that may be relevant to deriving MRLs for endrin aldehyde or endrin ketone?

COMMENT: No.

RESPONSE: *No response is necessary.*

QUESTION: Were all appropriate NOAELs and/or LOAELs identified for each study (both in the text and the Levels of Significant Exposure (LSE) tables and figures)? If not, did the text provide adequate justification for excluding NOAELs/LOAELs including, but not limited to, citing study limitations? Please suggest appropriate changes.

COMMENT: The NOAEL and LOAELs are identified and well justified.

RESPONSE: *No response is necessary.*

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

COMMENT: I struggled with these terms. They are semi quantitative which is a concern. I think the text should do a better job of completely defining these terms. I offer no other option short of leaving them out.

RESPONSE: *The definition of "less serious" and "serious" effects, along with discussion regarding professional judgement utilized to label effects as "less serious" versus "serious," can be found in introductory text at the beginning of Section 2.1. Additionally, all effects associated with "less serious" and "serious" LOAELs are presented in the LSE tables for transparency. ATSDR will consider the Reviewer's suggestion regarding revised definitions of these terms in future versions of the profile guidance.*

QUESTION: Have all possible mechanisms of action been discussed within their relevant health effect section? If not, please explain.

COMMENT: In the **Mechanisms of Hepatotoxicity** section the discussion of the possible role of lipid peroxidation and oxidative damage appears pertinent and in line with the mechanism of other chlorinated insecticides such as dieldrin. The data on the AHr receptor (which is negative) is well described. Although not addressed in the available literature on endrin, the other two receptors involved in liver toxicity and carcinogenicity (the PPAR alpha and the CAR/PXR) were not discussed. The authors might consider at least speculating that these receptors may participate based on other liver toxic chemicals.

RESPONSE: *Three studies relevant to PPAR alpha and CAR/PXR receptors and endrin were identified (Hernandez et al. 2009; Lemaire et al. 2004; Takeuchi et al, 2006). The text in* ***Mechanisms of Hepatotoxicity*** *was revised to include relevant information (see red text below).*

> In studies with dioxin-responsive and -nonresponsive strains of mice, there was no clear evidence for involvement of the Ah receptor in endrin-induced lipid peroxidative effects in liver (Bagchi et al. 1993d). Endrin is also not likely to exert hepatotoxicity via peroxisome proliferator-activated receptors (PPARs) because it was not an agonist for mouse PPARα or PPARγ in an *in vitro* reporter gene assay (Takeuchi et al. 2006). However, endrin was a human pregnane X receptor (hPXR) agonist in an *in vitro* reporter gene assay, resulting in induction of CYP3A4 and CYP2B6 in hepatocytes (Lemaire et al. 2004). Together, PXR and the constitutive androstane receptor (CAR) can mediate hepatotoxicity via alterations in metabolism and hepatic proliferations (Hernandez et al. 2009). No information on whether or not endrin can induce CAR was available (Hernandez et al. 2009).

Peer Review of Unpublished Study by Kettering Laboratory

QUESTION: Did the study use an adequate number of animals and practice good animal care?

COMMENT: Since dogs were used, the number was adequate, and the care appeared to be excellent

RESPONSE: *No response is necessary.*

QUESTION: Did the study account for competing causes of death?

COMMENT: Yes

RESPONSE: *No response is necessary.*

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

COMMENT: Yes

RESPONSE: *No response is necessary.*

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

COMMENT: The study was performed up to the standards of the day. Several things should have been further addressed. Including, the level of endrin was not apparently confirmed in the diet nor in the untreated control diets, so it is not clear what the actual level of endrin was in the diet. Second, the pathology data – as presented – is weak. Perhaps there is another report with complete pathology descriptions and details. In this report it is difficult to ascertain the actual changes without seeing more detailed description and pictures of the liver pathology.

RESPONSE: *While some issues with the study reporting were identified, the Reviewer agrees with the conclusions of the author and does not indicate that issues negate the utility of the study (see next Question). No response is necessary.*

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

COMMENT: Yes

RESPONSE: *No response is necessary.*

Chapter 7

QUESTION: Are you aware of any additional regulations or guidelines that we should add? Please provide citations.

COMMENT: No, I am not aware.

RESPONSE: *No response is necessary.*

QUESTION: Are there any that should be removed? Please explain.

COMMENT: No.

RESPONSE: *No response is necessary.*

Appendix A – Minimal Risk Levels (MRLs)

QUESTION: Do you agree or disagree with the proposed acute-duration oral MRL value? Explain. If you disagree, please specify the MRL value that you propose.

COMMENT: The proposed MRL is supported by the literature and the text.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree or disagree with ATSDR's selection of the point of departure? Explain. If you disagree, please specify the value that you propose.

COMMENT: I agree, it is supported by the data presented.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor(s) that you propose.

COMMENT: Yes, I agree.

RESPONSE: *No response is necessary.*

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

COMMENT: No additional comments.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree with ATSDR that the acute oral MRL of 0.0006 mg/kg/day would be sufficiently protective for intermediate exposures? If not, please explain

COMMENT: Yes, this dose would be protective.

RESPONSE: *No response is necessary.*

Appendix B – Literature Search Framework

QUESTION: Does Appendix B provide a sufficiently clear documentation of ATSDR's health effects literature search strategy and inclusion/exclusion criteria?

COMMENT: Yes.

RESPONSE: *No response is necessary.*

QUESTION: Does it provide enough transparency regarding ATSDR's implementation of its inclusion and exclusion criteria (e.g., how ATSDR chose the studies it included in the health effects chapter)?

COMMENT: The transparency is very good and the inclusion or exclusion of studies is well defined.

RESPONSE: *No response is necessary.*

Overall Usability of the Profile

QUESTION: Does the new chapter organization make it easier for you to find the information you need? For example, are you satisfied with the organization of the health effects chapter by organ system rather than exposure route?

