ADDENDUM TO THE TOXICOLOGICAL PROFILE FOR MIREX AND CHLORDECONE

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences (proposed)
Atlanta, GA 30333

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ADDENDUM for MIREX AND CHLORDECONE
Supplement to the 1995 Toxicological Profile for Mirex and Chlordecone

Background Statement

This addendum for the Toxicological Profile for Mirex and Chlordecone supplements the toxicological profile that was released in 1995.

Toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). CERCLA mandates that the Administrator of ATSDR prepare toxicological profiles on substances on the CERCLA Priority List of Hazardous Substances and that the profiles be revised "no less often than once every three years". CERCLA further states that the Administrator will "establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" [Title 42, Chapter 103, Subchapter I, § 9604 (i) (1) (B)].

The purpose of this addendum is to provide, to the public and federal, state, and local agencies a non-peer reviewed supplement of the scientific data that were published in the open peer-reviewed literature from 1995 through 2011since the release of the profile in 1995.

Chapter numbers in this addendum coincide with the toxicological profile for Mirex and Chlordecone (1995). This document should be used in conjunction with the profile. It does not replace it.

2. HEALTH EFFECTS

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

2.2.2 Oral Exposure

2.2.2.2 Systemic Effects

Hepatic Effects. An increase >2-fold in mean absolute liver weight was reported in adult male CD-1 mice (n=3) receiving mirex by daily gavage at 5 mg/kg/day for 21 days; the mean body weight of mirex-treated mice was not significantly different from controls (Dai et al. 2001).

Endocrine Effects. A statistically significant negative association (OR=0.3) was found between exposure to highest tertile of serum mirex levels and diabetes in a cross-sectional study of 352 Native American subjects (Codru et al. 2007). The study subjects were grouped into tertiles according to serum mirex levels, and comparisons were made between the lowest tertile and each of the higher tertiles. The prevalence of diabetes was 20.2%.

In a separate study, a significant association was reported between wet-weight or lipid-adjusted mirex levels and the prevalence of type 2 diabetes (Son et al. 2010). The 95% confidence interval (Cl) and the p-value for wet-weight mirex level in the highest tertile were 6.5 (1.1-40.1) and 0.04, respectively. However, mirex was not associated with total (diagnose and undiagnosed) diabetes or prediabetes (Everett and Matheson 2010).

2.2.2.5 Reproductive Effects

Gavage administration of mirex to adult male CD-1 mice at 5 mg/kg/day for 21 days resulted in approximately 27% decreased mean absolute seminal vesicle weight; the mean body weight of mirex-treated mice was not significantly different from controls (Dai et al. 2001).

2.2.2.6 Developmental Effects

No association was observed between blood mirex levels and menarcheal status within a group of 138 Native American girls 10–16.9 years of age (Denham et al. 2005). Blood mirex levels ranged between 0.02—1.17 ppm, with >50% of the samples below the detection limit of 0.02 ppm.

A cohort of 104 mother-son pairs was studied for effects of endocrine disrupting chemicals on the developing brain functions. The mirex median level in the placenta samples (27 placenta) was 1.4 (range: 0.5-19.1) ng/g placenta. This exposure level was statistically significant (p=0.01) and inversely associated with cognitive development at 4 years of age and caused a reduction of 5.15 points in working memory and 7.33 points in the quantitative area compared to unexposed children of the same age and gender (Puertas et al. 2010).

2.2.2.8 Cancer Effects

Possible associations between blood polychlorinated biphenyl (PCB) and organochlorine (including mirex) levels and risk of non-Hodgkin lymphoma (NHL) were assessed in a population-based case-control study of 422 pretreatment NHL cases and 460 matched controls in British Columbia, Canada (Spinelli et al. 2007). A detection limit of 1.43 ng/g was determined for mirex in blood. Subjects with measurable mirex levels (>1.43–60.46 ng/g; 174 cases and 154 controls) exhibited a significantly increased risk of NHL (OR=1.44; 95% CI, 1.08–1.92) compared to those with levels at or below the detection limit (248 cases and 308 controls).

No significant association was found between blood mirex levels and risk of postmenopausal breast cancer (OR=1.37; 95% CI, 0.78–2.39) in a case-control study of 154 postmenopausal breast cancer cases and 192 community controls in two counties of northwestern New York state (Moysich et al. 1998). Comparisons were made between women with detectable mirex levels (0.06–0.99 ng/g, 42 cases and 44 controls) and those with levels below the limit of detection (0.06 ng/g, 112 cases and 148 controls).

