Mirex; CASRN 2385-85-5

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Mirex

File First On-Line 09/30/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	10/01/1992
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	not evaluated	

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 — 10/01/1992

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. 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.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Liver cytomegaly, fatty metamorphosis, angiectasis; thyroid cystic follicles **Rat Chronic Dietary Feeding Study** **NTP, 1990**	NOAEL: 1 ppm (0.07 mg/kg/day) LOAEL: 10 ppm (0.7 mg/kg/day)	300	1	2E-4 mg/kg/day

*Conversion Factors -- None

I.A.2. Principal and Supporting Studies (Oral RfD)

NTP (National Toxicology Program). 1990. Toxicology and Carcinogenesis Studies of MIREX (CAS No. 2385-85-5) in F344/N Rats (Feed Studies). NTP TR 313.

Groups of 52 male and 52 female F344/N rats (initial body weight 120 and 100 g, respectively) were fed mirex (reported purity >96%) for 104 weeks. Reported mirex doses were in ppm and when converted to mg/kg-day were 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. In a second study, 52 female F344/N rats were fed diets containing mirex at doses of 3.9 and 7.7 mg/kg-day. The following parameters were used to assess toxicity: clinical signs, body weight, survival and histologic examination of adrenal gland, bone marrow, brain, esophagus, heart, kidney, liver, lymph node (submandibular and/or mesenteric), lung and bronchi, mammary gland, pancreas, parathyroid gland, pituitary gland, prostrate/testis or ovary/uterus, salivary gland, skin, small and large intestine, spleen, stomach, thymus, thyroid gland, trachea and urinary bladder.

Survival of male rats in the 1.8 and 3.8 mg/kg-day groups was significantly less than controls (64% and 71% non-accidental deaths before termination vs. 15% in controls, $p<0.001$). Male rats

in the 1.8 and 3.8 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% (1.8 mg/kg-day) and 18% (3.8 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. No clinical signs of toxicity in male or female rats were reported.

Histologic examinations revealed dose-related changes in the parathyroid gland, kidney, liver, spleen and thyroid. In the parathyroid gland, dose- related increased incidence of hyperplasia was observed in male rats at and above 0.007 mg/kg-day. The incidences of hyperplasia were as follows: control, 6/32 (19%); 0.007 mg/kg-day, 12/39 (31%); 0.07 mg/kg-day, 13/39 (33%); 0.7 mg/kg-day, 18/40 (45%); 1.8 mg/kg-day, 22/50 (44%); and 3.8 mg/kg-day, 24/45 (53%). A dose-related increase in severity of nephropathy was observed in male rats at and above 0.7 mg/kg-day and in female rats at and above 2 mg/kg-day. Medullary hyperplasia was also seen in male rats at and above 0.7 mg/kg-day. Parathyroid hyperplasia and renal medullary hyperplasia are consistent with and may have been secondary to nephropathy, which was more severe in the rats exposed to mirex. In the liver, fatty metamorphosis, cytomegaly and angiectasis were detected in male rats at and above 0.7 mg/kg-day with necrosis at and above 1.8 mg/kg-day. Fatty metamorphosis, cytomegaly and necrosis were also observed in female rats at and above 0.7 mg/kg-day. Splenic fibrosis and cystic follicles of the thyroid were seen in male rats at and above 0.7 mg/kg-day. Based on liver and thyroid effects, this study defines a NOAEL of 0.07 mg/kg-day and a LOAEL of 0.7 mg/kg-day.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — An uncertainty factor of 300 reflects 10 for intraspecies variability, 10 for interspecies extrapolation and 3 for lack of a complete database, specifically lack of multi-generational data on reproductive effects and cardiovascular toxicity data.

MF — 1.

I.A.4. Additional Studies/Comments (Oral RfD)

The previously verified RfD was based on the Shannon (1976) study. Shannon (1976) performed studies in which prairie voles (Microtus ochrogaster) were exposed in the diet to mirex at 0, 0.1 and 0.5 ppm. The studies consisted of: single generation, 90-day exposure; single-generation, continuous exposure; and multi-generation, continuous exposure. Shannon chose M. ochrogaster to examine the effects of mirex on a wildlife species. Offspring (10/sex/dose group) from the

first litter of the 0, 0.1 and 0.5 ppm groups of a single- generation, continuous exposure study were used as the first generation of the multi-generation, continuous exposure study. These animals were separated into 10 pairs (male and female) at approximately 60 days of age according to concentration of mirex exposure. The 0, 0.1 and 0.5 ppm mirex exposures continued through premating, mating, gestation and lactation for one litter. Shannon noted significant dose-related effects including decreased lactation index and increased percent mortality of pups in the first generation. In the second generation, significant differences were found in the percent survival of offspring to days 4 and 21 and in percent mortality of pups. Several difficulties were noted in this study; discrepancies in statistical analyses and lack of raw data to validate some of the results. The previous RfD was 2E-6 mg/kg-day.

