MIREX
CASRN 2385-85-5
EXTERNAL REVIEW DRAFT IRIS SUMMARY

Substance code 0251
Substance name: Mirex; CASRN 2385-85-5

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices, Regional Offices, and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR MIREX

File First On-Line 09/30/1987

Category (section)	Status	Last Reviewed
Oral RfD Assessment (I.A.)	on-line	00/00/0000
Inhalation RfC Assessment (I.B.)	no data	00/00/0000
Carcinogenicity Assessment (II.)	on-line	00/00/0000

_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name - Mirex
CASRN 2385-85-5
Last Revised -- 00/00/0000

The oral Reference Dose (RfD) is based on the assumption that thresholds generally exist for non-cancer effects. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of

substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

This RfD replaces a previous RfD value of 0.0002 mg/kg-day entered on October 1, 1992. The previous and new RfD values are based on data generated from the same study (NTP, 1990). The previous assessment was based on a NOAEL of 1 ppm (0.07 mg/kg-day) and a LOAEL of 10 ppm (0.7 mg/kg-day) for liver cytomegaly, fatty metamorphosis, angiectasis, and thyroid cystic follicles in F344/N rats as reported in the original NTP (1990) report and an uncertainty factor of 300 (3 for intraspecies variability, 10 for interspecies extrapolation, and 3 for lack of a complete data base, specifically lack of multi-generational data on reproductive effects and cardiovascular toxicity data).

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Liver lesions in F344/N rats (cytomegaly, fatty metamorphosis, necrosis) (NTP, 1990; PWG, 1992)	LED10: 0.15 mg/kg/day ED10: 0.20 mg/kg/day	300	1	0.0005 mg/kg/day

*The array of discontinuous mathematical models in the EPA Benchmark Dose Software were fit to male and female rat incidence data for toxic hepatitis (cytomegaly, fatty metamorphosis, and/or necrosis) (see Table 1 in section I.A.2.). The log-logistic model gave the best fit. The average of ED10 values for males (0.28 mg/kg/day) and females (0.13 mg/kg/day) is listed above, as is the average of LED10 (95% lower confidence limit on the ED10) values for males (0.20 mg/kg/day) and females (0.10 mg/kg/day).

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

NTP (National Toxicology Program). 1990. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Mirex (CAS No. 2385-85-5) in F344/N Rats (Feed Studies). NTP TR 313, NIH Publ. No. 90-2569.

PWG (Pathology Working Group). 1992. Pathology Working Group Report on Mirex Chronic Toxicity/Carcinogenicity Study in F344 Rats. Prepared by R.M. Sauer, PATHCO, Inc.

The NTP (1990) rat bioassay (with liver histopathology re-evaluated by the PWG [1992]) is selected as the principal study for RfD derivation because it provides the best available characterization of dose-response relationships for one of the sensitive targets of repeated oral exposure to mirex identified in animal studies. Evaluation of the available animal data indicate that an RfD based on liver effects in rats will be protective for other potential noncancer effects

from chronic exposure to mirex, including developmental and reproductive effects (see section I.A.4.).

The liver histopathological slides prepared during the original NTP (1990) study were re-evaluated by a group of pathologists convened by Pathco, Inc. (PWG, 1992) using more current criteria and terminology than those used in the original pathology report. Neoplastic nodules (a term used in the original pathology report) were reclassified as hepatocellular adenomas, eosinophillic foci of cellular alteration, or regenerative hyperplasia. The term toxic hepatitis was used to describe non-neoplastic liver lesions based on the occurrence of centrilobular hepatocytomegaly, centrilobular fatty change, apoptosis (individual cell necrosis), centrilobular necrosis, and bile duct proliferation. A U.S. EPA-sponsored review by Garman (U.S. EPA 1999b) of the PWG (1992) report concluded that the re-evaluation was appropriate and that the re-evaluated incidence data for rat liver tumors were valid for risk assessment. The Office of Emergency and Remedial Response recommended that the PWG incidence data be used for risk assessment at Superfund sites (U.S. EPA, 1999a).

NTP (1990) fed groups of 52 male and 52 female F344/N rats (initial body weight 120 and 100 g, respectively) 0, 0.1, 1, 10, 25, or 50 ppm mirex (reported purity >96%) in the diet for 104 weeks. A second study treated groups of 52 female F344/N rats with 0, 50, or 100 ppm mirex in the diet for 104 weeks, because early toxicity was not observed. Based on food consumption and body weight data, the NTP (1990) estimated these doses to be 0, 0.007, 0.07, 0.7, 1.8, and 3.8 mg/kg-day for males and 0, 0.007, 0.08, 0.7, 2.0, and 3.9 mg/kg/day for females. Doses were estimated at 0, 3.9, and 7.7 mg/kg-day for female rats in the second study. Average doses for male and female rats, thus, were 0, 0.007, 0.08, 0.7, 1.9, and 3.9 mg/kg/day in the first study. The following toxicological parameters were assessed: clinical signs, body weight, survival, gross pathology and histologic examination of adrenal gland, bone marrow, brain, esophagus, heart, kidney, liver, lung and bronchi, mammary gland, lymph nodes (submandibular and/or mesenteric), pancreas, parathyroid gland, pituitary gland, prostrate/testis or ovary/uterus, salivary glands, skin, small and large intestine, spleen, stomach, thymus, thyroid gland, trachea and urinary bladder.

No clinical signs of toxicity were reported for male or female treated rats. Statistically significant reductions in survival were seen in male rats treated with 1.9 or 3.9 mg/kg mirex (19/52 and 15/52, respectively, versus 44/52 for controls). The statistical significance of reported body weight changes were not provided. Male rats in the 1.9 and 3.9 mg/kg-day dose groups gained less weight than controls during the first 70 weeks of exposure and lost weight between 70 and 104 weeks of exposure; body weights after 104 weeks of exposure were 11% (1.9 mg/kg-day) and 18% (3.9 mg/kg-day) less than controls. In the first study, female rats in the 3.9 mg/kg-day group gained less weight than controls; body weights after 104 weeks of exposure were 8% less than controls. In the second study, females in the 3.9 and 7.7 mg/kg-day groups gained less weight than controls; body weights after 104 weeks of exposure were 8% (3.9 mg/kg-day) and 18% (7.7 mg/kg-day) less than controls.

Summarizing the histopathological findings from the NTP (1990) rat bioassay (with liver

histopathology re-evaluated by the PWG [1992]), exposure for 2 years to dietary dose levels of 0.007 or 0.08 mg/kg/day produced no statistically significant increased incidence of neoplastic or non-neoplastic lesions in male or female F344/N rats. At 0.7 mg/kg/day (and higher), statistically significant increased incidences of non-neoplastic lesions were found in several organs: toxic hepatitis consisting of centrilobular hepatocytomegaly, fatty change, apoptosis, necrosis, and bile duct proliferation (in both sexes), parathyroid hyperplasia in male rats only, nephropathy in females rats (only in the first study), and splenic fibrosis in male rats only. Exposure to 1.9 mg/kg/day produced statistically significant incidences of the following tumor types: liver adenomas in male rats, pheochromocytomas or malignant pheochromocytomas in male rats, and mononuclear cell leukemia in female rats. At 3.9 mg/kg/day significantly elevated incidences included liver adenomas in male and female (second study) rats, liver adenomas or carcinomas in male and female rats, benign or malignant pheochromocytomas in male rats, and mononuclear leukemia in male rats. In females exposed to 7.7 mg/kg/day in the second study, elevated incidences occurred for mononuclear cell leukemia, liver adenomas, and liver adenomas and carcinomas combined. Other statistically significant neoplastic responses were observed in several groups of exposed rats, but they were not as strongly associated with mirex exposure as liver neoplasms in both sexes, pheochromocytomas in male rats, or mononuclear cell leukemia in female rats, and are not interpreted as exposure-related. These included a statistically significant trend for increasing incidence of transitional cell papillomas of the renal pelvis in male rats with increasing exposure level, but the highest incidence for this neoplasm (3/52) was found in the highest dose group and was not significantly different from the control incidence by a number of statistical tests.

Table 1:Incidence of toxic hepatitis in F344/N male and female rats fed Mirex in the diet for 2 years

	Rat dose mg/kg-day					
	0	0.007	0.08	0.7	1.9	3.9
Male	1/52	2/52	5/52	11/52	28/52	29/52
Female	1/52	1/52	3/52	25/52	34/52	35/52

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 300 (10 for extrapolating from rats to humans, 10 to account for human variability, and 3 to account for data base deficiencies including the lack of two-generation reproductive toxicity studies)

MF = 1.