2.3 TOXICOKINETICS

2.3.4 Excretion

2.3.4.2 Oral Exposure

Human milk samples (497) from donors across Canada were analyzed for industrial chemicals and 24 selected organochlorine pesticides in a national survey conducted in 1986 and 1992 (Newsome et al. 1999). Mirex was detected in 58% of the samples at a mean concentration of 0.06 ng/g whole milk and 1.89 ng/g of milk fat. Analysis of human milk from 12 residents of Keewatin, an arctic region of northern Canada, resulted in a mean mirex concentration of 2.30 ng/g fat (Newsome and Ryan 1999).

2.3.5 Mechanisms of Action

Chlordecone also caused the translocation of estrogen receptors from the cytosolic to the nuclear fraction in both isolated rat uteri and ovariectomized immature rats. These results indicate that chlordecone may act directly on the uterus. Johnson (1996) found that chlordecone-induced uterine effects observed in ovariectomized immature rats were enhanced by coadministration of estradiol. These results suggest that both the estrogen and xenoestrogen are influencing uterine hypertrophy and hyperplasia by a single mechanism. Chlordecone demonstrated fairly high affinity for recombinant human estrogen receptors (Bolger et al. 1998; Scippo et al. 2004). Chlordecone exhibited approximately equal affinity for both subtypes of human estrogen receptors (ERα and ERβ) (Kuiper et al. 1998). In a study by Johnson et al. (1995), uterine levels of adenosine 3'5'-cyclic monophosphate (cAMP) decreased with increasing uterine weight following repeated exposure to chlordecone in ovariectomized immature rats. Levels of cAMP were not decreased in similarly-treated rats that were also given the antiestrogen (ICI-182,780), indicating that the chlordecone-induced effect on cAMP is estrogen receptor-dependent.
Also, chlordecone has been shown to increase the growth of rat cell leiomyoma, but not to the extent of estradiol (Hodges et al. 2000).

Results of a recent study by Das et al. (1997) indicate that chlordecone-induced uterine effects may also be induced via a pathway other than that which includes the estrogen receptor. Chlordecone up-regulate uterine expression of an estrogen-responsive gene, lactoferrin, in ERα knockout mice, whereas these effects were not elicited by 17β-estradiol. Neither the estrogen receptor antagonist ICI-182,780 nor 17β-estradiol inhibited the chlordecone-induced uterine expression of lactoferrin in these mice.

The ovarian hormone 17-β estradiol (E2) may be involved in mirex skin tumor promotion in mice. Porter et al. (2002) assessed the role of E2 in mirex skin tumor promotion by applying topical mirex to ovariectomized mice that had subcutaneous implants either with or without E2. E2-implanted ovariectomized mice exhibited normal physiological levels of serum E2 throughout the treatment period. The E2 implants restored approximately 80% of the mirex tumor promoting response of intact mice. E2 implants in male mice increased sensitivity to mirex tumor promotion as well, but not to the level of response seen in intact female mice.

Kim and coworkers (Kim and Smart 1995; Kim et al. 1997) reported that mirex promoted the development of papillomas involving a Ha-*ras* mutation in 7,12-dimethylbenz[a]anthracene (DMBA)-initiated mice.

Chlordecone has been evaluated for its potential to bind to receptors other than the estrogen receptor and was found to have relatively high affinity for recombinant human progesterone receptors (Scippo et al. 2004). In ovariectomized (NBZ × NZW) F1 mice, both estradiol (an estrogen) and chlordecone were shown to accelerate development of the autoimmune disorder, systemic lupus erythematosus (Wang et al. 2007a). However, it was found that chlordecone was not simply mimicking estrogen, based on contrasting effects on splenic B-cells populations. In a follow-up a study, also in ovariectomized (NBZ x NZW) F1 mice, (Wang et al. (2007b) compared the effects of chlordecone and estradiol treatment on serum levels of the autoimmune-accelerating hormone, prolactin. In chlordecone -treated mice, they found a dose-dependent decrease in prolactin levels (compared to controls). However, in estradiol-treated mice, prolactin levels were 10-20 folds higher than controls. In a related study, chlordecone exhibited characteristics of a partial androgen antagonist, based on reduced inhibition of 5α-dihydroxytestosterone-mediated activation of luciferase activity by 6.9 μM chlordecone in the human PC-3 prostate carcinoma cell line (Schrader and Cooke 2000).

