

**DISPOSITION OF PEER REVIEW COMMENTS FOR
TOXICOLOGICAL PROFILE FOR
MIREX AND CHLORDECONE**

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 Mirex and Chlordecone were:

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Comments provided by Reviewer #1

Chapter 1. Relevance To Public Health

COMMENT: It would be of interest to the reader a brief paragraph with considerations on the two compounds mirex and chlordane; what are they? What were they used for? Are they still used? Etc.

RESPONSE: *The following was added to Chapter 1: “Mirex and chlordane are structurally similar highly-chlorinated derivatives of cyclopentadiene. The only structural difference between mirex and chlordane is that mirex has two bridgehead chlorine atoms where chlordane has a carbonyl oxygen atom. Mirex was commercially introduced in the United States in 1959 for use in pesticide formulations and as an industrial fire retardant. In the 1960s, mirex was commonly used to control fire ants in southern States. Mirex was banned for use in the United States in 1978, except for use on pineapples until stocks on hand were exhausted. Chlordane was mainly registered for use in the United States to control banana root borer, although it was also used to control other pests. All registered products containing chlordane were effectively canceled in 1978.”*

COMMENT: The fact that two compounds with very similar chemical structures have different toxicological profiles is not unique but is nevertheless of much interest. It would be useful to add two figures with the structures of mirex and chlordane.

RESPONSE: *The addition of chemical structures is beyond the scope of the Chapter 1 overview. The reader can refer to Chapter 4 for images of the chemical structures.*

COMMENT: The two initial Figures (1-1 and 1-2) are of much help in placing in perspective the health effects of mirex and chlordane and the dose levels at which they are observed. The data for each temporal exposure (acute, intermediate and chronic) are indicated together with the target organ of toxicity or adverse health effect. The additional Figures 1-3 and 1-4 and Tables 1-1 and 1-2 are also good, as they clearly indicate the NOAEL values that were considered in all pertinent studies for the final setting of the MRL values.

RESPONSE: *No response is necessary.*

COMMENT: Given that neurological effects are at the basis of the new MRL for chlordane, it would be important to have a sub-section on neurotoxicity in Chapter 1.

RESPONSE: *Chapter 1 already contains a sub-section on neurological effects. The section on neurological effects is divided into separate subsections for mirex and chlordane. Headings were added to differentiate between the 2 substances.*

COMMENT: Overall, it may be useful to add in section 1 specific information on why a certain study was chosen for the determination of MRL, with indication of the relevant end-point. Also, the use of an additional uncertainty factor (other than the standard two factors of 1 for interspecies and intraspecies differences) could be better discussed in Chapter 1.

RESPONSE: *The intent of the MRL section of Chapter 1 is to inform the reader of the presence or absence of a particular MRL, the critical effect, point of departure, and uncertainty and modifying factors. The standard UFs (10 for extrapolation from animals to humans and 10 for human variability) were used. The modifying factor of 3 in one case is defined in a footnote. Other details are reserved for MRL Worksheets in Appendix A.*

Chapter 2. Health Effects

COMMENT: Chapter 2 contains an extensive review of the literature of health effects of mirex and chlordecone including both animal and human data when available. The main changes resulting from such new search were as follows: (A) the chronic duration MRL for mirex was changed, i.e. it was lowered from 0.0008 to 0.0003 mg/kg/day. The same main study was used (NTP, 1990) as well as the same NOAEL (0.075 mg/kg/day), but an additional uncertainty factor of 3 was added to account for developmental toxicity. The overall uncertainty factor thus changed from 100 to 300. (B) A provisional MRL for intermediate-duration oral exposure for chlordecone has been proposed based on a 90-day oral study in male rats (Linder et al. 1983). Starting from a NOAEL of 0.26 mg/kg/day for neurological effects and the use of an uncertainty factor of 100, the resulting MRL is 0.003 mg/kg/day.

RESPONSE: *No response is necessary.*

COMMENT: The two Figures (2-1 and 2-2) are useful in that they show the number of studies identified for each compound and sorted by end-point of toxicity. Hepatic effects and developmental toxicity stand out for mirex, while neurological effects, and to a lesser degree hepatic effects, are the main ones for chlordecone.

RESPONSE: *No response is necessary.*

COMMENT: The Tables and Figures presented in this long section are very useful in that they present in a succinct manner the main effects observed in several studies in humans and animals. This reviewer is not aware of any other study on mirex or chlordecone that was not included in this extensive literature review.