___I.A.4. ADDITIONAL STUDIES/COMMENTS (ORAL RfD)

Mirex has been detected in some monitoring studies of human adipose tissue and human breast milk samples (Burse et al., 1989; Guttes, et al., 1998; Kutz et al., 1974, 1985; Mes et al., 1993; Newsome et al., 1995), but no studies were located that investigated possible associations between mirex exposure and non-cancer health effects in humans.

Non-neoplastic toxic responses have been evaluated in dogs (Larson et al. 1979), rats (Chu et al., 1981a; Fulfs et al., 1977; Larson et al., 1979; NTP, 1990; Ulland et al., 1977; Yarbrough et al., 1981), mice (Fulfs et al., 1977), and monkeys (Fulfs et al. 1977) orally exposed to mirex for subchronic or chronic periods.

The liver appears to be one of the most sensitive targets of repeated oral exposure to mirex. Statistically significant non-neoplastic liver effects observed in animals chronically exposed to mirex include fatty metamorphosis, cytomegaly, and necrosis in F344/N rats exposed for 2 years to dietary doses of 0.7 mg/kg/day and greater, but not to doses of 0.007 or 0.08 mg/kg/day (NTP, 1990; PWG, 1992); hepatic cytomegaly, vacuolization, fatty metamorphosis, and necrosis in CD rats exposed for up to 18 months to survival-reducing doses of 7 mg/kg/day and greater (Ulland et al., 1977); and hepatic cellular hypertrophy, necrosis, and proliferation of smooth endoplasmic reticulum in CD-1 mice exposed for 18 months to doses of 0.9 mg/kg/day, but not to 0.2 mg/kg/day (Fulfs et al., 1977). Only "occasional" focal lymphocytic infiltrations of the liver without other liver lesions were observed in monkeys exposed to 0.25 or 1 mg/kg for up to 36 months (Fulfs et al., 1977), and no gross or histopathologic changes were observed in Sprague Dawley rats exposed for 12 months to 2 mg/kg/day mirex (Fulfs et al., 1977). Several studies of subchronically exposed animals provide supporting evidence that the liver is a sensitive target of mirex toxicity. Liver effects from subchronic exposure, generally observed at higher exposure levels than those producing liver lesions from chronic exposure, have been observed in rats (Chu et al., 1981a; Larson et al., 1979; Yarbrough et al., 1981) and dogs (Larson et al., 1979).

Non-neoplastic lesions in several other organs have been observed in animals repeatedly exposed to mirex, but these lesions appear either to occur at higher dose levels than those affecting the liver, to be less consistent across studies or gender, or to be less persistent than mirex-induced liver lesions. For example, thickening of the follicular epithelium, loss of colloid, and collapse of the follicles were observed in the thyroid of Sprague Dawley rats exposed to doses of 0.7 or 6.5 mg/kg/day for 28 days, but these lesions regressed in a 48-week post-exposure period (Chu et al., 1981a). In contrast, liver lesions in rats exposed to 6.5 mg/kg/day persisted through the 48-week period (Chu et al., 1981a). Increased incidences of similar non-neoplastic thyroid lesions were not observed in F344/N rats exposed for 2 years to dietary doses as high as 3.9 mg/kg/day in males or 7.7 mg/kg/day in females (NTP, 1990). In the NTP (1990)

chronic rat bioassay, the lowest dose level producing toxic hepatitis in male and female F344 rats (0.7 mg/kg/day) also produced increased incidence of parathyroid hyperplasia and splenic fibrosis in males (but not females), and increased incidence of nephropathy in females. The nephropathy in this study, however, appears to be more strongly associated with the age of the rats in this study than with exposure. Incidences of nephropathy were high in non-exposed controls and were not significantly elevated (compared with controls) in females in the second study exposed to doses as high as 7.7 mg/kg/day. The NTP study authors (1990) concluded that the "parathyroid hyperplasia is likely a secondary physiological response to the nephropathy" and thus support the interpretation that the parathyroid hyperplasia in male rats was not strongly associated with exposure. No such interpretation of the increased incidence of splenic fibrosis was proposed, but the splenic response was only observed in male rats (liver lesions occurred in both male and female rats exposed to mirex) and has not been reported in other animal studies involving subchronic or chronic oral exposure to mirex. Increased incidences of epithelial hyperplasia of the renal pelvis were observed in male rats exposed to higher doses ($\geq$ 1.9 mg/kg/day) than the lowest doses producing toxic hepatitis.

Another sensitive effect associated with oral exposure to mirex is cataract development in offspring of exposed female rats. Cataracts in offspring have been reported in studies with female rats orally exposed before mating, during gestation, and/or during lactation to dose levels as low as 0.4 mg/kg/day, but the effect has been more consistently observed at higher dose levels. Exposure during lactation appears to be a critical period for affecting this endpoint. An early study (Gaines and Kimbrough, 1970) showed that exposure of female Sherman rats to doses of approximately 2.3 mg/kg/day for 45 or 102 days before mating and continuing through gestation and lactation produced decreased numbers of live offspring and offspring surviving to weaning and increased incidences of offspring with cataracts (Gaines and Kimbrough, 1970). The same dose level administered to the rat dams only during lactation also produced cataracts in the offspring. Exposure of a group of females to 0.4 mg/kg/day prior to mating and during gestation and lactation did not affect these endpoints in this study, but increased incidence of cataracts and decreased survival to weaning were observed in a group of offspring of non-exposed females who were nursed by foster dams exposed to 0.4 mg/kg/day (5 ppm in diet) before mating and during gestation (Gaines and Kimbrough, 1970). In another study, in which male and female Sprague Dawley rats were exposed to mirex in the diet for 13 weeks before mating and during mating, followed by exposure of the dams during pregnancy and lactation, statistically significant increased incidence of cataracts in female offspring (but not male offspring) were observed in the group exposed to 0.4 mg/kg/day (5 ppm in diet) (Chu et al., 1981b). Cataracts were detected in male offspring of parents exposed to 1.5 mg/kg/day (20 ppm in diet).

Studies of dose-response relationships for cataracts in offspring established 1 mg/kg/day as a no-effect level and 2.5 mg/kg/day as the lowest effect level when lactating Sherman or Long Evans rat dams were given gavage doses on post natal days 1 through 4 (Chernoff et al., 1979a). Dose levels of 10 and 15 mg/kg were identified as the no-effect level and lowest effect level, respectively, for cataracts in offspring when Long Evans rat dams were given gavage doses only on post natal day 1 (Chernoff, 1979a). Mirex-induced cataracts in rat offspring have been

observed in several other studies in which rat dams were exposed to dose levels ≥ 5 mg/kg/day during lactation (Rogers and Grabowski, 1984; Scotti et al., 1981) or ≥6 mg/kg/day during gestation (Rogers and Grabowski, 1983; Rogers et al., 1984). In addition, increased incidence of offspring with cataracts were reported in studies in which lactating female CD-1 mice were given gavage doses ≥ 3mg/kg/day on post-natal days 1-4 (Chernoff et al., 1979a).

Other developmental effects including fetal edema, external abnormalities, and reduced fetal survival have been observed in other studies of pregnant rats exposed during gestation to doses of 3 mg/kg/day and greater. In studies with CD albino rats exposed to gavage doses on gestation days 7-16, signs of maternal toxicity (increased relative liver weight and decreased weight gain) and developmental toxicity (edematous live fetuses and decreased sternal ossification) were observed at doses ≥7 mg/kg/day, but not at 5 mg/kg/day (Chernoff et al., 1979a). At dose levels ≥ 19 mg/kg/day, more severe developmental effects (e.g., increased fetal mortality and decreased birth weight) were observed (Chernoff et al., 1979a). Other gestational exposure studies identified increased incidence of CD rat fetuses with external abnormalities (edema, ectopic gonads, and hydrocephaly) at 6 mg/kg/day and higher (Kavlock et al., 1982); and, in Wistar rat fetuses, increased incidences of fetal mortality and external abnormalities at 6 and 12.5 mg/kg/day, increased resorptions at 3 mg/kg/day, and no developmental effects at 1.5 mg/kg/day (Khera et al., 1976). Altered electrocardiographic patterns have also been observed in rat offspring of dams exposed during gestation to doses of 5-6 mg/kg/day (Grabowski, 1983a,b; Grabowski and Payne, 1980, 1983a, 1983b).