Dai et al. (2001) hypothesized that modulation of testosterone metabolism via induction of specific CYP isoforms may be a contributing factor in mirex-induced antiandrogenic effects. Evidence includes significantly increased (3.1-fold greater than controls) total CYP contents in homogenated livers of adult male CD-1 mice administered mirex by gavage at 5 mg/kg/day for 21 days (Dai et al. 2001). Western blot analysis indicated that CYP2E1 and CYP3A were the isoforms induced to the greatest extent. Incubation of testosterone with microsomes from the treated mice resulted in an approximately 2.5-fold increase in testosterone hydrolase activity.

Starcevic et al. (2001) designed an experiment to test whether chlordecone disrupts adherens junctions in human breast epithelial cells cultured on Matrigel. When exposed to chlordecone, MCF-10ATG3B human breast epithelial cells exhibited significantly decreased E-cadherin and beta-catenin protein levels; desmoglein and α- and γ-catenin levels did not vary significantly from control levels. Chlordecone also caused disruption in E-cadherin- γ–catenin association. These results indicate that chlordecone disrupts cellular architecture, which may ultimately play a role in development of neoplastic lesions.

Chlordecone in combination with other xenobiotic chemicals such as carbon tetrachloride and ether reduced the threshold values of toxicity by several folds for those chemicals and decreased the aromatase activity by 50% in some cases. Prolonged exposures to low doses of xenobiotics amplified aromatase inhibition by 50 times. Because chlordecone is known to bioaccumulate, chronic, low level exposures may result in body burden levels that could also affect cell signaling mechanisms (Benachour et al. 2007)

2.4 RELEVANCE TO PUBLIC HEALTH

Other Routes of Exposure

Hepatic Effects. Carpenter et al. (1996) examined ultrastructural, protein, and lipid profiles in the livers of chlordecone-exposed mice. Male C57BL/6N mice were administered chlordecone intraperitoneally, followed 3 days later by intraperitoneal injection of radiolabeled chlordecone. Livers and kidneys were subsequently removed for assessment of radioactivity. Livers were examined for histological and ultrastructural changes and total lipid content and fatty acid profiles in livers and kidneys were determined. Pretreatment with unlabeled chlordecone resulted in dose-dependent decreased accumulation of radiolabeled chlordecone in the liver; renal accumulation was not affected. Chlordecone induced marked hepatic mitochondrial swelling, decreased the number of cytoplasmic lipid droplets in hepatocytes, induced proliferation and vesiculation of smooth endoplasmic reticulum, and increased the number of intracellular peroxisome-like structures. Chlordecone did not alter the total lipid content of the liver or kidney. The changes in the liver suggest that chlordecone caused alterations in hepatocellular transport, storage, and metabolism pathways via increased hepatocyte secretory activity.

Developmental Effects. Laessig et al. (2007) assessed the effects of prenatal chlordecone exposure of Sprague-Dawley rats on sexually differentiated behavior in their offspring. Chlordecone (5 mg/kg) was administered in a single intraperitoneal dose to pregnant Sprague-Dawley rats on gestation day 16. Their offspring were gonadectomized on postnatal day (PND) 52-53 to eliminate effects of circulating hormones and then sequentially tested for sex-typic spontaneous behaviors in open field (PND 60) and elevated plus maze (PND 61–63) tests. Gonadectomized male and female offspring were also assessed for reproductive behavior following sex-specific steroid treatment. On PND 68 or 69, male and female offspring were treated with a chemical paradigm that induces lordosis (a female sexual behavior). On PND 70, male offspring received a testosterone implant; these males were assessed 6 weeks later for mounting behavior with a sexually-responsive female. On PND 120, blood was collected from male and female offspring for assessment of serum testosterone levels. There were no apparent chlordecone treatment-related effects on time to parturition, litter size, sex ratio, or growth indices of offspring

compared to controls. Chlordecone-exposed (*in utero*) gonadectomized female offspring exhibited significantly increased ratio of inner to total crossings in the open field; significant increases in lordosis response with steroid priming and mounting with prolonged testosterone administration were observed in both male and female offspring. These results suggest that chlordecone may interfere with estrogen-dependent events during sexual differentiation of the brain that impact later activation of hormone-dependent behavior.