COMMENT: For this compound the target organ approach is very useful since the majority of the studies are oral exposure. If there many more routes of exposure, it might get confusing.

RESPONSE: *No response is necessary.*

QUESTION: Are the new tables and figures clear and useful? Do they make the toxicological profile easier to read?

COMMENT: The tables are much easier to read and much easier to follow.

RESPONSE: *No response is necessary.*

QUESTION: If you have previously used any Toxicological Profile(s) for your work, which parts or content are the most useful to you, and what do you use it for?

COMMENT: Since I am predominantly a mechanistic toxicology who gets involved in risk assessment, the health effects chapter (2) and the regulations chapter (7) is the most useful for me.

RESPONSE: *No response is necessary.*

QUESTION: Does the profile contain all of the information you need? If no, please elaborate on what additional information would be helpful.

COMMENT: Yes, in particular there is a much limited database for this compound compared to others that have more extensive literature base.

RESPONSE: *No response is necessary.*

QUESTION: Is there information you would like to see in the profile that is not currently included? If yes, please elaborate on the additional information you would like to see in the profile.

COMMENT: No changes suggested.

RESPONSE: *No response is necessary.*

Annotated Comments

The Reviewer suggested a number of changes to boilerplate text or figure templates. These suggestions will be considered by ATSDR in future versions of the profile guidance. The Reviewer also 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. Responses to Reviewer comments that were not suggested changes to boilerplate/templates or considered editorial/stylistic are presented below.

COMMENT: Figure 1.1 –body weight changes should specify an increase or a decrease in body weight.

RESPONSE: *Text in the figure was changed from "body weight effects" to "decreased body weight."*

COMMENT: Section 1.2, Renal effects. Should provide a little more detail on the renal histopathology [for Hassan et al. 1991]. ie was there proximal tubule necrosis, glomerular effects, distal tubule effects??

RESPONSE: *Text was revised to include observed lesions (see red text below):*

A single study involving acute exposure to a high dose reported renal histopathologic effects in rats, mice, and hamsters, including moderate tubular necrosis and congestion, inflammation, and interstitial edema (Hassan et al. 1991).

COMMENT: Section 1.2, Cancer effects. Specify the cancers reported [for Ditraglia et al. 1981].

RESPONSE: *Text was revised to specify cancers (see red text below):*

In two industries manufacturing endrin, small excesses of certain cancers were reported, including malignant neoplasms of the esophagus, rectum, liver, and lymphatic and hematopoietic systems (Ditraglia et al. 1981).

COMMENT: Section 2.9, paragraph 8: What is meant by longer?

RESPONSE: *The term "longer" was replaced with the term "chronic".*

COMMENT: Section 2.16, paragraph 4: Clarify? Bacterial or viral or parasitic infection [in Eisenlord et al .1968]

RESPONSE: *The text in Section 2.16, paragraph 4, was edited for clarification (see red text below).*

Interpretation of the study results is confounded by the potential presence of ~~infection~~ viral pneumonitis in controls and, thus, possibly in all animals in the study

COMMENT: Section 2.19, paragraph 1: Were other factors i.e. smoking and alcohol consumption also examined in these workers with regard to cancer incidence [in Ditraglia et al. 1981]?

RESPONSE: *Ditraglia et al (1981) did not report smoking or drinking status of workers. No discussion of potential confounding factors was included in this report, or in Ribbens (1985) or Versteeg and Jager (1973). The text in Section 2.19, paragraph 1, was revised to reflect this (see red text below).*

Studies of workers in the endrin manufacturing industry have not shown an association between occupational exposure to endrin and overall mortality rates due to cancer (Ditraglia et al. 1981; Ribbens 1985; Versteeg and Jager 1973); see Table 2-1 for study details. While there was no specific cancer risk at any manufacturing sites, several cancer mortalities reported in aldrin/ dieldrin/endrin plants in one study may warrant further investigation, including slight excesses of cancer of the esophagus, liver, rectum, and the lymphatic and hematopoietic systems (Ditraglia et al. 1981). However, the study authors noted that excesses were not statistically significant, and acknowledged that the elevated standardized mortality ratios (SMRs) were based on small numbers of observed deaths (one to three deaths except for lymphatic/

hematopoietic cancers, which were based on six deaths). Limitations of these studies include small cohort size, limited follow-up, and lack of control for confounding factors (e.g., smoking, alcohol consumption).

COMMENT: Section 2.20, Clastogenicity section: Was [induced spontaneous crossing over in *D. melanogaster* males] significant statistically [in Pontecorvo and Fantaccione 2006]?

RESPONSE: *The text in Section 2.20, Clastogenicity, was revised to indicate that findings in this study were statistically significant (see red text below).*

Sister chromatid exchanges were not observed in human lymphoid cells exposed to endrin in vitro (Sobti et al. 1983). In vivo, chromosomal aberrations in rat testicular cells were observed following an intratesticular injection of endrin (Dikshith and Datta 1973). The number of recombination events was slightly, but significantly, ~~and endrin slightly induced spontaneous crossing over~~ increased in *Drosophila melanogaster* males (cross overs detected in 3 out of 60 males; p=0.05) (Pontecorvo and Fantaccione 2006).

Comments provided by Reviewer #2

General Comments

COMMENT: I have extensively reviewed the extensive report submitted on Endrin and its toxicological manifestation. Basically, this toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA).

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

The report was very meticulously conducted, which examined and demonstrated the health effects found in animals following oral exposure to endrin.

Overall, the report was very extensive and accomplished well be the toxicology Team.

RESPONSE: *No response is necessary.*

COMMENT: I found some of the important references are missing in this document. Addition of the following references will significantly strengthen the report.