No adequate multiple-generation reproductive toxicity study has been conducted for mirex, but results from single-generation rat studies indicate that exposure to mirex can affect male and female reproductive ability. Impaired male fertility has been observed in Wistar rats exposed to gavage doses of 6 mg/kg/day for 10 days (but not in rats exposed to 3 mg/kg/day) before mating with non-exposed females (Khera et al., 1976) and in male Sprague Dawley rats exposed to 2.8 mg/kg-day for 13 weeks prior to mating and during mating to similarly exposed females (Chu et al., 1981b). In the latter study, no decreases were observed in the percentage of pregnant females at lower exposure levels up to 1.4 mg/kg-day in the diet, and no sperm was detected in vaginal smears of females at 2.8 mg/kg-day, but decreased average number of pups per litter occurred in groups exposed to 0.4, 0.8, or 1.5 mg/kg/day (Chu et al., 1981b). Decreased sperm counts have been reported in male Sprague Dawley rats exposed for 28 days to doses as low as 0.5 mg/kg/day (5 ppm in diet), with severe testicular degeneration occurring at doses of 5 or 7.5 mg/kg/day (50 or 75 ppm in diet) (Yarbrough et al. 1981). Male fertility was not affected in Sherman rats exposed to 2.3 mg/kg/day (25 ppm in diet) for 45 or 102 days before mating with non-exposed female rats, but a group of female Sherman rats exposed for 102 days to 25 ppm in the diet before mating with non-exposed males delivered fewer number of litters than a group of non-exposed male and female Sherman rats (Gaines and Kimbrough, 1970). The mode of action of this effect of mirex on female reproductive ability in Sherman rats is unexplained. Subcutaneous mirex did not display typical estrogenic effects in immature female Sprague Dawley rats (Gellert, 1978) and did not appear to directly act on the ovary in inhibiting ova release in Long Evans rats induced by pregnant mare serum (Fuller and Draper, 1975).

Current understanding of modes of action by which mirex adversely affects the liver, ocular development in offspring, offspring survival during gestation or lactation, or male or female reproductive performance is poor and inadequate to disregard the possible relevance of these effects to humans exposed to mirex. A hypothesis has been presented that humans and other primates may be less susceptible to the hepatotoxicity of mirex than rats and mice (Abraham et al., 1983), but support for this hypothesis is not strong. A study of rhesus monkeys exposed to gavage doses of 0.25 or 1 mg/kg/day (6 days/week) for 3 years (reported by Abraham et al., 1983 and Fulfs et al., 1977) found only "occasional" focal lymphocytic infiltrations of the liver without other liver lesions, but the limited number of animals in the study, the short duration of exposure (as a percentage of a reference lifetime of 18 years for rhesus monkeys), and the lack of other corroborative primate data preclude drawing definitive conclusions regarding the relative susceptibility of rodents and primates to the hepatotoxicity of chronic exposure to mirex.

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study – high
Data Base – medium
RfD -- medium to high

The overall confidence in this RfD assessment is medium to high reflecting high confidence in the principal study and medium confidence in the data base. Confidence in the principal study is high, because it included sufficient numbers of animals of both sexes for statistical analysis, adequate numbers of exposure levels to provide good descriptions of dose-response relationships for relevant endpoints, and was adequately designed, conducted, and reported. Confidence in the data base is medium. Several subchronic and chronic oral exposure studies are available in rats and mice identifying the liver as a sensitive target of mirex toxicity, and analysis of the data base indicates that the RfD based on liver effects will be protective of other identified sensitive effects from mirex exposure including splenic fibrosis from chronic exposure, developmental effects including cataracts and reduced pre-weaning offspring survival, and impaired male or female reproductive performance. Confidence in the data base could be increased with data from two-generation reproductive toxicity studies and comparative mechanistic studies providing more information regarding possible differences between primates and rodents in susceptibility to mirex toxicity.

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Source Document -- U.S. EPA (2003) Toxicological Review of Mirex (CAS No. 2385-85-5) In Support of Summary Information on the Integrated Risk Information System (IRIS).

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS summary. A record of these

comments is included as an appendix to U.S. EPA (2003).

Agency Consensus Date -- __/__/__

___I.A.7. EPA CONTACTS (ORAL RfD)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (FAX), or RIH.IRIS@EPAMAIL.EPA.GOV (internet address).

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name – Mirex
CASRN -- 2385-85-5
Last Revised -- 00/00/0000

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is generally expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

No inhalation RfC is derived due to the lack of appropriate inhalation exposure toxicity data for humans or animals and the lack of rat and human PBPK models for mirex that would facilitate extrapolating across exposure routes.

_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name – Mirex

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per μg/L drinking water or risk per $\mu g/m^3$ air breathed. The third form in which risk is presented is a concentration of the chemical in drinking water or air associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/887/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Draft Revised *Guidelines for Carcinogen Risk Assessment* also utilize those Guidelines where indicated (U.S. EPA, 1999a). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

__II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CHARACTERIZATION

Studies designed to investigate possible associations between mirex exposure and cancer in humans are limited to a case-control study of postmenopausal women with breast cancer that found no statistically significant association between detectable mirex in serum and the occurrence of breast cancer (Moysich et al., 1998). Thus, the available human data are inadequate for assessing the potential carcinogenicity of mirex in humans.

Significantly increased incidences of liver tumors were found in F344/N rats of both sexes (NTP, 1990; PWG, 1992), in male CD rats (Ulland et al., 1977), and in B6C3F1 and B6AKF1 mice of both sexes (Innes et al., 1969). The liver tumors were reported to be mostly benign in F344/N rats and an equal mix of benign and malignant tumors in CD rats. Innes et al. (1969) reported that metastases of liver tumors were rare, but did not report the occurrences.

In addition, statistically significant increased incidences of tumors at several other sites were observed, but these observations were not as consistent across studies as the tumorigenic response in the liver. Increased incidences of adrenal pheochromocytomas (mostly benign) were observed in groups of male F344/N rats exposed to 25 and 50 ppm in the diet, in one group of female F344/N rats exposed to 50 ppm, but not in another group of female F344/N rats exposed to 50 ppm (NTP, 1990). Increased incidences of mononuclear cell leukemia were found in male F344/N rats exposed to 25 ppm, but not in males exposed to 50 ppm, and in F344/N females exposed to 25 and 50 ppm in a first study, but only in females exposed to 100 ppm in a second study (NTP, 1990). Significantly increased incidence of tumors at these sites were not

found in the studies of CD rats (Ulland et al., 1977). In B6C3F1 and B6AKF1 mice, no lymphomas were induced by oral administration of mirex, but examination for neoplastic lesions in other organs was not comprehensive in this study (Innes et al., 1969). In the only other animal studies related to the potential carcinogenicity of mirex, subcutaneous injection of large (1000 mg/kg) single doses produced increased incidences of reticulum cell sarcomas in B6C3F1 mice (Innes et al., 1969), and dermally applied mirex promoted skin tumors in mice given initiating dermal doses of 7,12-dimethylbenz[a]anthracene (Kim and Smart, 1995; Moser et al., 1992, 1993). Overall, the database provides adequate evidence of carcinogenic hepatic responses to lifetime oral exposure to mirex in rats and mice, and less consistent evidence of carcinogenic responses at other sites.

Results from short-term genotoxicity testing indicate that mirex is not genotoxic, and thereby suggest that mirex may produce carcinogenic responses via a non-genotoxic mode of action. Mirex did not produce reverse mutations in *Salmonella typhimurium* or in *Escherichia coli* with or without metabolic activation, forward mutations at the HGPRT locus in human fibroblast cells, unscheduled DNA synthesis in rat, mouse, or hamster hepatocytes, or sister chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells. Mirex did not induce dominant lethal mutations in offspring of male rats exposed to oral doses as high as 6 mg/kg/day for 10 days and did not produce hepatic DNA damage in mice exposed to oral doses > 80 mg/kg/day for 5 days or in rats exposed to two oral doses of 120 mg/kg.

Following U.S. EPA (1986) Guidelines for Carcinogen Risk Assessment, mirex is placed in Cancer Group B2- *Probable Human Carcinogen,* based on inadequate human evidence and adequate evidence of carcinogenicity in animals (increased incidence of liver tumors in two strains of each of two species, rats and mice).

Following U.S. EPA (1999a) Draft Revised *Guidelines for Carcinogen Risk Assessment*, the hazard descriptor, *Likely to be Carcinogenic to Humans*, is appropriate for mirex based on consistent findings of hepatic carcinogenic responses, and less consistent findings of tumors in other tissues, in several studies of rats and mice chronically exposed to mirex in the diet. The human relevance of the animal evidence of carcinogenicity is assumed in the absence of adequate human data or mechanistic data to indicate that the mode of carcinogenic action in animals is not relevant to humans.