RESPONSE: *No response is necessary.*

COMMENT: The study by Linder et al. (1983) appears to be of relevance as it allows the setting of a new intermediate duration of exposure MRL for chlordecone, based on neurological effects (tremors). Since tremors are the main adverse neurological effects also observed in human, it would be of relevance to expand a discussion of the Linder et al. (1983) study, which is now only very briefly mentioned.

RESPONSE: *Section 2.15 is intended to generally summarize the human and animal data regarding neurotoxicity rather than to provide more detailed study results. Appendix A provides a detailed summary of the results of Linder et al. 1983.*

COMMENT: The main change in the MRL of mirex is based on an additional correction (uncertainty factor of 3) based on developmental toxicity. As such, and to justify the choice, it is important that this

aspect of mirex toxicity is well described and discussed. The section on mirex developmental toxicity on p. 103-104 reads like a list of effects and references with little interpretation of the findings. It would be useful to reconsider this section and indicate the end-points and the levels of exposure that are of concern and that led to the additional uncertainty factor. Even in Appendix A (p. A-10) it is only indicated that “a modifying factor of 3 was applied to protect for developmental toxicity” without further explanations. Also of importance would be a better discussion on why the data on developmental toxicity of chlordane, many of which were obtained in humans, were not considered of relevance for the MRL.

RESPONSE: *The intent of Section 2.17 is to generally summarize the database of information regarding compound-related developmental toxicity in humans and animals. This section is considered to adequately present the available information. A statement was added to the acute-duration oral MRL section for mirex in Appendix A to note that a modifying factor of 3 was applied to derivation of the acute-duration oral MRL for mirex to protect for developmental toxicity because the study that identified the lowest LOAEL for developmental effects reported a serious effect at the lowest dose tested (i.e., a no-adverse-effect-level was not identified, in which case an MRL could not be derived based on results from that study). The modifying factor of 3 is intended to be protective of mirex-induced developmental toxicity. The statement regarding the modifying factor was revised to the following: “A modifying factor of 3 was applied to be protective of mirex-induced developmental toxicity (see Section 2.17), including arrhythmias in neonatal pups following maternal exposure during gestation at a dose level as low as 0.1 mg/kg/day in the absence of an identified NOAEL (Grabowski 1983a).”*

The following was added to the beginning of the section in which the critical effect was identified: “Studies that evaluated chlordane toxicity in humans did not include dose-response data; therefore, human data were not considered for MRL derivation.” As discussed in the MRL Worksheet for the intermediate-duration oral MRL for chlordane, a comparison of the LOAEL values across endpoints supports the identification of the nervous system and male reproductive system as the most sensitive targets of toxicity. Developmental effects in animals occurred at a higher dose level. Thus, an MRL based on developmental effects would be higher than the MRL based on neurological effects.

COMMENT: Tables 2-7 and 2-8 on genotoxicity of mirex and chlordane in vivo and in vitro are good and useful.

RESPONSE: *No response is necessary.*

COMMENT: The section on Mechanisms of Action is well written and very informative. The subsection on developmental toxicity should contain some information on mirex, as this end-point is relevant for this compound.

RESPONSE: *The following statement was added at the beginning of the developmental toxicity portion of Section 2.21: “No information was located regarding possible mechanisms of mirex developmental toxicity.”*

Chapter 7. Regulations and Guidelines

COMMENT: Chapter 7 presents in a Table a list of regulations and guidelines for mirex and chlordane. This reviewer is not aware of additional information that should be added nor of any data presented that could be removed. Of interest to the reader would be to understand how in some cases limit values for inhalation exposure were calculated (e.g. NIOHS, DOE).

RESPONSE: *The reader can refer to the specific references for such information. The references are located in Chapter 8 of the Toxicological Profile for Mirex and Chlordecone.*

Appendix A. Minimal Risk Levels (MRLs)

COMMENT: Appendix A provides detailed considerations on how each MRL value was derived (or why it was not derived). The worksheets are very well prepared and are very informative, as the main study driving the assessment is described in detail. As indicated earlier, the addition of an uncertainty factor of 3 for the chronic MRL of mirex needs to be discussed in more detail (p. A-10).