Genotoxic Effects. Chlordecone (≥300 μM) induced significantly increased frequencies of ssDNA (single-stranded DNA) breaks in testicular cells from human organ transplant donors and from Wistar rats (Bjorge et al. 1996). Miyagawa et al. (1995) reported 4- to 9.5-fold increases in replicative DNA synthesis within hepatocytes of 8-week-old male B6C3F1 mice at 24–39 hours following gavage administration of mirex at 60 mg/kg

2.6 INTERACTIONS WITH OTHER CHEMICALS

Several studies (Dalu and Mehendale 1996; Dalu et al. 1995, 1998; Murali et al. 2004) provide additional insight to earlier findings of age-related differences in the lethality and hepatotoxicity induced by exposure of rats to nontoxic levels of chlordecone and subsequent exposure to otherwise nonlethal levels of carbon tetrachloride Results of Blain et al. (1999) indicate both sex- and age-dependent influences on chlordecone-carbon tetrachloride induced hepatotoxicity in rats.

Fernandez et al. (2007) assessed the association between placental concentrations of organohalogenated compounds (that included mirex) and the incidence(s) of male urogenital malformations in a case control study of 702 mother-newborn pairs. Children with cryptorchidism and/or hypospadias born during the study period were compared to 114 male children without malformations (matched by gestational age, date of birth, and parity). Placenta samples were analyzed for organohalogenated compounds (DDT, lindane, mirex, and endosulfan alpha). The authors found an increased risk for male urogenital malformations related to the concentration of the organohalogenated mixture in the placentas. However, the mean concentration of mirex in placentas from the control group was 3.7± 3.37 ng/g of lipid, compared to only 1.4± 1.1 ng/g of lipid in placentas from the group with urogenital malformations, a finding which underscores the fact that this association could not be attributed to mirex *per se*, but only to a combination of mirex and other mirex-like compounds.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

In studies performed by Sobel and coworkers (Sobel et al. 2005, 2006; Wang et al. 2008), chronic exposure of systemic lupus erythematosus-prone female (NZB x NZW) F_1 mice to chlordecone via subcutaneously-implanted pellets significantly shortened the time to onset of elevated autoantibody titers and renal disease in a dose-related manner. These effects were not seen in nonlupus-prone BALB/c mice. These results indicate that humans with lupus may be particularly sensitive to chlordecone toxicity.

3. CHEMICAL AND PHYSICAL INFORMATION

No update data.

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

No update data.

5. POTENTIAL FOR HUMAN EXPOSURE

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

In the Fourth National Report on Human Exposures to Environmental Chemicals (CDC 2009), mirex levels in serum (lipid adjusted) were reported according to various age groups, gender, and race/ethnicity. The results are presented in Table 5-1.

Table 5-1 Geometric Means and Selected Percentiles of Serum Concentrations (lipid adjusted) of Mirex for the U.S. Population Aged 12 and Older

	Survey years	mean (95% conf. interval)	50th	75th	90th	95th	Sample size
			(95% confidence interval)				
Total	99-00	*	< LOD	< LOD	< LOD	< LOD	1853
	01-02	*	< LOD	< LOD	**15.8** (<LOD-73.7)	**57.1** (13.2-230)	2257
	03-04	*	< LOD	< LOD	**8.40** (<LOD-13.0)	**13.2** (7.90-29.6)	1951
Age group							
12-19 years	99-00	*	< LOD	< LOD	< LOD	< LOD	659
	01-02	*	< LOD	< LOD	< LOD	< LOD	728
	03-04	*	< LOD	< LOD	< LOD	< LOD	592
20 years and older	99-00	*	< LOD	< LOD	< LOD	< LOD	1194
	01-02	*	< LOD	< LOD	**19.6** (<LOD-108)	**71.0** (14.6-305)	1529
	03-04	*	< LOD	< LOD	**9.10** (<LOD-15.6)	**15.4** (8.10-37.1)	1359
Gender							
Males	99-00	*	< LOD	< LOD	< LOD	< LOD	887
	01-02	*	< LOD	< LOD	**16.1** (<LOD-65.6)	**50.8** (12.3-225)	1052
	03-04	*	< LOD	< LOD	**9.70** (<LOD-15.4)	**15.5** (9.70-24.4)	949
Females	99-00	*	< LOD	< LOD	< LOD	< LOD	966
	01-02	*	< LOD	< LOD	**15.0** (<LOD-108)	**63.0** (12.0-374)	1205
	03-04	*	< LOD	< LOD	< LOD	**11.6** (<LOD-31.3)	1002
Race/ethnicity							
Mexican Americans	99-00	*	< LOD	< LOD	< LOD	< LOD	617
	01-02	*	< LOD	< LOD	< LOD	< LOD	548
	03-04	*	< LOD	< LOD	< LOD	< LOD	459
Non-Hispanic blacks	99-00	*	< LOD	< LOD	**15.5** (<LOD-42.2)	**39.5** (<LOD-115)	398
	01-02	*	< LOD	**13.7** (<LOD-47.3)	**51.3** (15.4-230)	**153** (30.5-425)	500
	03-04	*	< LOD	< LOD	**18.1** (8.70-40.8)	**40.3** (15.5-82.7)	484
Non-Hispanic whites	99-00	*	< LOD	< LOD	< LOD	< LOD	688
	01-02	*	< LOD	< LOD	**15.1** (<LOD-104)	**66.7** (12.5-291)	1049
	03-04	*	< LOD	< LOD	< LOD	**11.6** (<LOD-23.4)	884