The modes of action whereby mirex induces liver tumors in animals are poorly understood, but available data suggest that a nongenotoxic mode involving mirex-induced hepatic cell proliferation is plausible. Short-term genotoxicity testing, both *in vitro* and *in vivo*, has produced no evidence of genotoxic actions from mirex, and metabolic studies indicate that animals are not able to metabolize mirex and produce potentially reactive metabolic intermediates that may be genotoxic. Mirex is a promoter, but not an initiator, of skin tumors in the 2-stage mouse skin model, providing indirect support for an hypothesis that mirex may cause liver tumors via promotion of previously initiated cells. Short-term and repeated oral exposure to mirex are known to cause hepatic cytomegaly, vacuolization, fatty metamorphosis, and necrosis, which may be precursor events to the eventual development of liver tumors, but this

hypothesis is not fully established.

Following U.S. EPA (1999a) guidance, a linear approach to dose-response assessment should be taken for agents such as mirex that are not DNA reactive and for which all plausible modes of action are not fully established. It is acknowledged, however, that the evidence for a nongenotoxic mode of action involving non-neoplastic liver cell changes as precursor events is stronger than evidence for a genotoxic mode of action without a threshold.

___II.A.2. HUMAN CARCINOGENICITY DATA

Studies designed to investigate possible associations between mirex exposure and cancer in humans are limited to a case-control study of postmenopausal women with breast cancer that found no statistically significant association between detectable mirex in serum and the occurrence of breast cancer (Moysich et al., 1998). Thus, the available human data are inadequate for assessing the potential carcinogenicity of mirex in humans.

___II.A.3. ANIMAL CARCINOGENICITY DATA

There are three adequate studies that have investigated the carcinogenicity of mirex in rats and mice orally exposed for chronic periods (Innes et al., 1969; NTP, 1990; Ulland et al., 1977). Two other chronic duration oral exposure studies have been published that focus on liver responses to mirex (Abraham et al. 1983; Fulfs et al., 1977), but they are of restricted usefulness because they are only focused on liver endpoints and incidence data for liver lesions were not adequately reported.

NTP (1990) fed groups of 52 male and 52 female F344/N rats (initial body weight 120 and 100 g, respectively) 0, 0.1, 1, 10, 25, or 50 ppm mirex (reported purity >96%) in the diet for 104 weeks. A second study treated groups of 52 female F344/N rats with 0, 50, or 100 ppm mirex in the diet for 104 weeks, because early toxicity was not observed. Based on food consumption and body weight data, the NTP (1990) estimated these doses to be 0, 0.007, 0.07, 0.7, 1.8, and 3.8 mg/kg-day for males and 0, 0.007, 0.08, 0.7, 2.0, and 3.9 mg/kg/day for females. Doses were estimated at 0, 3.9, and 7.7 mg/kg-day for female rats in the second study. Average doses for male and female rats, thus, were 0, 0.007, 0.08, 0.7, 1.9, and 3.9 mg/kg/day in the first study. The following toxicological parameters were assessed: clinical signs, body weight, survival, gross pathology and histologic examination of adrenal gland, bone marrow, brain, esophagus, heart, kidney, liver, lung and bronchi, mammary gland, lymph nodes (submandibular and/or mesenteric), pancreas, parathyroid gland, pituitary gland, prostrate/testis or ovary/uterus, salivary glands, skin, small and large intestine, spleen, stomach, thymus, thyroid gland, trachea and urinary bladder.

No clinical signs of toxicity were reported for male or female treated rats. Statistically significant reductions in survival were seen in male rats treated with 1.9 or 3.9 mg/kg mirex

(19/52 and 15/52, respectively, versus 44/52 for controls). The statistical significance of reported body weight changes were not provided. Male rats in the 1.9 and 3.9 mg/kg-day dose groups gained less weight than controls during the first 70 weeks of exposure and lost weight between 70 and 104 weeks of exposure; body weights after 104 weeks of exposure were 11% (1.9 mg/kg-day) and 18% (3.9 mg/kg-day) less than controls. In the first study, female rats in the 3.9 mg/kg-day group gained less weight than controls; body weights after 104 weeks of exposure were 8% less than controls. In the second study, females in the 3.9 and 7.7 mg/kg-day groups gained less weight than controls; body weights after 104 weeks of exposure were 8% (3.9 mg/kg-day) and 18% (7.7 mg/kg-day) less than controls.

NTP (1990) concluded that this study provided *clear evidence of carcinogenic activity* for male and female F344/N rats, based on "marked increased incidences of benign neoplastic nodules of the liver, as well as by increased incidences of pheochromocytomas of the adrenal glands and transitional cell papillomas of the kidney in males and by increased incidences of mononuclear cell leukemia in females." The dose-responsive increases in the incidences of hepatic neoplastic nodules were statistically significant ($p < 0.05$) in mirex-treated male rats at and above 0.7 mg/kg and in female rats of the second study at 3.9 and 7.7 mg/kg mirex. No statistically significant increase in the incidences of hepatic carcinomas were observed in the exposed groups compared with controls. The combined incidences for benign pheochromocytomas or malignant pheochromocytomas were statistically significantly elevated in male rats exposed to 1.9 or 3.9 mg/kg/day, in female rats exposed to 3.9 mg/kg/day in the first study, but not in females exposed to 3.9 or 7.7 mg/kg/day in the second study. A statistically significant trend was found for increased incidence of transitional cell papillomas of the kidney in males rats, but the incidence for these neoplasms was not significantly elevated in the highest dose groups compared with controls. Incidences of mononuclear cell leukemia were significantly elevated in male rats exposed to 1.9 mg/kg/day (but not at 3.9 mg/kg/day), in female rats exposed to 1.9 and 3.9 mg/kg/day in the first study, and in female rats exposed to 7.7 mg/kg/day in the second study. Combined analysis of the female groups found statistically significant elevations of incidence of mononuclear cell leukemia at 0.7 mg/kg and above.

The combined incidence of thyroid follicular cell adenomas or carcinomas was statistically significantly increased in male rats exposed to 3.9 mg/kg/day, but NTP (1990) concluded that an "association between follicular cell tumors and exposure to mirex is unlikely", because increased incidence of these tumors were not observed in males exposed to 1.9 mg/kg/day or in any exposed groups of female rats. In addition, no statistically significant exposure-related increases were observed in incidences of non-neoplastic thyroid lesions, although Chu et al. (1981a) reported that 28-day exposure to dietary concentrations as low as 5 ppm produced increased incidence of reversible thyroid lesions in Sprague Dawley rats (follicular epithelial thickening, colloid loss, and follicular collapse).

The liver histopathological slides prepared during the original NTP (1990) study were re-evaluated by a group of pathologists convened by Pathco, Inc. (PWG, 1992) using more current criteria and terminology than those used in the original pathology report. Neoplastic nodules were reclassified as hepatocellular adenomas, eosinophillic foci of cellular alteration, or

regenerative hyperplasia. The term toxic hepatitis was used to describe non-neoplastic lesions based on the occurrence of centrilobular hepatocytomegaly, centrilobular fatty change, apoptosis (individual cell necrosis), centrilobular necrosis, and bile duct proliferation. A U.S. EPA-sponsored review by Garman (U.S. EPA, 1999b) of the PWG (1992) report concluded that the re-evaluation was appropriate and that the re-evaluated incidence data for rat liver tumors were valid for risk assessment. The Office of Emergency and Remedial Response recommended that the PWG incidence data be used for risk assessment at Superfund sites (U.S. EPA, 1999a). Table 4 highlights the incidence of liver lesions for male and female rats based on the re-evaluation by the PWG (1992).

The re-evaluation found statistically significant increases in the incidence of hepatocellular adenomas in male rats treated with 1.9 and 3.9 mg/kg/day, and in female rats of the second study exposed to doses of 3.9 and 7.7 mg/kg/day (see Table 2). Thus, the re-evaluation indicated 1.9 mg/kg/day as the lowest dose level inducing a significant tumor response, whereas the NTP (1990) original pathological examination showed statistically significant increased incidence of "neoplastic nodules" at 0.7 mg/kg/day. The incidence of hepatocellular carcinoma was not affected by mirex-treatment (regardless of criteria or terminology used in the pathological exam). Statistically significant increases in the incidences of foci of cellular alteration and toxic hepatitis occurred in both male rats and female rats exposed to 0.7 mg/kg mirex; angiectasis and cystic degeneration were more frequent in male rats exposed to at least 0.7 m/kg mirex. Regenerative hyperplasia reportedly only occurred in the presence of toxic hepatitis or leukemia.