RESPONSE: *See earlier response regarding this same issue.*

Appendix B. Literature Search Framework for Mirex and Chlordecone

COMMENT: Appendix B presents the strategy utilized by ATSDR to search the literature for information regarding the health effects of mirex and chlordecone. The strategy, which is very well presented, led to the identification of 2288 articles from the different databases. The Appendix then describes the process of selecting the relevant articles for inclusion in this revised toxicological profile.

RESPONSE: *No response is necessary.*

Comments provided by Reviewer #2

ATSDR Charge Questions and Responses

Chapter 1

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

COMMENT: The last sentence (section 1.2 page 2, lines 29 to 31), where it is stated that the “*effects observed in occupationally-exposed workers...//...were related to chlordane levels much higher than environmentally-relevant levels*” does not make much sense because this is obvious. Moreover, section 1.2 does not mention any effects observed at environmental doses (summarized in Tables 2-1 and 2-2 of Chapter 2 and described elsewhere in Chapter 2).

RESPONSE: *Regarding Section 1.2, although the statement appears obvious, it is considered important to make this point.*

COMMENT: It is unclear if the first paragraph of the section “*Body Weight Effects*” (p 8, lines 17 to 23) apply to Mirex or chlordane. See also comment n° 9 below.

RESPONSE: *Subheadings for mirex and chlordane were added to text in Chapters 1 and 2 for clarity. Text was revised to maintain this separation.*

Chapter 2

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

COMMENT: I am not aware of any studies other than those mentioned in this toxicological profile that would be important for deriving MRLs. All available studies have been considered.

RESPONSE: *No response is necessary.*

COMMENT: This toxicological profile contains important bibliographic updates concerning epidemiological studies using internal measures of exposures (blood, milk), which are summarized in Tables 2-1 and 2-2. However, some references are missing and should be considered:

For Mirex:

Araki A, Miyashita C, Mitsui T, Goudarzi H, Mizutani F, Chisaki Y, Itoh S, Sasaki S, Cho K, Moriya K, Shinohara N, Nonomura K, Kishi R. Prenatal organochlorine pesticide exposure and the disruption of steroids and reproductive hormones in cord blood: The Hokkaido study. *Environ Int.* 2018 Jan;110:1-13.

Rosenbaum PF, Weinstock RS, Silverstone AE, Sjödin A, Pavuk M. Metabolic syndrome is associated with exposure to organochlorine pesticides in Anniston, AL, United States. *Environ Int.* 2017 Nov;108:11-21.

Koutros S, Langseth H, Grimsrud TK, Barr DB, Vermeulen R, Portengen L, Wacholder S, Freeman LE, Blair A, Hayes RB, Rothman N, Engel LS. Prediagnostic Serum Organochlorine Concentrations and Metastatic Prostate Cancer: A Nested Case-Control Study in the Norwegian Janus Serum Bank Cohort. *Environ Health Perspect.* 2015 Sep;123(9):867-72.

Guo H, Jin Y, Cheng Y, Leaderer B, Lin S, Holford TR, Qiu J, Zhang Y, Shi K, Zhu Y, Niu J, Bassig BA, Xu S, Zhang B, Li Y, Hu X, Chen Q, Zheng T. Prenatal exposure to organochlorine pesticides and infant birth weight in China. *Chemosphere.* 2014 Sep;110:1-7.

For chlordecone

Saunders L, Kadhel P, Costet N, Rouget F, Monfort C, Thomé JP, Guldner L, Cordier S, Multigner L. Hypertensive disorders of pregnancy and gestational diabetes mellitus among French Caribbean women chronically exposed to chlordecone. *Environ Int.* 2014 Jul;68: 171-6.

RESPONSE: *The identified additional studies were retrieved and relevant information was added to the toxicological profile as follows:*

Araki et al. (2018)

- *Section 1.2 (Developmental Effects): One human study provides suggestive evidence that gestational exposure to mirex may disrupt reproductive hormones in boys (Araki et al. 2018).*
- *Table 2-1: The following entries were made:*

Reference and study population: Prospective birth cohort (Hokkaido Study Sapporo Cohort) of 232 pregnant women (23–35 weeks of gestation) who presented at an obstetrics and gynecology hospital between July 2002 and October 2005, lived in the Sapporo City area, planned to deliver at the facility, and provided maternal serum and cord blood samples for analysis of maternal organochlorine pesticide levels and cord blood levels of selected steroid and reproductive hormones

Exposure: Maternal serum mirex level (LOD 0.5 pg/g wet weight).