RESPONSE: *See responses for each suggested reference below.*

COMMENT: Metabolites of endrin - Please cite this reference on page 72, in section 3.1.3 Metabolism section

Petrella VJ, McKinney JD, Fox JP, Webb RE. Identification of metabolites of endrin. Metabolism in endrin susceptible and resistant strains of pine mice. J Agric Food Chem. 1977; 25(2): 393-398.

RESPONSE: *Petrella et al. (1977) was added to Section 3.1.3. (see text in red below).*

The metabolism of endrin varies among species, regardless of the route of exposure. In all species, oxidation of the methylene bridge in endrin (Compound I in Figure 3-1) to syn-, but mostly anti-12 hydroxyendrin occurs (Compounds II and III), followed by dehydrogenation to 12-ketoendrin (Compound VI). Minor independent pathways involve the hydrolysis of the epoxide to a transdiol (Compound V in Figure 3-1) and hydroxylation of the C-3 position (Compound IV) (Bedford et al. 1975b; Hutson 1981; Petrella et al. 1977). Hydroxylation at C-3 and C-4 is inhibited by the presence of the bulky hexachlorinated fragment (Hutson 1981). In rats, both anti-12-hydroxyendrin and 12-ketoendtrin are produced at higher rates in the male rat, with higher formation of anti-12-hydroxyendrin O-sulphate in female rats (Hutson et al. 1975). Richardson et al. (1970) also reported sex differences in the proportion of fecal metabolites in rats; however, metabolites were identified as "1" and "2" and not further characterized except to state that they were not ketone rearrangement products of endrin. In mice, strains resistant to acute endrin toxicity produce anti-12-hydroxyendrin at higher rates (~2-fold) compared with strains that are susceptible to acute endrin toxicity (Petrella et al. 1977).

COMMENT: Metabolism of endrin - Please cite these two references on page 72, in section 3.1.3 Metabolism section

1. Richardson A, Robinson J, Baldwin MK. Metabolism of endrin in the rat. Chem Ind 1970; 15: 502-503
2. Matsumura F, Khanvilkar VG, Patil KC, Boush GM. Metabolism of endrin by certain soil microorganisms. J Agric Food Chem. 1971; 19(1): 27-31.

RESPONSE: *Matsumura et al. (1971) was not added to the profile because it reports on metabolism in soil microorganisms, which is not covered in ATSDR Toxicological Profiles. Richardson et al. (1970) was added to Sections 3.1.2 (Distribution), 3.1.3 (Metabolism), and 3.1.4 (Excretion); see text in red below.*

Section 3.1.2: Endrin tends to bioaccumulate in fat because of its high lipid solubility. Three days after an acute oral dose of 2.5 mg/kg of radio-labeled endrin, the percentages of the administered dose in male rat organs were 1.2% in liver, 0.6% in kidney, 1.7% in fat, 2.3% in skin, and 12.2% in the carcass. Female rats retained higher concentrations in tissues: 2% of the dose in liver, 0.35% in kidney, 8% in fat, 4% in skin, and 28.2% in carcass (Hutson et al. 1975). Richardson et al. (1970) also reported an unidentified metabolite of endrin in the brain, liver, and adipose tissue of male rats following a single oral exposure.

Section 3.1.3: The metabolism of endrin varies among species, regardless of the route of exposure. In all species, oxidation of the methylene bridge in endrin (Compound I in Figure 3-1) to syn-, but mostly anti-12 hydroxyendrin occurs (Compounds II and III), followed by

dehydrogenation to 12-ketoendrin (Compound VI). Minor independent pathways involve the hydrolysis of the epoxide to a transdiol (Compound V in Figure 3-1) and hydroxylation of the C-3 position (Compound IV) (Bedford et al. 1975b; Hutson 1981; Petrella et al. 1977). Hydroxylation at C-3 and C-4 is inhibited by the presence of the bulky hexachlorinated fragment (Hutson 1981). In rats, both anti-12-hydroxyendrin and 12-ketoendrin are produced at higher rates in the male rat, with higher formation of anti-12-hydroxyendrin O-sulphate in female rats (Hutson et al. 1975). Richardson et al. (1970) also reported sex differences in the proportion of fecal metabolites in rats; however, metabolites were identified as "1" and "2" and not further characterized except to state that they were not ketone rearrangement products of endrin. In mice, strains resistant to acute endrin toxicity produce anti-12-hydroxyendrin at higher rates (~2-fold) compared with strains that are susceptible to acute endrin toxicity (Petrella et al. 1977).

Section 3.1.4: In rats, the major route of elimination is the feces, with a smaller percentage eliminated in the urine, and there are apparent sex differences. Twenty-four hours after oral exposure to 0.5–2.5 mg/kg, 55–57% of 14C-endrin was metabolized in the bile; the predominant metabolite was the glucuronide of anti-12 hydroxyendrin (Hutson et al. 1975). Other minor components (<10%) were the glucuronides of 3 hydroxy- and 12-ketoendrin. Male rats eliminated 69% of the radioactive label within 3 days and females eliminated 45%. Another study in male rats reported elimination of 49% of the radioactive label within 3 days following oral exposure (Richardson et al. 1970).

COMMENT: Protein kinase C Activation by Endrin - Please cite this reference on page 50, in section 2.9 Hepatic Section

Bagchi D, Bagchi M, Tang L, Stohs SJ. Comparative in vitro and in vivo protein kinase C activation by selected pesticides and transition metal salts. Toxicol Lett. 1997; 91(1): 31-37

RESPONSE: *This reference was added to the* ***Mechanisms of Hepatotoxicity*** *discussion in Section 2.9 (see red text below).*

Administration of single doses of endrin to rats was associated with increased lipid peroxidation, decreased membrane fluidity, and deoxyribonucleic acid (DNA) damage (single strand breaks) in hepatocytes (Bagchi et al. 1995a,1995b, 1992a, 1993a, 1993c, 2000, 2002; Hassoun et al. 1993). The authors suggested that membrane alterations and DNA damage may result from the enhanced formation of free radical or reactive oxygen species. These reactive species could lead to altered cell proliferation and differentiation, potentially through activation of the protein kinase C (PKC) pathway (Bagchi et al. 1997).