Table 2. Incidences for liver lesions in F344/N rats fed mirex in the diet for 2 years Incidence for females in the second study are indicated by FII. Sources: NTP, 1990; PWG, 1992.

Dietary Concentration	0 ppm	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm	100 ppm
Dose (mg/kg/day)	0	0.007	0.08	0.7	1.9	3.9	7.7
Lesion	(# affected rats/ # exposed rats)						
Eosinophilic foci	6/52 M 4/52 F 2/52 FII	4/52 M 4/52 F	5/52 M 5/52 F	14/52 M * 13/52 F *	17/52 M * 20/52 F *	21/52 M * 21/52F * 27/52 FII *	 26/52 FII *
Toxic hepatitis	1/52 M 1/52 F 1/52FII	2/52 M 1/52 F	5/52 M 3/52 F	11/52 M * 25/52 F *	28/52 M * 34/52 F *	29/52 M * 35/52 F * 45/52 FII *	 37/52 FII *
Liver adenomas	1/52 M 3/52 F 0/52 FII	1/52 M 1/52 F	2/52 M 1/52 F	4/52 M 0/52 F	6/52 M* † 2/52 F	10/52 M * † 3/52 F 5/52 FII * †	 5/52 FII * †
Liver carcinomas	3/52 M 0/52 F 0/52 FII	0/52 M 0/52 F	2/52 M 0/52 F	1/52 M 0/52 F	2/52 M 1/52 F	3/52 M 1/52 F 0/52 FII	 1/52 FII
Liver adenomas or carcinomas	4/52 M 3/52 F 0/52FII	1/52 M 1/52 F	4/52 M 1/52 F	5/52 M 0/52 F	7/52 M 3/52 F	13/52 M* † 4/52 F 5/52FII* †	 6/52FII* †

*Statistically significant ($p < 0.05$) difference from controls by Fisher Exact Test performed by Syracuse Research Corporation.
†Statistically significant ($p < 0.05$) difference from controls by Peto Pairwise Test performed by PWG (1992).

Toxic hepatitis refers to findings of centrilobular hepatocytomegaly, centrilobular fatty change, apoptosis, centrilobular necrosis, and bile duct proliferation.

The PWG (1992) concluded that "increased incidences of hepatocellular adenomas in both sexes were limited to doses of mirex which also induced hepatotoxicity and eosinophillic foci" (see Table 4), that a correlation between the latter two lesions was observed at doses up to 1.9 mg/kg mirex, and that "hepatotoxicity was also observed at doses lower than those with increased incidences of tumors." Despite the strong association between non-neoplastic liver lesions and the hepatocellular adenomas, not all rats with hepatocellular adenomas were diagnosed with non-neoplastic liver lesions. Examination of the PWG's (1992) chairperson's worksheets indicates that among all exposed male rats, 17 of 24 diagnoses of liver adenoma were concurrent with the diagnosis of other liver lesions. In the 1.9- and 3.9-mg/kg/day groups (the groups with significantly increased incidences of liver adenomas), toxic hepatitis or eosinophillic foci were diagnosed in 4/6 and 8/10 male rats with liver adenomas, respectively. At least one

pathologist in the PWG diagnosed the presence of non-neoplastic liver lesions (hyperplasia or regeneration) in every rat diagnosed with adenoma, but these incidences reflect consensus opinions that no non-neoplastic lesions were identified in some animals with adenomas.

The Innes et al. (1969) study (also reported as IARC, 1979) reports the effects of lifetime feeding of mirex or 119 other test compounds to mice, starting at 7 days of age. Two strains were used: (C57BL/6 x C3H/Anf)F1 (strain B6C3F1) and (C57BL/6 x AKR)F1 (strain B6AKF1). Four untreated-control groups and one gelatin-control group of each sex and strain (15-18/group) were included in the study. Innes et al. (1969) administered nothing, gelatin, or 10 mg/kg mirex in gelatin to groups of 18 male and 18 female mice of the two strains by gavage from 7-28 days of age; then mice were fed diets containing 0 or 26 ppm mirex for the remainder of their lifetimes. Assuming an average chronic reference body weight of 0.024 kg and food intake of 0.0063 kg/day for male and female B6C3F1 mice (U.S. EPA, 1988), an estimated daily dietary dose of 7 mg/kg/day is calculated. This was considered a maximum tolerated dose. Mirex-treatment decreased survival: control animals survived to 78-89 weeks; all treated males had died by 59 weeks on study, and all the females had died by 70 weeks. Whether the animals died spontaneously or were terminated is unclear from the report, but it could be inferred that mirex was severely toxic to the mice. Control animals were sacrificed between 78 and 89 weeks. At sacrifice, the thoracic and abdominal cavities were given a "thorough examination" with histological examination of major organs and of all grossly visible lesions. The incidence data for non-neoplastic lesions were not discussed in the report. Statistical analysis of tumor incidence data (for liver tumors, pulmonary tumors, and lymphomas) were performed using separate and combined control group data. The term "hepatoma" was used for all liver tumors regardless of metastasis; the authors reported that metastases were rare.

In mirex-treated animals, the increases in incidence of hepatomas in mirex-treated animals were statistically significant: B6C3F1 males: controls 8/79 (10%), treated 6/18 (33%); B6C3F1 females: controls 0/87 (0%), treated 8/16 (50%); B6AKF1 males: controls 5/90 (6%), treated 5/15 (33%); B6AKF1 females: controls 1/82 (1.2%), treated 10/16 (62.5%). The tumor incidences in all treated groups were significantly elevated relative to the pooled controls. No pulmonary tumors or lymphomas were observed in treated mice. In this study, 10 other compounds of the 120 total tested also induced statistically significant elevations in the incidences of tumor formation (Innes et al., 1969).

Groups of 26 male and 26 female Charles River CD rats were fed 40 or 80 ppm mirex in the diet (99% pure) for 10 weeks (Ulland et al., 1977). These doses were the predicted maximum tolerated dose and half maximum tolerated dose. Because no significant adverse effects were observed, the doses were increased to 50 or 100 ppm, respectively. Rats were dosed for a total of 18 months. After cessation of treatment, animals were observed for 6 months. The time weighted doses were calculated to be 4 or 7 mg/kg for males and 4 or 8 mg/kg for females. Groups of 20 male and 20 female rats were maintained as controls. All rats were necropsied and subjected to histopathologic examination of the adrenal glands, cerebrum, cerebellum, esophagus, heart, kidneys, liver (2-3 sections), lungs, pancreas, parathyroid gland, pituitary glands, spinal cord, small and large intestine, spleen, stomach, thymus, thyroid, urinary bladder,

and either testes or ovaries and uterus. Food and water consumption data were not reported. Treatment had no effect on body weight. Survival was significantly reduced in both groups of treated males and in high-dose females. Neoplastic and non-neoplastic hepatic lesions occurred at elevated incidences in exposed rats compared with controls.

Statistically significant increased incidence of hepatic neoplastic nodules occurred only in the high-dose male group, although incidences in both exposed female groups were marginally elevated compared with controls ($p = 0.053$) (Ulland et al., 1977). Among rats bearing neoplastic nodules, one low-dose and four high-dose males, and one high-dose female also had hepatocellular carcinomas. Carcinomas in male rats occurred with a statistically significant positive trend. The first liver tumor in control males was detected after 80-85 weeks; the first liver tumor in the treated males occurred in the high-dose group after 60-65 weeks. Livers of low-dose females appeared normal by gross examination; other exposed rats showed enlarged, mottled, or spotted livers. Histologic analyses of livers found that mirex induced fatty metamorphosis, megalocytosis, cystic degeneration, necrosis, and biliary hyperplasia with periportal fibrosis. Incidences of megalocytosis were statistically significantly elevated in exposed groups of both sexes. Megalocytosis was diffuse and was associated with periportal and perivascular areas; hepatocyte cytoplasm was enlarged with finely granular eosinophilic material. Areas of cellular alteration were characterized by hepatocyte enlargement and cytoplasmic vacuolation with a finely granular eosinophilic material; occasional cystic degeneration was observed. Features of the neoplastic nodules were swollen hepatocytes with vacuolated or granular eosinophilic cytoplasm that occupied the space of several lobules and compressed adjacent tissue. Carcinomas appeared well-differentiated. No other neoplastic or non-neoplastic changes in other tissues were attributed to treatment.