*Minimum: 0.88 pg/g
25th percentile: 4.11 pg/g
50th percentile: 6.04 pg/g
75th percentile: 8.53 pg/g
Maximum: 30.11 pg/g*

Categorized by quartile:

*Q1: ≤ 4.12 pg/g
Q2: 4.13–6.04 pg/g
Q3: 6.05–8.52 pg/g
Q4: ≥ 8.53 pg/g*

Linear regression adjustments: maternal age, parity, gestational age

Outcomes: Among boys: maternal serum mirex inversely associated with cord blood testosterone, cortisol, cortisone, prolactin; testosterone-androstenedione (T-A) ratio, androstenedione-dehydroepiandrosterone (A-DHEA) ratio; positively associated with cord blood DHEA, FSH, adrenal androgen-glucocorticoid (AA-G) ratio, FSH-inhibin B ratio

β (95% CI); $p < 0.05$

Testosterone: -0.262 (-0.492, -0.032)

Cortisol: -0.588 (-0.959, -0.218)

Cortisone: -0.572 (-1.002, -0.142)

Prolactin: -0.262 (-0.492, -0.032)

T-A ratio: -0.202 (-0.350, -0.053)

A-DHEA ratio: -0.274 (-0.494, -0.054)

DHEA: 0.213 (0.007, 0.420)

FSH: 0.229 (-0.004, 0.453)

AA-G ratio: 0.744 (0.249, 1.239)

FSH-inhibin B ratio: 0.299 (0.009, 0.589)

Adjusted regression coefficients (β values) based on 10 fold increase of maternal serum mirex and log10 transformed hormone level)

Among boys: least square means of cord blood hormone levels by quartile of maternal serum mirex revealed inverse associations for cord blood testosterone (ptrend 0.039) and for T-A ratio (ptrend 0.016)

Section 2.17 (Developmental) Araki et al. (2018) reported significant ($p < 0.05$) inverse associations between maternal serum mirex and male cord blood testosterone, prolactin, cortisol, cortisone, androstenedione/dehydroepiandrosterone, and testosterone/androstenedione. Significant ($p < 0.05$) significant positive associations were noted for maternal serum mirex and male cord blood dehydroepiandrosterone, follicle stimulating hormone (FSH), adrenal androgen/glucocorticoid, and FSH/inhibin B. In categorical quartiles of maternal serum mirex, significant inverse associations for cord blood testosterone (ptrend 0.039) and for testosterone/androstenedione (ptrend 0.016). These results provide suggestive evidence for mirex-induced effects on reproductive hormones in male fetuses. The study was part of the Hokkaido Study Sapporo Cohort, a prospective birth cohort in Japan. Rosenbaum et al. (2017):

- *Table 2-1: The following entries were made:*

Reference and study population: Cross-sectional study of 548 residents of Anniston, Alabama included in the Anniston Community Health Survey (68% female; mean age 53.6 \pm 16.2 years; 56% white, 44% African American, 59% met criteria for metabolic syndrome)

Exposure: Serum mirex level (LOD not specified)

Categorized by quintile (parts per trillion):

Q1: 1.30–24.24

Q2: 24.25–48.44

Q3: 48.45–74.16

Q4: 74.17–128.96

Q5: 128.97–2,574.40

Logistic regression adjustments: age; educational status, sex; marital status, race; body mass index, family history of heart disease, diabetes; liver disease; alcohol consumption; current smoking status; total lipids

Logistic regression adjustments: age; educational status, sex; marital status, race; body mass index, family history of heart disease, diabetes; liver disease; alcohol consumption; current smoking status; total lipids

Outcomes: No association between serum mirex level and risk of metabolic syndrome

OR (95% CI):

0.59 (0.27, 1.29); Q2 vs Q1

0.77 (0.34, 1.74); Q3 vs Q1

0.64 (0.26, 1.57); Q4 vs Q1

0.58 (0.23–1.45); Q5 vs Q1

- *Section 2.18 (Other Noncancer) Mirex. Rosenbaum et al. (2017) found no association between serum mirex level and occurrence of metabolic syndrome in a cross-sectional study of 548 residents of Anniston, Alabama.*

Koutros et al. (2015)

- *Table 2-1: The following entries were made:*

Reference and study population: Nested case-control study using data from the population-based Janus Serum Bank cohort of Norway. Subjects were 149 cases of metastatic prostate cancer with no history of cancer (except nonmelanoma skin cancer) and were diagnosed at least 2 years after serum collection and 314 controls matched by region, date of blood draw, and age at blood draw