COMMENT: Toxicity of Endrin - Please cite this reference on page 89, in section 5.3.2 Water Sub-Section

Kachole MS, Pawar SS, Mahajan AG. The toxicity of endrin and the effect of pretreatment of phenobarbital and hexobarbital on mortality in four fresh water fishes. Bull Environ Contam Toxicol. 1977;17(6): 768-70.

RESPONSE: *This reference was not added to the profile. The suggested reference pertains to ecotoxicity, which is not covered in ATSDR Toxicological Profiles. The only fish studies included in the profile pertain to bioconcentration.*

COMMENT: Toxicity of Endrin - Please cite this reference on page 72, in section 3.1.3 Metabolism section

Soto AR, Deichmann WB. Major metabolism and acute toxicity of Aldrin, dieldrin, and endrin. Environ Res. 1967; 1(4): 307-22.

RESPONSE: *This reference was not added to the profile because it is a secondary source. It is ATSDR practice to not to cite secondary sources in this section of the profile. Review of the suggested reference did not identify any data not covered by primary sources cited in the profile.*

COMMENT: Growth Response - Please cite this reference on page 69, in section 2.21 Mechanism of Toxicity section

Batterton JC, Boush GM, Matsumura F. Growth response to blue-green algae to Aldrin, dieldrin, endrin and their metabolites. Bull Environ Contam Toxicol. 1971; 6(6): 589-94.

RESPONSE: *This reference was not added to the profile. The suggested reference pertains to ecotoxicity, which is not covered in ATSDR Toxicological Profiles. The only algal data included in the profile pertains to bioconcentration.*

COMMENT: Review - Please cite this reference on page 3, in section 1.2 Summary of Health Effects Sowell WL, Lawrence CH, Coleman RL. Endrin: A review. J Okla State Med Assoc. 1968; 61(4): 163-9.

RESPONSE: *It is ATSDR practice to not to cite secondary sources in this section of the profile. The secondary source was reviewed for studies not currently cited in the profile that were recent or had data that could potentially address data gaps. A dietary study in rats by Nelson et al. (1956) and a human poisoning report by Jacobziner and Raybin (1959) were identified and reviewed for consideration. The Nelson et al. (1956) study was considered inadequate for inclusion in the profile due to massive weight loss and decreased food consumption indicating palatability issues, which may have contributed to observed mortality. Additionally, it is unclear if exposure estimates are accurate based on body weight and food consumption effects (data reporting inadequate for independent analysis). The human case report by Jacobziner and Raybin (1959) was added to Section 2.15; see red text below.*

In a severe case of poisoning in a 1-year-old child, severe convulsions, coma, decerebrate rigidity, and permanent brain injury occurred after the child played in his room following application of an endrin-containing pesticide (endrin content and other compounds present not available) (Jacobziner and Raybin 1959). The floors and walls of the boy's room had endrin residue; therefore, the exposure was likely a combination of dermal and oral (due to hand-to-mouth activities of young children).

COMMENT: Endrin in the Environment/ Bioaccumulation - Please cite these six references on page 96, in section 5.5 Levels in the Environment

1. Matsumoto E, Kawanaka Y, Yun SJ, Oyaizu H. Bioremidiation of the organochlorine pesticides, dieldrin and endrin, and their occurrence in the environment. Appl Microbiol Biotechnol. 2 009; 84(2): 205-16.
2. Niu L, Xu C, Zhu S, Liu W. Residue patterns of currently, historically and never-used organochlorine pesticides in agricultural soils across China and associated health risks. Environ Pollut. 2016; 219: 315-22.
3. Chopra AK, Sharma MK, Chamoli S. Bioaccumulation of organochlorine pesticides in aquatic system – an overview. Environ Monit Assess. 2011; 173(1-4): 905-16.
4. Mount ME, Oehme FW. Insectide levels in tissues associated with toxicity: a literature review. Vet Hum Toxicol. 1981; 23(1): 34-42.

5. Ramos JJ, Huetos O, González S, Esteban M, Calvo E, Pérez-Gómez B, Castaño A; Bioambientes. Organochlorinated pesticides levels in a representative sample of the Spanish adult population: The Bioambient.es project. Int J Hyg Environ Health. 2017; 220 (2 Pt A): 217- 26.
6. Dang VD, Kroll KJ, Supowit SD, Halden RU, Denslow ND. Tissue distribution of organochlorine pesticides in largemouth bass (Micropterus salmoides) from laboratory exposure and a contaminated lake. Environ Pollut 2016; 216: 877-83.

RESPONSE: *References 1–4 and 6 were not added to the profile, as they pertain to disposal (Section 5.2), environmental fate (Section 5.4), levels in the environment (Section 5.5), or general population exposure (Section 5.6). This partial update was focused on health effects data and did not include revision of Chapter 5 (Potential for Human Exposure). Reference 5 was not added to the profile, as it pertains to ecotoxicity, which is outside the scope of ATSDR profiles.*

COMMENT: Breastmilk and Endrin - Please cite these two references in page 77, in section 3.2 Children and other populations that are unusually susceptible.

1. Pohl HR, Tylenda CA. Breast-feeding exposure of infants of selected pesticides: a public health viewpoint. Toxicol Ind Health. 2000; 16(2): 65-77.
2. Polanco Rodríguez ÁG, Inmaculada Riba López M, Angel DelValls Casillas T, León JA, Prusty AK, Álvarez Cervera FJ. Levels of persistent organic pollutants in breast milk of Maya women in Yucatan, Mexico. Environ Monit Assess. 2017; 89(2): 59-64.