Groups of 100 male and 100 female CD-1 mice received 1, 5, 15 or 30 ppm mirex (0.2, 0.9, 3, or 5 mg/kg-day) in the diet for at least 19 months with paired control groups of 100 male and female mice (400 and 400, total) (Fulfs et al., 1977). Groups of 6 were sacrificed at 2, 4, 6, 9, 10, 15, and 18 months. Body weights were reported to be not affected by treatment, but were not otherwise reported. Due to poor survival in the 5 mg/kg group, these animals were removed from the study. Survival was not otherwise reported. Increased relative liver weights were seen in 5-mg/kg mice at 2 months, in 0.9- or 3-mg/kg mice at 6 months and later, and in 1-mg/kg mice (females only) at 18 months. Livers from exposed mice were reportedly enlarged and showed "nodules" by gross examination. The nodules, which were not otherwise described, were reported to appear after 6 months in the 3-mg/kg mice and after 15 months in the 0.2-mg/kg mice. Centrilobular hypertrophy of the hepatocytes was reported to occur in "most" exposed mice. Individual or multicellular necrosis was observed at dose levels of 0.9 mg/kg/day and higher, but was not observed in the 0.2-mg/kg/day group of mice. Incidence data were not reported. Ultrastructurally, minimal proliferation of smooth endoplasmic reticulum in hepatocytes was reported at the 0.2-mg/kg/day level, with more pronounced proliferation at the higher dose levels.

Sprague Dawley rats were fed 5 ppm mirex for 12 months or 30 ppm mirex for 8 months

(estimated doses of 0.3 or 2 mg/kg). Gender, use of controls, and numbers per group were not specified. It was reported that no differences were observed between control versus treated animals for body weight, liver weight, gross pathology, histopathology, or biochemistry (Fulfs et al., 1977).

Groups of 2 male and 2 female rhesus monkeys were treated with 0, 0.25, or 1 mg/kg mirex by gavage, 6 days per week, for up to 26 months. Baseline liver biopsies were taken from all 12 monkeys before administration, from high-dose animals at 16, 19, and 26 months, and from low-dose animals at 36 months. Livers from exposed monkeys were reported to appear normal, except for the occurrence of "occasional focal lymphocytic infiltration" (Fulfs et al., 1977).

Groups of 10 male Sprague Dawley rats were fed 0 or 100 ppm mirex (0 or 8 mg/kg-day) in the diet for 13 months (Abraham et al., 1983). Body weight was measured at study initiation and termination. An unspecified number of animals were injected with tritiated thymidine 1 hour prior to sacrifice; livers were examined for normal, abnormal and adjacent areas; from which samples were taken for analysis of nuclei, histology, and autoradiography. Livers of control-treated rats were reportedly normal; livers of mirex-treated rats exhibited centrilobular and pericentral hepatocyte hypertrophy and necrosis. Hypertrophic nodules, evolved nodules with trabeculi and acini, and advanced carcinomas were observed; however, incidence and statistical significance of these findings were not reported. Mirex treatment caused statistically significant increases in DNA synthesis (measured by thymidine-uptake) in hepatocytes in normal tissue adjacent to carcinomas and in littoral cells in areas of carcinoma.

Carcinogenic responses to subcutaneously administered mirex have been observed in two strains of mice (NCI, 1968). Groups of 18 males and 18 female mice of B6C3F1 and B6AKF1 mice received single subcutaneous injections of 1000 mg/kg mirex in 0.5% gelatin at 28 days of age. Surviving animals were sacrificed at 18 months. The term hepatoma was used to describe all liver tumors, except in cases of unmistakable pulmonary metastases, when the term hepatic carcinoma was used. Several tumor types, including those arising in the liver, thymus, spleen, abdominal lymph nodes, and Peyer's Patches, were included in the group of reticulum cell carcinoma. Statistically significant differences in tumor incidence between control and mirex-treated mice for total number, reticulum cell sarcoma, and hepatoma (by Chi-square methods) were reported. Because results were not evaluated by gender and strain, these results were verified by an evaluation of the raw data. Statistically significant elevations, compared with control incidences from multiple concurrent experiments, were observed for reticulum cell sarcoma in B6C3F1 males and B6AKF1 females and for hepatomas in B6AKF1 males. Pooling across sexes and strains, incidences for reticulum sarcomas or hepatomas in exposed mice were significantly elevated compared with controls.

Moser et al. (1992) observed that dermal exposure to 25, 50, or 100 nmol mirex (in 200 µL acetone) per application 3 times/week for 34 weeks or 200 nmol for 20 weeks promoted time- and dose-dependent skin tumor formation in female CD-1 mice exposed to single initiating dermal doses of 200 nmol 7,12-dimethylbenz[a]anthracene (DMBA) in 200 µL acetone. Without

initiation, dermal exposure to 100 or 200 nmol mirex failed to induce skin tumor formation, epidermal hyperplasia, epidermal protein kinase C activity, or ornithine decarboxylase activity. After 34 weeks of promotion with 25, 50, or 100 nmol mirex, 27%, 85% and 100% of mice developed skin tumors, respectively; the respective average numbers of tumors/mouse were 0.7, 7, and 12. No skin tumors occurred in mice initiated with DMBA and promoted with acetone for 34 weeks. In parallel studies of a number of biochemical and morphological events, mirex, at concentrations that produced a strong tumor promotion activity, did not induce ornithine decarboxylase or produce a strong cell proliferation response in mouse skin; these responses were observed with the strong phorbol ester mouse skin tumor promoter,12-*O*-tetradecanoyl-phorbol-13-acetate (Moser et al., 1992).

Moser et al. (1993) provided evidence that female mice are more susceptible to skin tumor promotion by mirex than male mice, and that ovarian hormones may enhance tumor promotion by mirex. Skin tumors formed in 96% of female mice (n = 30) exposed to initiating doses of DMBA followed by dermal exposure to 200 nmol mirex, three times per week for 20 weeks; an average of 14.7 tumors per mouse was observed. In contrast, in a group of 30 male mice similarly exposed, 67% showed skin tumors at 20 weeks with an average of 4.7 tumors/mouse. No skin tumors were found in groups of mice initiated with DMBA and promoted with acetone or initiated with DMBA and promoted with 200 nmol mirex. More than 90% of skin tumors in male and female mice showed a mutated Ha-*ras* gene. To investigate the effects of ovarian hormones on tumor promotion, Moser et al. (1993) initiated female CD-1 mice with a single dermal application of 200 nmol DMBA; two weeks later either sham-surgery (controls) or ovariectomies were performed. After an additional two weeks, starting when mice were 12 weeks old, all mice were exposed to 200 nmol mirex three times per week for 20 weeks. A statistically significant decrease in tumor formation was seen in ovariectomized mice compared to ovary-intact mice (1.8 versus 6.0 tumors per mouse, respectively). The results suggest that ovarian hormones play a role in the tumor-promoting effect of mirex in female mice. The ability of mirex to promote skin tumors in female CD-1 mice following initiation has also been reported by Kim and Smart (1995) and Kim et al. (1997).

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

No evidence of mirex genotoxicity has been identified in *in vitro* tests. Stevens et al. (1979) reported that they were unable to demonstrate mirex binding to DNA or RNA. The NTP (1990) found that mirex was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535 or TA1537, with or without exogenous metabolic activation. Mirex did not induce chromosomal aberrations or sister chromatid exchanges in Chinese hamster ovary cells with or without metabolic activation. Other studies confirm that mirex did not induce reverse mutations in multiple strains of *Salmonella typhimurium* (Hallett et al., 1978; Mortelmans et al., 1986; Probst et al., 1981; Schoeny et al., 1979) with or without hepatic microsomal activation. Mirex did not induce mutations in the WP2 and WP2 uvrA- strains of *Escherichia coli*, (Probst et al., 1981) with or without hepatic microsomal activation. Mirex did not significantly induce unscheduled DNA synthesis in rat, mouse, or hamster hepatocytes *in vitro* (Probst et al., 1981;

Williams, 1980; Maslansky and Williams, 1981; Telang et al., 1981). Mirex did not induce gene mutations in the HGPRT locus of human fibroblasts *in vitro* (Tong et al., 1981).

Animal studies have not identified mirex genotoxicity. No dominant lethal effects, measured by viable embryos or deciduomas in pregnant females mated to male Wistar rats treated with 0, 1.5, 3.0, or 6.0 mg/kg mirex by gavage 10 consecutive days and were then mated for 14 consecutive days, were observed (Khera et al., 1976). Mitra et al. (1990) observed that at doses of mirex that induced hepatic ornithine-decarboxylase activity (up to 240 mg/kg) in female Sprague Dawley rats, DNA damage was not induced, as measured by alkaline elution.