Exposure: Plasma level of mirex (LOD not specified); median levels were 1.8 ng/g lipid (range 0.1–37.1) for cases and 1.7 ng/g lipid (range 0.1–18.3) for controls; categorized by quartile to approximate equal numbers of cases per quartile

Statistical analysis adjustments: county, age at blood draw, date at blood draw

Outcomes: Negative association between lipid-adjusted serum mirex concentration and risk of prostate cancer

OR (95% CI) per unit increase ln-transformed ng/g lipid:

1.01 (0.55, 1.86); Q2 vs Q1

0.94 (0.50, 1.77); Q3 vs Q1

0.1.73 (0.90, 3.31); Q4 vs Q1

ptrend 0.07

- *Section 2.19 (Cancer) In another nested case-control study using data from the Norwegian Janus Serum Bank Cohort, Koutros et al. (2015a, 2015b) found no evidence of a positive association between lipid-adjusted serum mirex concentration and risk of metastatic prostate cancer. This study included 149 cases of metastatic prostate cancer with no history of cancer (except nonmelanoma skin*

cancer) and were diagnosed at least 2 years after serum collection and 314 controls matched by region, date of blood draw, and age at blood draw.

Guo et al. (2014)

- *Table 2-1: The following entries were made:*

Reference and study population: A total of 81 pairs of mothers and newborns enrolled at four hospitals in four different cities in China; the study evaluated possible associations between mirex in maternal serum and birth weight and between mirex in newborn cord serum and birth weight

Exposure: Maternal serum mirex detected in 47/71 samples:

Mean 0.36 ng/g lipid

Median 0.23 ng/g lipid

Minimum <0.4 pg/ml (LOD)

Maximum 66.36 ng/g lipid

Cord serum mirex detected in 13/60 samples:

Mean 0.27 ng/g lipid

Median <LOD

Minimum <LOD

Maximum 23.94 ng/g lipid

Multivariate linear regression adjustments: maternal age, maternal body mass index at delivery, infant gender, gestational week

Outcomes: β (95% CI):

Maternal serum mirex not associated with birth weight:

-32.9 (-138.4, 72.6); $p=0.535a$

Cord serum mirex not associated with birth weight:

-111.6 (-339.3, 116.2); $p=0.330$

- *Section 2.17 (Developmental) No association was found between maternal serum mirex level and birth weight or newborn cord serum mirex and birth weight in a small study of mother/newborn pairs enrolled at hospitals in China (Guo et al. 2014).*

Saunders et al. (2014)

- *Table 2-2: The following entries were made:*

Cardiovascular effects

Reference and study population: Subpopulation of 779 pregnant women in the TIMOUN prospective mother-child cohort study (Guadeloupe, French West Indies) between November 2004 and December 2007

Exposure: Serum chlordecone level (LOD 0.06 $\mu\text{g/L}$)

Q1: <0.17 $\mu\text{g/L}$; referent

Q2: 0.17–0.38 µg/L
Q3: 0.39–0.80 µg/L
Q4: >0.80 µg/L

Multiple logistic regression adjustments: maternal place of birth, place of enrollment, maternal age, pre-pregnancy body mass index, maternal weight gain during pregnancy, total lipids in maternal plasma

Outcomes: Serum chlordecone negatively associated with hypertensive disorders during pregnancy

Quartile	n	OR (95% CI)
Q1	28	1.0 (referent)
Q2	19	0.6 (0.3, 1.1); Q2 vs Q1
Q3	7	0.2 (0.1, 0.5); Q3 vs Q1
Q4	11	0.3 (0.1, 0.6); Q4 vs Q1

Serum chlordecone not associated with preeclampsia

Quartile	n	OR (95% CI)
Q1	7	1.0 (referent)
Q2	8	1.1 (0.3, 2.8); Q2 vs Q1
Q3	9	1.2 (0.4, 3.4); Q3 vs Q1
Q4	7	1.0 (0.4, 1.7); Q4 vs Q1

Diabetes

Reference and study population: Subpopulation of 779 pregnant women in the TIMOUN prospective mother-child cohort study (Guadeloupe, French West Indies) between November 2004 and December 2007

Exposure: Serum chlordecone level (LOD 0.06 µg/L)