Limit of detection (LOD, see Data Analysis section) for Survey years 99-00, 01-02, and 03-04 are 14.6, 10.5, and 7.8, respectively.
< LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample.
* Not calculated: proportion of results below limit of detection was too high to provide a valid result.

Source: http://www.cdc.gov/exposurereport/pdf/FourthReport.pdf

6. ANALYTICAL METHODS

No update data.

7. REGULATIONS AND ADVISORIES

Table 7-1 Regulations and Guidelines Applicable to Mirex

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	Group 2B[a]	IARC 2009
WHO	Air quality guidelines	No	WHO 2000
	Drinking water quality guidelines	Excluded from guideline value derivation[b]	WHO 2006
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	No	ACGIH 2008
NIOSH	REL (10-hour TWA)	No	NIOSH 2005
	IDLH	No	
OSHA	PEL (8-hour TWA) for general industry	No	OSHA 2009 29 CFR 1910.1000, Table Z-1
b. Water			
EPA	Drinking water standards and health advisories	No	EPA 2006
	National primary drinking water standards	No	EPA 2009
c. Other			
ACGIH	Carcinogenicity classification	No	ACGIH 2008
	Biological exposure indices	No	
EPA	Carcinogenicity classification	No	IRIS 2009
	RfC	No	
	RfD	2.0×10^{-4} mg/kg/day	
NTP	Carcinogenicity classification	Reasonably anticipated to be a human carcinogen[c]	NTP 2011b

[a]Group 2B: possibly carcinogenic to humans.
[b]Unlikely to occur in drinking water.
[c]Based on sufficient evidence of carcinogenicity in experimental animals.

ACGIH = American Conference of Governmental Industrial Hygienists; CFR = Code of Federal Regulations; DWEL = drinking water equivalent level; EPA = Environmental Protection Agency; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization

Table 7-2 Regulations and Guidelines Applicable to Chlordecone

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	Group 2B[a]	IARC 2009
WHO	Air quality guidelines	No	WHO 2000
	Drinking water quality guidelines	No	WHO 2006
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	No	ACGIH 2008
NIOSH	REL (10-hour TWA)	0.001 mg/m^3	NIOSH 2005
	IDLH	No	
	Potential occupational carcinogen	Yes	
	Target organs	Eyes, skin, respiratory system, central nervous system, liver, kidneys, reproductive system	
OSHA	PEL (8-hour TWA) for general industry	No	OSHA 2009 29 CFR 1910.1000, Table Z-1
b. Water			
EPA	Drinking water standards and health advisories	No	EPA 2006
	National primary drinking water standards	No	EPA 2009
c. Other			
ACGIH	Carcinogenicity classification	No	ACGIH 2008
	Biological exposure indices	No	
EPA	Carcinogenicity classification	No	IRIS 2009
	RfC	No	
	RfD	No	

Table 7-2 Regulations and Guidelines Applicable to Chlordecone

Agency	Description	Information	Reference
NATIONAL*(cont.)*			
NTP	Carcinogenicity classification	Reasonably anticipated to be a human carcinogen[b]	NTP 2011a

[a]Group 2B: possibly carcinogenic to humans.
[b]Based on sufficient evidence of carcinogenicity in experimental animals.

ACGIH = American Conference of Governmental Industrial Hygienists; CFR = Code of Federal Regulations; DWEL = drinking water equivalent level; EPA = Environmental Protection Agency; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization

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