RESPONSE: *These references were not added to Section (3.2), which pertains to populations that may be unusually susceptible to toxic effects of endrin. However, the reference by Polanco-Rodriguez et al. (2017) was added to Section 3.1.4 (Excretion); see red text below. Additionally, the interaction weight-of-evidence determinations for endrin and other organochlorine pesticides reported by Pohl and Tylenda (2000) was added to Section 3.4 (Interactions with other chemicals). This secondary source was reviewed to identify relevant recent studies and studies addressing data gaps not currently cited in the profile. The interaction study by Keplinger and Deichmann (1967) was also added to Section 3.4 of the profile.*

Section 3.1.4: "Endrin has also been detected in human breast milk, cord blood, and placental tissues in several studies worldwide (Alawi et al. 1992; Bedi et al. 2013; Bordet et al. 1993 Fujii et al. 2012; Gladen et al. 1999; Guillette et all. 1998; Lopez-Espinosa et al. 2007; Polanco-Rodriguez et al. 2017; Romero et al. 2000; Schaalan et al. 2012)."

Section 3.4: Pohl and Tylenda (2000) conducted binary weight-of-evidence (WOE) determinations of the potential for joint toxic action between endrin and other organochlorine pesticides. Based on their analyses, there is direct mechanistic data indicating a synergistic effect between endrin and the following organochlorines: DDT, aldrin, dieldrin, chlordane, hexachlorobenzene (HCB), and α-, β-, and δ-hexachlorochylohexane (HCH). For γ-HCH, there is direct mechanistic data indicating an antagonistic effect on endrin. Demonstrated toxicological significance was only available for chlordane (see Ludke, 1976 above); for remaining compounds, Pohl and Tylenda (2000) inferred toxicological significance.

Section 3.4: Keplinger and Deichmann (1967) evaluated potential interactions between endrin and several other pesticides based on observed versus expected LD_{50} values in mice. After determining LD_{50} values for each compound, the expected LD_{50} value of a mixture was calculated and compared to the observed LD_{50} value of the mixture. The study authors considered ratios between 0.79 and 1.27 essentially additive, with higher ratios indicating greater-than-additive effects, and lower ratios indicating less-than-additive effects. Greater-than-additive effects were noted for endrin and

chlordane (ratio of 2.22) and endrin and aldrin (ratio of 1.83). The interactions observed for endrin plus dieldrin, diazinon, toxaphene, or malathion were additive, and the interactions observed for endrin plus parathion, DDT, and Delnav were less than additive (ratios of 0.65, 0.53, and 0.44, respectively). When a mixture of aldrin, chlordane, and endrin was administered, observed effects were considered additive (ratio of 1.27).

COMMENT: Carcinogenicity and Endrin - Please cite this reference in page 64, preferably in the first paragraph of Section 2.19 Cancer Section

Reuber MD. Carcinogenicity of endrin. Sci Total Environ. 1979; 72(2): 101-35

RESPONSE: *This reference was not added to the profile because it is a secondary source. It is ATSDR practice to not to cite secondary sources in this section of the profile. The secondary source was reviewed to identify relevant studies not currently cited in the profile. The review did not identify studies of adequate quality that should be included in the profile*

COMMENT: Distribution in Freshwater - Please cite these 4 references in page 99, in Section 5.5.2 Water sub-section of the Section 5.5 Levels in the Environment

1. Grant BF. Endrin toxicity and distribution in freshwater: a review. Bull Environ Contam Toxicol. 1976; 15(3): 283-90.
2. Unyimadu JP, Osibanjo O, Babayemi JO. Levels of organochlorine pesticides in Brackish water fish from Niger river, Nigeria. J Envirn Public Health. 2018 Jun 28;2018: 2658306. doi: 10.1155/2018/2658306. eCollection 2018.
3. Dahshan H, Megahed AM, Abd-Elall AM, Abd-El-Kader MA, Nabawy E, Elbana MH. Monitoring of pesticides water pollution – The Egyptian river Nile. J Environ Health Sci Eng. 2016 Oct 7;14: 15. eCollection 2016.
4. Navarrete IA, Tee KAM, Unson JRS, Hallare AV. Organochlorine pesticide residues in surface water and groundwater along Pampanga river, Philippines. Environ Monit Assess. 2018; 190(5): 289-96.

RESPONSE: *These references were not added to the profile. This partial update was focused on toxicological data and did not include revisions to Chapter 5 (Potential for Human Exposure).*

COMMENT: Finally, I congratulate the Toxicology Team to complete the comprehensive review so professionally

RESPONSE: *No response is necessary.*

Comments provided by Reviewer #3

General Comments

COMMENT: Overall, the Toxicological Profile for Endrin provides an accurate and succinct report on the known toxicology of the pesticide endrin that should be useful for public health professionals and clinicians. The Profile has acquired all known, available data for health effects of endrin on animal species and humans and provided reasonable and justified conclusions (e.g., MRLs) when possible.

RESPONSE: *No response is necessary.*

COMMENT: p. 1, Overview. In Line 13, it would be helpful to give the reader upfront an indication of when the pesticide was used (e.g., recently, decades ago). In line 15, it would be helpful to the reader to explain here or note elsewhere the significance of the endrin aldehyde and endrin ketone. How are these species formed, e.g., metabolism, environment? As a reference, the Toxicological Profile for Aldrin/Dieldrin provides a nice summary of dieldrin/aldrin use (i.e., timeline) and most likely routes of exposure for the public.