Q1: <0.17 µg/L; referent
Q2: 0.17–0.38 µg/L
Q3: 0.39–0.80 µg/L
Q4: >0.80 µg/L

Multiple logistic regression adjustments: maternal place of birth, place of enrollment, maternal age, pre-pregnancy body mass index, maternal weight gain during pregnancy, total lipids in maternal plasma

Outcomes: Serum chlordecone not associated with diabetes mellitus during pregnancy

Quartile	n	OR (95% CI)
Q1	20	1.0 (referent)
Q2	25	1.1 (0.6, 2.2); Q2 vs Q1
Q3	10	0.5 (0.2, 1.1); Q3 vs Q1
Q4	16	0.7 (0.3, 1.5); Q4 vs Q1

- *Section 2.5 (Cardiovascular) Maternal serum chlordecone was not associated with hypertensive disorders or preeclampsia in a subpopulation of pregnant women in the TIMOUN prospective*

mother-child cohort study in Guadeloupe, French West Indies where pesticides (including chlordecone) were extensively used on banana plantations (Saunders et al. 2014).

- *Section 2.18 (Other noncancer) Chlordecone: No association was found between maternal serum chlordecone and risk of diabetes mellitus in a subpopulation of pregnant women participating in the TIMOUN prospective mother-child cohort study in Guadeloupe, French West Indies where pesticides (including chlordecone) were extensively used on banana plantations (Saunders et al. 2014).*

COMMENT: The sentence “no increase in birth defects among offspring conceived after termination of exposure was mentioned (Taylor 1982, 1985)” (2.18, p105, lines 4 – 6) is misleading. This author did not seek to know whether birth defects occurred. To the best of my knowledge, these aspects have never been researched in Hopewell. Therefore, we cannot conclude whether such defects occurred or not.

RESPONSE: *The sentence in question was deleted from Section 2.18.*

COMMENT: Epidemiological studies described in Tables 2-1 and 2-2 should also be included in the comment linking their conclusions to the observed effects in lab animals or humans exposed to high doses, as occurred in Hopewell. I understand that the main purpose of this report is to derive MRLs and that these epidemiological studies are based on internal and not external exposure measures. However, some of these studies, even when carried out in the context of low environmental exposure, highlight effects consistent with those observed in situations of high occupational exposure. For example, the studies by Dallaire et al. (2012) and Boucher et al. (2013) reported that prenatal exposure to chlordecone at environmental dose levels is associated with reduced novelty-preference and fine-motor function scores. These events are consistent with the poor recent memory and intention tremors, respectively, observed for the high-dose exposure levels at Hopewell. Similarly, the studies of Spinelli et al. (2007) for Mirex and Multigner et al. (2010) for chlordecone, showing that these chemicals were positively and significantly associated with a risk of Non-Hodgkin’s lymphoma and prostate cancer, respectively, provide additional support to the carcinogenic potential of these chemicals.

RESPONSE: *Regarding Sections 2.15 and 2.17, it is not considered appropriate to compare neurological effects in humans occupationally exposed to rather high concentrations of chlordecone in the workplace to neurodevelopmental effects associated with rather low environmentally-relevant exposure of mothers during gestation. Section 2.19 of the Toxicological Profile for Mirex and Chlordecone already includes summaries of the results from Spinelli et al. (2007) and Multigner et al. (2010). Furthermore, agencies that evaluate the carcinogenicity of substances have made their determinations for mirex and chlordecone based on animal data. For more information on how various agencies evaluate the carcinogenicity of substances, the agencies can be contacted directly.*

COMMENT: The toxicological profile details the circumstances and events that occurred in Hopewell (for chlordecone) and correctly stresses that Mirex and chlordecone are no longer produced or used today. Nevertheless, populations are still exposed because of the persistence of these chemicals in the environment (and not only in waste sites). This aspect merits further commentary that should clarify that *i*) Mirex is a universally widespread pollutant in the environment, as shown by epidemiological studies conducted in the US, Canada, South Korea, Spain, etc. and *ii*) chlordecone is present in some areas of the World. Agricultural soil in French West Indies is still polluted due to chlordecone use between 1973 and 1993, leading to the contamination of foodstuffs, which in turn, affects populations.