Abraham et al. (1983) observed that dietary administration of 100 ppm mirex to male Sprague Dawley rats for 13 months disturbed the distribution of diploid versus tetraploid nuclei in livers; the effects were most significant in hepatocellular carcinomas.

Mirex is structurally similar to chlordecone (i.e., kepone) in which two chlorine atoms have been substituted by a ketone oxygen. Chordecone induced sister chromatid exchanges in CHO Chinese hamster ovary cells (NTP, 1990), and has been classified by IARC (1987) as *possibly carcinogenic to humans* (Group 2B), on the basis of insufficient human data and the induction of liver tumors (hepatocellular carcinomas) in Osborne Mendel rats and B6C3F1 mice (NCI, 1976).

The mechanism by which mirex causes non-neoplastic and neoplastic lesions in the liver is poorly understood. Mirex has not been genotoxic in numerous short-term *in vitro* and a few *in vivo* tests, leading to the hypothesis that tumorigenic responses to mirex in the liver do not directly involve a genotoxic mechanism and may involve proliferation of cells initiated spontaneously, or by some other agent, to become tumors. Support for this hypothesis is provided by results in the two-stage mouse skin tumor bioassay showing that mirex does not initiate mouse skin tumors, but is a potent promoter of skin tumors initiated by DMBA (Kim and Smart, 1995; Kim et al., 1997; Moser et al., 1992, 1993).

Molecular details of how mirex may promote tumor formation, presumably through promotion of cell proliferation, are unknown, but results from several lines of investigation provide some suggestions of interactions with endocrine systems in mirex-induced tumor promotion and promotion of hepatocellular growth. In the two-stage mouse skin bioassay, ovariectomized mice showed a lesser skin tumor promotion response to mirex than sham-operated mice with intact ovaries (Moser et al., 1993). Exposure of Sprague Dawley rats to single high oral doses of mirex (100 mg/kg) induced rapid liver growth (about 70% increase in relative liver weight) without changing levels of serum enzymes indicative of liver damage or affecting some functional indices such as sulfobromophthalein clearance (Robinson and Yarbrough 1978). Numerous studies of this phenomenom by Yarbrough and colleagues have led to the hypothesis that mirex-induced liver growth is composed of hypertrophic (enhanced growth of existing cells) and hyperplastic (enhanced cell division) components and that interactions with endocrine systems may be involved (see Yarbrough et al., 1984 for review). For example, adrenalectomized male rats showed a liver growth response to 100 mg/kg mirex that was only

about 50% of that in rats with intact adrenal glands. In mirex-exposed adrenalectomized rats given corticosterone supplements, the liver growth response to mirex was restored, but was not preceded with a peak in hepatocellular DNA synthesis as noted in rats with intact adrenal glands (Yarbrough et al., 1984). Yarbrough et al. (1984) suggested that, in adrenalectomized rats, mirex induced liver growth predominately by a hyperplastic mode and that corticosterone supplement shifted the growth response to a hypertrophic response. In another study with thyroidectomized rats, the magnitude of liver growth in response to mirex was similar to that in rats with intact thyroids, but liver growth was not preceded by a peak in hepatocellular DNA synthesis, indicating a shift to a hypertrophic mode of response (Yarbrough et al., 1984). Supplementation of thyroidectomized rats with thyroxine (T4) and mirex caused a further stimulation in liver growth over that in rats with intact thyroids and restored the preceding peak in hepatocellular DNA synthesis. Further details regarding the possible connection of endocrine systems to the modes of action whereby chronic oral exposure to mirex produces hepatocelluar cytomegaly and necrosis and liver tumors are unknown.

Another hypothesis related to mirex-induced hepatic responses involves mirex induction of ornithine decarboxylase, the first enzyme in the biosynthetic pathway for polyamines that play roles in regulation of various cell functions and metabolism. Oral exposure of rats to two doses of 120 mg mirex/kg, 21 and 4 hours prior to sacrifice, or to single doses of 180 mg/kg induced hepatic ornithine decarboxylase activity by 70- or 55-fold, respectively (Mitra et al., 1990). In contrast, mirex did not induce epidermal ornithine decarboxylase at a dermal dose level that strongly promoted mouse skin tumors after DMBA initiation, whereas tumor promoting dose levels of the phorbol ester,12-*O*-tetradecanoyl-phorbol-13-acetate, did induce ornithine decarboxylase (Kim et al., 1995; Kim and Smart, 1997; Moser et al., 1992;1993).

Another hypothesis proposes that mirex is preferentially cytotoxic to tetraploid and octaploid hepatocytes and that this is a key phenomenon in the induction of mirex hepatotoxicity and carcinogenicity (Abraham et al., 1983). In a group of 10 male Sprague-Dawley rats exposed to 100 ppm mirex in the diet for 13 months, livers exhibited hypertrophy with necrosis, nodules, or carcinomas (incidences of these lesions were not reported). Control livers showed greater numbers of tetraploid nuclei than diploid nuclei (the reported ratio was 244:147, tetraploid:diploid), whereas, in exposed livers, decreasing numbers of tetraploid nuclei were observed in tissues with increasing severity of effect. The change in ploidy pattern was dramatic in liver tissue adjacent to carcinomas and in carcinomas; numbers of diploid nuclei were 3- to 4-fold greater than numbers of tetraploid nuclei. Abraham et al. (1983) noted that hepatocytes in primates and humans are predominately diploid (>99%) and that exposure of rhesus monkeys to mirex in the diet for 3 years did not produce histopathological changes in liver sections. Although Abraham et al. (1983) reported that exposure was to 5 or 20 ppm in the diet in this monkey study, the published report of this study (Fulfs et al., 1977), of which Abraham was a co-author, noted that the monkeys were given gavage doses of 0.25 or 1 mg/kg/day (6 days/week) for 3 years. Abraham et al. (1983) speculated that mirex may be less hepatotoxic to primates and humans than to rodents due to the absence of hepatocyte polyploid nuclei. Subsequent studies to further test this hypothesis are not available.

Other investigations have shown that acute or repeated oral exposure of Sprague Dawley rats to mirex at concentrations of 100 ppm in the diet can impair hepatobiliary function without elevating levels of serum enzymes indicative of liver cell damage (see Mehendale, 1981 for review). In these studies, it was shown that clearance of phenophthalein glucuronide was impaired by mirex exposure; clearance of other markers, such as sulfobromophthalein, were less sensitive to impairment by mirex. Other studies have shown that mirex inhibits uptake of endogenous organic anions [estradiol-17β(β-D-glucuronide), taurocholate, and L-alanine) by isolated rat hepatocytes (Teo and Vore, 1990) and significantly decreased bile acid concentration and bile acid secretory rate in rats exposed to 50 mg/kg for 3 days compared with controls (Teo and Vore, 1991). Mirex impairment of hepatobiliary excretion functions has been hypothesized to involve inhibition of ATPase activities involved in membrane transport (Curtis and Mehendale, 1981). The possible role that this effect of mirex may have in the development of non-neoplastic and neoplastic hepatic lesions from chronic exposure is unknown.

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

___II.B.1. SUMMARY OF RISK ESTIMATES

____II.B.1.1.

Oral Slope Factor - 0.5 per mg/kg/day
LED10 for liver tumors - 0.2 mg/kg/day

____II.B.1.2. Drinking Water Unit Risk

0.01 per mg/L

____II.B.1.3. Extrapolation Method

A model with two explanatory variables, dose and time to tumor, was used. The resultant model was a three-degree exponential polynomial for dose and Weibull for time to tumor.

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	0.01 mg/L
E-5 (1 in 100,000)	0.001 mg/L
E-6 (1 in 1,000,000)	0.0001 mg/L

___II.B.2. DOSE-RESPONSE DATA (CARCINOGENICITY, ORAL EXPOSURE)

Source: NTP, 1990; PWG, 1992

Diet ppm	Rat Dose mg/kg/day	Human Dose mg/kg/day	Rat Incidence Data: Combined liver adenoma & carcinoma			Rat Incidence Data: Toxic hepatitis		
			Male Study I	Female Study I	Study II	Male Study I	Female Study I	Study II
0	0	0	4/52	3/52	0/52	1/52	1/52	1/52
0.1	0.007	0.002	1/52	1/52		2/52	1/52	
1	0.08	0.02	4/52	1/52		5/52	3/52	
10	0.7	0.2	5/52	0/52		11/52	25/52	
25	1.9	0.5	7/52	3/52		28/52	34/52	
50	3.9	1.0	13/52	4/52	5/52	29/52	35/52	45/52
100	7.7	2.1			6/52			37/52

The NTP (1990) rat study provides the best available data for describing dose-response relationships for liver tumors and non-neoplastic liver lesions. Incidences for hepatocellular adenomas and carcinomas (as re-evaluated by PWG, 1992) were significantly elevated at the 25- and 50-ppm level in males and the 50- and 100-ppm levels in females, but were not elevated at the 0.1, 1, or 10-ppm levels. This observation is consistent with the existence of a threshold for liver cancer above the 10-ppm dietary exposure level, but is not definitive evidence given the limited number of animals (n = 50/sex) included in this type of bioassay. The apparent threshold for non-neoplastic liver lesions (e.g., toxic hepatitis) was above the 1-ppm level; statistically significant elevated incidences of hepatotoxic effects were observed at dietary concentrations of 10 ppm and greater. Most (but not all) rats that had liver tumors in this study were diagnosed with non-neoplastic liver lesions such as cytomegaly, fatty metamorphosis, vacuolization, or necrosis.