RESPONSE: *The second paragraph in Section 1.1 was revised to inform the reader when endrin was last used in the United States and to explain that the profile also covers endrin aldehyde and endrin ketone, which are degradation products of endrin (see red text below).*

> Endrin [2,7: 3,6-dimethanonaphth(2,3-b)oxirene, 3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-(1aα,2β,2aβ,3α,6α,6aβ,7β,7aα)-, CAS No. 72-20-8] was used as a pesticide. It ~~is no longer~~ has not been produced or used in the United States since 1991 (Bishop 1984, 1985, 1986; EPA 1983e; USDA 1995), which greatly reduces the potential for human exposure. This profile also covers endrin aldehyde and endrin ketone, which were never commercial products, but occurred as impurities of endrin or as degradation products (EPA 1985e; IARC 1974; SRI 1987). Future levels of endrin, endrin aldehyde, and endrin ketone in environmental media are expected to be low. The most significant route of exposure is most likely ingestion of imported foods contaminated with endrin; however, there may also be some localized risks from exposures near waste disposal sites or from groundwater contaminated with endrin.

COMMENT: p. 2, Figure 1-1. "Death" as an effect is shown multiple times with dose for chronic exposure being greater than that of acute and intermediate, which seems counterintuitive.

RESPONSE: *Figure 1-1 was revised to indicate what species death was observed in for clarification. The "death" endpoint reported for intermediate-duration exposure at 0.24 mg/kg/day was for dogs. There are no acute dog studies, and chronic dog studies do not report lethality (highest chronic dose tested was 0.19 mg/kg/day). In rodents, death occurred at ≥0.5 mg/kg/day for all durations.*

COMMENT: p. 21, Figure 2-2. The significance of the figure is of question given 2 data points.

RESPONSE: *This figure was retained for consistency with other profiles and to avoid the potential reporting bias from leaving it out. The minimal number of data points conveys the paucity of available inhalation data.*

COMMENT: p. 22, Table 2-3. In the title for Table 2-2, only endrin is listed, however, endrin/endrin aldehyde/endrin ketone are all shown in the title for Table 2-3. Only on page 9, line 23, is a short explanation listed (i.e., the administered compound is endrin unless otherwise noted with only 3 studies including the ketone and aldehyde). Recommend adding this explanation to the Table 2-3 title as well

RESPONSE: *The text referring to the LSE tables in Section 2.1 was revised for clarity (see red text below)*

> Summaries of the human observational studies are presented in Table 2-1. Animal inhalation studies are presented in Table 2-2 and Figure 2-2, animal oral studies are presented in Table 2-3 and Figure 2-3, and animal dermal studies are presented in Table 2-4. For the inhalation and dermal tables (Table 2-2 and Table 2-4, respectively), all studies evaluated endrin. For the oral table (Table 2-3), the experimental compound (endrin, endrin ketone, or endrin aldehyde) is indicated for each study.

COMMENT: pp. 73-74, 3.1.3 Metabolism. The structure I is incorrect and should have the hydroxyl on the methylene bridge removed if this is supposed to be endrin, the parent compound. It would be helpful to note on the Figure 3-1 the primary route for human metabolism, perhaps color-code. Metabolism of compound IV to sulfate (XI) and glucuronide (XII) conjugates is not clear as the acceptor nucleophile on IV is not apparent. Compound VII structure needs to be corrected as the sulfur (S) needs to be between the O3 and O (i.e., HO3SO-) as a sulfate.

RESPONSE: *Incorrect structures for compound I (endrin) and compound IV were corrected in accordance with Bedford et al. (1975). The structure for compound VII was not altered (consistent with Bedford et al. (1975). The terms "major" and "minor" were added to the figure to indicate which metabolic pathways were major pathways (oxidation of the methylene bridge) and which were minor pathways (hydrolysis of the epoxide to a transdiol and hydroxylation of the C-3 position).*

ATSDR Charge Questions and Responses

Chapter 1

QUESTION: 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.

COMMENT: Yes, I agree with that effects reported occur in humans following exposure. As noted in the text, there are case reports for neurotoxicity (e.g., behavior, convulsions, altered EEG) in humans, and such findings are corroborated via data from animal studies that consistently demonstrated endrin-mediated neurological effects via various routes of exposure. Data for other types of human toxicity are limited or inadequate as noted in the document.

RESPONSE: *No response is necessary.*

QUESTION: 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.

COMMENT: Effects only observed in animal studies are likely to be relevant for humans following exposure to endrin for several reasons. First, a lack of observed effect in humans but not animals could

be due study design, such as a carefully crafted animal dosing experiment compared to case control or cohort epidemiological reports for humans, with the latter including confounders (e.g., unknown exposure level; Table 2-1). Second, animal studies involving multiple species have demonstrated consistent neurological and hepatic effects following exposure to endrin, according to the text. Such a finding should be of concern to humans given similar or conserved biochemical/biological processes. Third, for neurological endpoints, several endpoints of neurotoxicity have been documented for humans (Table 2-1), corroborating the statement that the central nervous system is a target of endrin for animals and humans. Fourth, metabolism of endrin between species (humans and animals) may be similar with a shared initial route (hydroxylation of methylene bridge followed oxidation to a ketone) and metabolic products (as described on p. 73). Fifth, there may be some variability in target organ toxicity between humans and animals, especially in cases where the results of animal experiments are weak or inconsistent across species (e.g., endocrine, renal, developmental); however, the data showing adverse effects in animals indicate some form of risk for humans following exposure.

RESPONSE: *No response is necessary.*

QUESTION: Have exposure conditions been adequately described? If you disagree, please explain.

COMMENT: The text adequately describes exposure conditions, whether it includes several routes or a specific one. Figure 1-2 is very helpful as it specifies oral exposure, a potentially major route.

RESPONSE: *No response is necessary.*

QUESTION: Do you believe the derived acute oral MRL value is justifiable? If you disagree, please explain. (see also Appendix A)

COMMENT: The derived acute oral MRL is justifiable, overall. As noted in the text, the reader should refer to Appendix A to determine the specific endpoint (e.g., for neurological or hepatic effects) and be aware the MRL shown may include significant variability and species differences (as described on pp. 3-6). It might be helpful for Figure 1-2 to include the page reference in Appendix A showing the basis for the MRL and noting endpoint measured.