RESPONSE: Chapter 1 (Section 1.1) includes a statement that the most likely route of exposure of the general population to mirex or chlordane is via ingestion of contaminated food. The following addition was made to the statement: "because these chemicals persist in soil for decades following cessation of application as pesticides." Additional discussion is not considered necessary for exposure of the general population within the United States based on very low levels measured in blood samples collected from the general population.

COMMENT: At the beginning of Chapter 2 (p13, lines 13 to 18), it is mentioned that Mirex and chlordane "produce similar toxicities", whereas in the following sentence it is stated that their toxicological profiles "differ significantly", which is somewhat contradictory. Indeed, there are many more differences than similarities between these two chemicals, despite structural similarity.

RESPONSE: The statement in question in Section 2.1 was revised to state: "As suggested by this similarity in structure, these two chemicals share some similarities in their toxicity profiles. However, the toxicity profiles of these two chemicals differ in a number of aspects. Therefore, each chemical will be discussed separately below."

COMMENT: The report attempts in each section or sub-section to distinguish between results concerning Mirex and those concerning chlordane and to distinguish between animal data human data. However, the result is sometimes confusing. There are many paragraphs in which we do not know whether they concern Mirex or chlordane until we have read several lines. Some sentences do not specify which substance they are discussing (e.g. 2.10, p91, line 25-29). Some sections (e.g. 2.10 p91) start with Mirex, then continue with chlordane (p92, lines 5-31), and conclude with Mirex (p92, lines 33-34) or vice-versa. Some sections start with animal data and others human data. For example, section 2.4 begins with human data on chlordane (p 81, lines 23-27), continues with a sentence on animal data for Mirex (line 29), and then continues on animal data for chlordane (lines 29-33). For others (e.g. 2.21, Hepatotoxicity, p 115, lines 22 and following) it is difficult to distinguish sentences that concern Mirex from those that concern chlordane.

For greater clarity, I suggest:

- introducing an intertitle for Mirex and another for chlordane within sections 2.2 to 2.21 and always in the same order,
- clearly separating animal data from human data below each intertitle, and always in the same order, and making it clear if there are no animal or human data,
- avoiding the sentences "Like Mirex, chlordane causes ...", "Both Mirex and Chlordane ..."

RESPONSE: Subheadings for mirex and chlordane were added to text in Chapters 1 and 2 for clarity. Text was revised to maintain this separation.

COMMENT: The sentence "A major limitation of these studies is the lack of chlordane exposure data" (2.17, p 104, lines 33-34) is incorrect. Indeed, these studies included exposure data based on internal (blood or milk) measures. The limitation is that it is not possible to infer external exposure measures (by specific exposure routes, as employed to determine MRLs) from internal exposure measures.

RESPONSE: The sentence in question in Section 2.17 was revised to the following: "A major limitation of these studies is the lack of data regarding chlordane exposure levels."

QUESTION: Second, we would like you to focus on the current data assessment which resulted in the revision of the previously derived mirex MRL in the 1995 toxicological profile; and the addition of a new chlordecone MRL.

MRLs: The chronic-duration oral MRL for Mirex and the intermediate-duration oral MRL for chlordecone were revised from 1995 toxicological profile only.

Mirex – Chronic-Duration Oral MRL: A revised chronic-duration oral MRL for mirex is included in this profile.

The previous MRL was 0.0008 mg/kg/day and was derived based on dose-related hepatic changes from a 2-year oral study of male and female F344/N rats (NTP 1990). The NOAEL of 0.075 mg/kg/day had been divided by a total uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

The new MRL is 0.0003 mg/kg/day using the same study and adding an additional uncertainty factor of 3. Now the total uncertainty factor is 300 based on $10 \times 10 \times 3 = 300$. The new MRL thus becomes $0.075/300 = 0.0003$ mg/kg/day.

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

COMMENT: I agree with the current data assessment and do not have specific comments

RESPONSE: *No response is necessary.*

QUESTION: Chlordecone – Intermediate-Duration Oral MRL (Revised from 1995 toxicological profile):

A provisional MRL of 0.003 mg/kg/day has been derived for intermediate-duration oral exposure to chlordecone based on neurological effects from a 90-day oral study of male Sprague-Dawley rats (Linder et al. 1983). The NOAEL of 0.26 mg/kg/day was divided by a total uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to derive intermediate-duration MRL of 0.003 mg/kg/day.