A linear approach to cancer dose-response assessment has been taken for mirex, following U.S. EPA (1999a) guidance for agents that are not DNA reactive and for which all plausible modes of action are unknown. It is acknowledged, however, that the evidence for a nongenotoxic mode of action involving non-neoplastic liver cell changes as precursor events for mirex-induced cancer is stronger than evidence for a genotoxic mode of action without a threshold.

Incidence data for male rats in the NTP (1990) bioassay (with liver histopathology re-evaluated by the PWG [1992]) were used in the linear analysis of liver tumor incidence data as male rats appeared to be more susceptible to mirex-induced liver tumors than female rats.

One approach involved fitting a model with an exponential polynomial function of dose and a Weibull time-to-tumor function to the incidence data for combined adenomas and carcinomas in male rats and associated rat doses converted to human equivalent doses (based on the assumption of equivalence, across species, of doses in units of mg/kg divided by body weight to the 3/4 power). A licensed computer program, *Multi-Weib* (K.S. Crump and Company, Ruston, LA), was used to fit the model to the data. A three-degree polynomial form of the dose function provided the best fit of the data. The lower 95% confidence limit of the dose associated with a 10% extra risk (LED10) for tumors was 0.193 mg/kg/day (calculated for a full lifetime, 105 weeks). Using linear extrapolation from the LED10 to the origin, predicted doses associated with extra risks of 10^{-4}, 10^{-5}, and 10^{-6} are 0.0002, 0.00002, and 0.000002 mg/kg/day, respectively. Using the upper 95% confidence limit on the slope in the low-dose region (i.e., the q1* or oral slope factor = 0.53 per mg/kg/day), predicted doses associated with extra risks of 10^{-4}, 10^{-5}, and 10^{-6} are the same: 0.0002, 0.00002, and 0.000002 mg/kg/day, respectively.

An approach without the time-to-tumor analysis was also applied to the male rat tumor incidence data using the array of discontinuous mathematical models in the EPA Benchmark Dose Software. For liver adenomas and carcinomas combined, a probit model provided the best fit among the models examined. The ED10 and LED10 values predicted by the model were 0.6 and 0.5 mg/kg/day. Using linear extrapolation from the LED10, predicted doses associated with extra risks of 10^{-4}, 10^{-5}, and 10^{-6} are 0.0005, 0.00005, and 0.000005 mg/kg/day.

The model that included time-to-tumor as an explanatory variable was selected as the approach of choice for these data, because there was statistically significantly reduced survival of male rats in the two highest dose groups in the NTP (1990) bioassay. The modeling provides a means of adjusting for less-than-lifetime exposure for the rats with tumors that died early, and estimating risk for liver tumors with full life-time exposure.

___II.B.3. ADDITIONAL COMMENTS (CARCINOGENICITY, ORAL EXPOSURE)

___II.B.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, ORAL EXPOSURE)

Confidence in the principal study for the dose-response is high because it included sufficient numbers of animals of both sexes for statistical analysis, adequate numbers of exposure levels to provide good descriptions of dose-response relationships for relevant endpoints, comprehensive histopathological analysis for non-neoplastic and neoplastic lesions in all major tissues and organs, and was adequately conducted and reported.

The evidence for a nongenotoxic mode of action involving non-neoplastic liver cell changes as precursor events that have a threshold is stronger than evidence for a genotoxic mode

of action without a threshold, but mirex's mode of carcinogenic action is not fully established and molecular mechanistic details are unclear. The human relevance of the animal evidence of mirex carcinogenicity is assumed in the absence of adequate human cancer data or adequate mechanistic data to indicate that the mode of carcinogenic action in animals is not relevant to humans.

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

No inhalation quantitative estimate was derived in the absence of appropriate data from inhalation toxicity studies or appropriate empirical PBPK models for mirex in rats and humans to facilitate extrapolation across routes of exposure.

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

Source Document -- U.S. EPA (2003) Toxicological Review of Mirex (CAS No. 2385-85-5) In Support of Summary Information on the Integrated Risk Information System (IRIS).

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS summary. A record of these comments is included as an appendix to U.S. EPA (2003).

___II.D.2. EPA REVIEW (CARCINOGENICITY ASSESSMENT)

Agency Consensus Date -- __/__/__

___II.D.3. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (FAX), or RIH.IRIS@EPAMAIL.EPA.GOV (internet address).

_III. [reserved]
_IV. [reserved]
_V. [reserved]

_VI. BIBLIOGRAPHY

Substance Name - Mirex
CASRN -- 2385-85-5
Last Revised -- 00/00/0000

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None.

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_VII. REVISION HISTORY

Substance Name

CASRN -- __-__-_

Date	Section	Description
03/01/1988	I.A.5.	Confidence levels revised
04/01/1991	I.A.4.	Citations added
04/01/1991	VI.	Bibliography on-line
01/01/1992	IV.	Regulatory actions updated
08/01/1992	I.A.	Withdrawn; new oral RfD verified (in preparation)
08/01/1992	IV.	Regulatory actions withdrawn
08/01/1992	VI.A.	Bibliography withdrawn
10/01/1992	I.A.	Oral RfD summary replaced; RfD changed
10/01/1992	IV.	Regulatory actions returned in conjunction with RfD
10/01/1992	VI.A.	Bibliography replaced
07/01/1993	II.	Carcinogenicity assessment now under review
08/01/1995	II.	EPA's RfD/RfC and CRAVE workgroups were discontinued in May, 1995. Chemical substance reviews that were not completed by September 1995 were taken out of IRIS review. The IRIS Pilot Program replaced the workgroup functions beginning in September, 1995.
04/01/1997	III., IV., V.	Drinking Water Health Advisories, EPA Regulatory Actions, and Supplementary Data were removed from IRIS on or before April 1997. IRIS users were directed to the appropriate EPA Program Offices for this information.
01/12/2000	I.,II.,VI	This chemical is being reassessed under the IRIS Program.
00/00/0000	I, II, V	Revised RfD, cancer assessment.

_VIII. SYNONYMS

Substance Name
CASRN -- __-_- _
Last Revised -- __/__/__

2385-85-5
BICHLORENDO
CG-1283
CYCLOPENTADIENE, HEXACHLORO-, DIMER
DECANE,PERCHLOROPENTACYCLO-
DECHLORANE

DECHLORANE 4070
1,1a,2,2,3,3a,4,5,5,5a,5b,6-DODECACHLOROOCTAHYDRO-1,3,4-METHENO-1H-CYCLOBUTA (cd)PENTALENE
DODECACHLOROOCTAHYDRO-1,3,4-METHENO-2H-CYCLOBUTA (c,d)PENTALENE
DODECACHLOROPENTACYCLO(3.2.2.0(sup 2,6),0(sup 3,9),0(sup 5,10)) DECANE
DODECACHLOROPENTACYCLODECANE
ENT 25,719
FERRIAMICIDE
GC 1283
HEXACHLOROCYCLOPENTADIENE DIMER
1,2,3,4,5,5-HEXACHLORO-1,3-CYCLOPENTADIENE DIMER
HRS l276
1,3,4-METHENO-1H-CYCLOBUTA(cd)PENTALENE, DODECACHLOROOCTAHYDRO-
1,3,4-METHENO-1H-CYCLOBUTA(cd)PENTALENE, 1,1a,2,2,3,3a,4,5,5,5a,5b,6-DODECACHLOROOCTAHYDRO-
NCI-C06428
PERCHLORODIHOMOCUBANE
PERCHLOROPENTACYCLO(5.2.1.0(sup 2,6).0(sup 3,9).0(sup 5,8)) DECANE
PERCHLOROPENTACYCLODECANE