RESPONSE: *Figure 1-2 presents the lowest LOAELs available from animals studies as well as the MRL values. Figure 1-2 does not contain additional MRL information, such as critical endpoint; this information is in the text (as noted) as well as on the next page of the profile in Table 1-1. ATSDR will consider the Reviewer's suggestion in future versions of the profile guidance.*

QUESTION: Do you believe the derived acute oral MRL is also protective of intermediate exposure durations?

COMMENT: Yes, I believe the acute MRL may be protective of the intermediate exposure duration based on the available (and limited) data in Appendix A. More explicit description would be helpful for the reader, such as why the acute versus chronic oral MRL was selected. Perhaps this information could be added as a subnote in Table 1-1 (instead of the mention of the Provisional MRL).

RESPONSE: *No response is necessary.*

QUESTION: Do you agree that the data do not support derivation of acute, intermediate, and chronic inhalation MRLs?

COMMENT: Yes, I agree that the data available do not support derivation of acute, intermediate or chronical inhalation MRL values. As noted in the text, limited studies are available, such as single studies or confounding conditions (e.g., co-exposure).

RESPONSE: *No response is necessary.*

Chapter 2

QUESTION: Do the health effect conclusions made in Chapter 2 adequately reflect the findings in the published literature for endrin?

COMMENT: Yes, the health effect conclusions adequately reflect the findings in the available published literature, which includes 29 human and 68 animal studies. The overview shown in Figure 2-1 is accurate and adequate based on known data.

RESPONSE: *No response is necessary.*

QUESTION: 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)? Were the major study limitations sufficiently described in the text without going into lengthy discussions? If study limitations were not adequately addressed, please suggest appropriate changes.

COMMENT: The human studies identified in the text are appropriately selected and adequately presented to communicate the type (e.g., cohort, case-control), number of exposed, serum endrin levels, likely route of exposure. Limitations were adequately described (e.g., exposure levels not reported). Other potentially useful information (e.g., gender or age) may not be known, which appears to be the case for studies dating back >10 years.

RESPONSE: *No response is necessary.*

QUESTION: 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.

COMMENT: Yes, adequately designed animal studies were identified and well-summarized for critical parameters (e.g., species, number, gender, dose level, route of exposure) and outcomes.

RESPONSE: *No response is necessary.*

QUESTION: 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?

COMMENT: Yes, results reported were from studies utilizing the appropriate animal species, including rats, mice, monkeys, hamsters, rabbits, dog. All animal species in described studies are well-accepted for toxicological testing as relevant models for humans.

RESPONSE: *No response is necessary.*

QUESTION: Are you aware of any studies that are not included in the profile that may be important in evaluating the toxicity of endrin? Please provide a copy of each study and indicate where in the text each study should be included.

COMMENT: No, I am not aware of any additional and relevant animal studies that would contribute value added to the profile.

RESPONSE: *No response is necessary.*

QUESTION: Are you aware of any studies that are not included in the profile that may be relevant to deriving MRLs for endrin aldehyde or endrin ketone?

COMMENT: No, I am not aware of any studies not included in the profile relevant to deriving MRLs for endrin ketone or endrin aldehyde. It appears there are limited data regarding these forms or metabolites of endrin (e.g., such as noted in the Provisional Peer-Reviewed Toxicity Values for Endrin Ketone; EPA/690/R-12/015F Final 7-12-2012).

RESPONSE: *No response is necessary.*

QUESTION: Were all appropriate NOAELs and/or LOAELs identified for each study (both in the text and the Levels of Significant Exposure (LSE) tables and figures)? If not, did the text provide adequate justification for excluding NOAELs/LOAELs including, but not limited to, citing study limitations? Please suggest appropriate changes.

COMMENT: Looking at all data with emphasis on results from studies dating to 1996 (only 1 from 1996) and following, appropriate NOAELs and LOAELs are identified for each study and noted in the text and tables

RESPONSE: *No response is necessary.*

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

COMMENT: The categorization of “less serious” and “serious” is acceptable given the description on page 8 and the described “Effects” in the table which provide valuable explanation to discriminate between “less serious” and “serious” effects. Without the described “Effect”, the categorization could be confusing or misleading.

RESPONSE: *No response is necessary.*

QUESTION: Have all possible mechanisms of action been discussed within their relevant health effect section? If not, please explain.

COMMENT: The most likely mechanisms of toxicity/action for endrin based on available data have been discussed. Multiple pathways may be responsible for the adverse effects with outcomes being dose, species and metabolism-dependent. The Profile does not unnecessarily or inappropriately speculate on mechanisms of toxicity/action.

RESPONSE: *No response is necessary.*

Peer Review of Unpublished Study by Kettering Laboratory

QUESTION: The updated Endrin profile includes an unpublished study by Kettering Laboratory used to derive the chronic oral MRL in the original 1996 profile. Please comment on the quality of the study.

COMMENT: The quality of the study by the Kettering Laboratory (1969) appears to be good quality despite not being published. It is unknown if the study received peer review.

RESPONSE: *No response is necessary.*

QUESTION: Did the study use an adequate number of animals and practice good animal care?

COMMENT: Good animal care appears to be reported as a veterinarian was involved in examining dogs on arrival; however, it is not clear if good animal care was maintained throughout the study. A total of 60 dogs were grouped via gender with 3 to 7 per gender for each dosing group (i.e., 6 groups total; negative control with no endrin in feed plus 5 treatment groups). It is not known if a power analysis or statistical calculation was performed to estimate number needed.

RESPONSE: *No response is necessary.*

QUESTION: Did the study account for competing causes of death?