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

COMMENT: I do not understand the reason why it is not considered an additional uncertainty factor of 3 (to protect for developmental toxicity) as is the case for the new Mirex chronic-duration oral MRL. Although this study (Linder et al. 1993) was conducted among male animals, there is no objective reason for such effects do not affect females, which in turn may become pregnant.

RESPONSE: *A modifying factor was not applied to derivation of a provisional intermediate-duration oral MRL for chlordecone because available developmental toxicity results identified NOAELs at doses higher than the LOAEL of 0.83 mg/kg/day for neurological and reproductive effects observed in the principal study.*

Chapter 7

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

COMMENT: I have no knowledge of new regulations and guidelines and I have no reason to remove any of them.

RESPONSE: *No response is necessary.*

Appendix A – Minimal Risk Levels (MRLs)

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

COMMENT: See my comment n°12

RESPONSE: *A modifying factor was not applied to derivation of a provisional intermediate-duration oral MRL for chlordane because available developmental toxicity results identified NOAELs at doses higher than the LOAEL of 0.83 mg/kg/day for neurological and reproductive effects observed in the principal study.*

Appendix B – Literature Search Framework

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

COMMENT: I agree with the process and I do not have any specific comments.

RESPONSE: *No response is necessary.*

Comments provided by Reviewer #3

ATSDR Charge Questions and Responses and General Comments

Chapter 1

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

COMMENT: I found that Chapter 1 did a good job of summarizing the known health effects of mirex and chlordecone by various routes of exposures. The description of the method of searching the literature for this data in Appendix B was quite impressive and provides confidence in the scope of the literature search.

RESPONSE: *No response is necessary.*

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

Second, we would like you to focus on the current data assessment which resulted in the revision of the previously derived mirex MRL in the 1995 toxicological profile; and the addition of a new chlordecone MRL.

MRLs: The chronic-duration oral MRL for Mirex and the intermediate-duration oral MRL for chlordecone were revised from 1995 toxicological profile only.

Mirex – Chronic-Duration Oral MRL: A revised chronic-duration oral MRL for mirex is included in this profile.

The previous MRL was 0.0008 mg/kg/day and was derived based on dose-related hepatic changes from a 2-year oral study of male and female F344/N rats (NTP 1990). The NOAEL of 0.075 mg/kg/day had been divided by a total uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

The new MRL is 0.0003 mg/kg/day using the same study and adding an additional uncertainty factor of 3. Now the total uncertainty factor is 300 based on $10 \times 10 \times 3 = 300$. The new MRL thus becomes $0.075/300 = 0.0003$ mg/kg/day.

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

COMMENT: I thought the MRL worksheets were well done and provided the reasoning behind each value. My only suggestion would be that the MRL for the revised chronic-duration oral MRL for Mirex by the addition of the uncertainty factor of 3 should provide a little more justification for the need to add the factor to take into account developmental effects. This may be done by referring to other parts of the document.

RESPONSE: *In the portion of the MRL Worksheet in Appendix A for the intermediate-duration oral MRL for mirex that describes the modifying factor, a statement was added to refer the reader to Section 2.17 (Developmental Effects).*

QUESTION: Chlordecone – Intermediate-Duration Oral MRL (Revised from 1995 toxicological profile):

A provisional MRL of 0.003 mg/kg/day has been derived for intermediate-duration oral exposure to chlordecone based on neurological effects from a 90-day oral study of male Sprague-Dawley rats (Linder et al. 1983). The NOAEL of 0.26 mg/kg/day was divided by a total uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to derive intermediate-duration MRL of 0.003 mg/kg/day.

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

COMMENT: I think this revision is consistent with the other values based on animal studies.

RESPONSE: *No response is necessary.*

Chapter 7

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

COMMENT: I know of no other regulations or guidelines that would be appropriate.

RESPONSE: *No response is necessary.*

Appendix A – Minimal Risk Levels (MRLs)

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

COMMENT: As I said above, I found the MRL worksheets to be very useful. I only think the addition of a uncertainty factor of 3 for the chronic-duration oral MRL for Mirex requires more justification for the health endpoint chosen.

RESPONSE: *In the portion of the MRL Worksheet in Appendix A for the intermediate-duration oral MRL for mirex that describes the modifying factor, a statement was added to refer the reader to Section 2.17 (Developmental Effects).*

Appendix B – Literature Search Framework

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

COMMENT: I was very well impressed with the description of the method of the literature search used to find the health effects data. Congratulations. Good job!

RESPONSE: *No response is necessary.*