COMMENT: It appears thorough pathological analysis involving multiple organ systems was performed to study toxicity and cause of death.

RESPONSE: *No response is necessary.*

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

COMMENT: The dosing scheme ranged from 0.1 to 4.0 ppm and captured the range of effects from no adverse outcomes to toxicity. Dogs receiving 1 ppm or less exhibited no adverse effects while animals receiving 2 ppm or greater demonstrated signs of toxicity. Food consumption was monitored to calculate dose to animals.

RESPONSE: *No response is necessary.*

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

COMMENT: Despite the limited number of animals used, the study appears to be experimentally sound on many other accounts including: preparation of dosing vehicle and feeding, separation of animals by gender, thorough pathology and biochemical analysis (clinical chemistry) of specimens.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

COMMENT: No comment.

RESPONSE: *No response is necessary.*

Chapter 7

QUESTION: Are you aware of any additional regulations or guidelines that we should add? Please provide citations.

COMMENT: The regulations and guidelines listed appear adequate.

RESPONSE: *No response is necessary.*

QUESTION: Are there any that should be removed? Please explain.

COMMENT: The regulations and guidelines shown are appropriate and not redundant. One classification not noted is teratogenicity, which there may be limited or no data for.

RESPONSE: *No response is necessary.*

Appendix A – Minimal Risk Levels (MRLs)

QUESTION: Do you agree or disagree with the proposed acute-duration oral MRL value? Explain. If you disagree, please specify the MRL value that you propose.

COMMENT: The approach taken by ATSDR is appropriate given the conservative estimate of a 100-fold uncertainty factor (10 for human variability and 10 for extrapolation to humans). The calculations used to determine BMDL/POD (0.06 mg/kg/day) are well-described (p. A-8) and appear appropriate with adequate model fit (Table A-2 and Figure A-1).

RESPONSE: *No response is necessary.*

QUESTION: Do you agree or disagree with ATSDR's selection of the point of departure? Explain. If you disagree, please specify the value that you propose.

COMMENT: As noted above, the calculation for the POD/BMDL appears well-justified given the data (LOAEL of 0.08 mg/kg/day) and adequate model fit (Table A-2 and Figure A-1).

RESPONSE: *No response is necessary.*

QUESTION: Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor(s) that you propose.

COMMENT: I agree with the total uncertainty factor components (10 for human variability and 10 for animal to human extrapolation), which provide a conservative calculation.

RESPONSE: *No response is necessary.*

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

COMMENT: The MRL database assessment appears adequate.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree with ATSDR that the acute oral MRL of 0.0006 mg/kg/day would be sufficiently protective for intermediate exposures? If not, please explain

COMMENT: Given the limited/inadequate data, use of the acute oral MRL as the intermediate oral MRL is the only viable option (pp. A-16 to A-17). The limited data available for calculating intermediate oral MRL yields a value of 0.008 mg/kg/day, which is higher than the acute oral MRL. Therefore, use of the acute oral MRL as the intermediate oral MRL is recommended to provide a point of reference for protection.

RESPONSE: *No response is necessary.*

Appendix B – Literature Search Framework

QUESTION: Does Appendix B provide a sufficiently clear documentation of ATSDR's health effects literature search strategy and inclusion/exclusion criteria?

COMMENT: Appendix B provides adequate documentation of ATSDR's health effects literature search strategy (including databases) and terms used for inclusion/exclusion.

RESPONSE: *No response is necessary.*

QUESTION: Does it provide enough transparency regarding ATSDR's implementation of its inclusion and exclusion criteria (e.g., how ATSDR chose the studies it included in the health effects chapter)?

COMMENT: The described search protocol provides adequate transparency for how ATSDR included and excluded studies for the health effects chapter.

RESPONSE: *No response is necessary.*

Overall Usability of the Profile

QUESTION: Does the new chapter organization make it easier for you to find the information you need? For example, are you satisfied with the organization of the health effects chapter by organ system rather than exposure route?

COMMENT: Yes, the chapter organization makes it easy to find content. I appreciate having the health effects listed per organ system rather than exposure route.

RESPONSE: *No response is necessary.*

QUESTION: Are the new tables and figures clear and useful? Do they make the toxicological profile easier to read?

COMMENT: Yes, the new tables and figures are very clear and comprehensive.

RESPONSE: *No response is necessary.*

QUESTION: If you have previously used any Toxicological Profile(s) for your work, which parts or content are the most useful to you, and what do you use it for?

COMMENT: I have used the Toxicological Profile for work involving aldrin/dieldrin and found particularly helpful, the comprehensive and collected overview of the biological and environmental half-life of the pesticides as well as the primary routes of metabolism and soil degradation. In addition, the Profile contained useful and interesting information on the history and use, including amount and regional, on use of aldrin/dieldrin. Such data can be difficult to locate in the primary literature.

RESPONSE: *No response is necessary.*

QUESTION: Does the profile contain all of the information you need? If no, please elaborate on what additional information would be helpful.

COMMENT: Yes. The Profile contains information I would need should I pursue research (i.e., mechanistic toxicology) on endrin, such as history, use, biological fate/metabolism and mechanisms of toxicity known.

RESPONSE: *No response is necessary.*

QUESTION: Is there information you would like to see in the profile that is not currently included? If yes, please elaborate on the additional information you would like to see in the profile.

COMMENT: Overall, the Profile is comprehensive; however, one suggestion as noted below would be to make sure endrin aldehyde and endrin ketone are adequately explained early on, such as where do these compounds originate from.

RESPONSE: *As discussed above in the response to General Comments for Reviewer 3 (see above for revised text), the second paragraph in Section 1.1 was revised to inform the reader when endrin was last used and to explain that the profile also cover endrin aldehyde and endrin ketone, which are degradation products of endrin.*