Effects of mirex on the parathyroid and kidney reported in NTP (1990) have not been corroborated in chronic (Ulland et al., 1977) or subchronic (Larson et al., 1979) studies. However, NTP (1990) detected a dose-related increase in severity of nephropathy against a high but not unusual incidence of age- related nephropathy in rats (98% in controls). Thus, mirex may enhance the severity of age-related nephropathy, in which case, effects on the kidney would be detected only in a chronic study in which a rigorous severity assessment of the nephropathy was performed. The Ulland et al. (1977) study does not qualify as such a study; furthermore, histologic examinations were performed in the Ulland et al. (1977) study 6 months after exposure to mirex ended. Effects on the liver and thyroid reported in NTP (1990) have been corroborated (Gaines and Kimbrough, 1970; Fulfs et al., 1977; Ulland et al., 1977; Larson et al., 1979; Chu et al., 1981a; Yarbrough et al., 1981). Effects on the testis (hypocellularity and depressed spermatogenesis) reported in Yarbrough et al. (1981) were not detected in NTP (1990), however, these effects may have been masked in the NTP (1990) study by age-related degenerative changes in the testis. Reproductive and developmental effects (decreased fertility, fetal cataracts and edema) have been reported in several studies (Yarbrough et al., 1981; Gaines and Kimbrough, 1970; Chu et al., 1981b; Chernoff et al., 1979a,b; Chernoff and Kavlock, 1982; Grabowski and Payne, 1980; Kavlock et al., 1982; Scotti et al., 1981; Ware and Good, 1967). Effects on the fetal electrocardiogram have also been reported (Grabowski, 1983; Grabowski and Payne, 1980, 1983a,b).

Ulland et al. (1977) fed diets containing 0, 50 or 100 ppm mirex (reported purity 99%) to groups of 26 male and 26 female CD rats for 18 months. Reported mirex doses were 0, 1.5 and 3 mg/kg-day. Histologic evaluations made 6 months after exposure to mirex ended included adrenal glands, cerebrum, cerebellum, esophagus, heart, kidneys, liver, lungs, ovaries, pancreas, parathyroid gland, pituitary glands, spinal cord, small and large intestine, spleen, stomach, testis, thymus, thyroid, urinary bladder and uterus. Mortality of male rats in the dose groups at and above 50 ppm and females in the 100 ppm group was greater than rats in the control group. Histologic evaluation of the liver revealed cytomegaly, vacuolization, fatty metamorphosis and

necrosis in rats exposed to mirex. No other treatment- related non-neoplastic lesions were reported in other tissues. This study identifies a FEL of 50 ppm (1.5 mg/kg-day).

Fulfs et al. (1977) conducted chronic bioassays in mice and monkeys. Groups of 100 male and 100 female CD-1 mice were fed diets containing 0, 1, 5, 15 or 30 ppm mirex (purity not specified) for 18 months. Estimated mirex doses based on U.S. EPA (1987) and assumed average body weights of 0.036 kg were: 0, 0.17, 0.86, 2.6 and 5.2 mg/kg-day. Although survival was not specifically addressed, Fulfs et al. (1977) report that the 30 ppm group was removed from the study due to poor survival. This suggests that the 30 ppm dose is an FEL. Toxicity was assessed from biochemical, histochemical and histological (light and electron microscopy) evaluations of the liver. Female mice in the 1 ppm group had a significant increase in relative liver weight. Histologic evaluations of the liver revealed cellular hypertrophy, cellular or multicellular necrosis, and proliferation of the smooth endoplasmic reticulum (SER) at and above 5 ppm and nuclear inclusions at 30 ppm. Histochemical evaluations of the liver revealed centrilobular depletion of glucose-6- phosphatase activity at and above 5 ppm. Liver hypertrophy and SER proliferation are consistent with observed induction of mixed function oxidase over the same dose range in these animals (Byard et al., 1975). This study (Fulfs et al., 1977) identifies a NOAEL of 1 ppm (0.17 mg/kg-day) and a LOAEL of 5 ppm (0.86 mg/kg-day).

In the monkey study, Fulfs et al. (1977) administered oral gavage doses of 0 or 0.25 mg/kg-day mirex (purity not specified) in corn oil, 6 days/week for 36 months (0.21 mg/kg-day when multiplied by 6/7 to adjust to 7 days/week); or 1 mg/kg-day, 6 days/week for 16, 19 or 26 months (0.85 mg/kg-day when multiplied by 6/7 to adjust to 7 days/week) to groups of 2 male and 2 female rhesus monkeys (Macaca mulatta). Histochemical and histologic evaluations of the liver revealed "occasional" focal lymphocytic infiltration in treated monkeys (dose unspecified). This study identifies a 0.21-0.85 mg/kg-day LOAEL.

Yarbrough et al. (1981) conducted a 28-day study in which groups of 10 male Sprague-Dawley rats (60-85 g initial body weight) were fed diets containing 0, 0.5, 5.0, 50 or 75 ppm mirex (repurified from technical grade, reported purity 99.5%). Estimated mirex doses based on reported average food intake for controls of 14 g/day (which was not significantly different from mirex-treated groups) and reported average initial body weight (72 g) and weight gain (183 g) were 0, 0.05, 0.5, 5 and 7 mg/kg-day. Toxicity was assessed from measurements of serum enzymes, hematologic parameters, sperm counts, organ weights, and histologic evaluation of liver, thyroid and testis. There appeared to be a significantly decreased sperm count (53% decrease at 0.5 ppm, $p<0.01$), but this may have been due to the coincidence of the termination of the experiment and the inception of sexual maturity in all test groups. Thus, sexual maturity may have been delayed in dosed test groups due to mirex effects. Histologic evaluation of the liver revealed cytoplasmic alterations (increased density) that were "subtle and inconsistent" at 0.5 ppm, consistently observed at 5 ppm, and progressed to cytoplasmic inclusions with cell

swelling at and above 50 ppm. Histologic evaluation of the testis revealed hypocellularity, decreased spermatogenesis, and luminal nucleated and giant cells, characteristic of testicular degeneration (dose not specified). Histologic evaluation of the thyroid revealed epithelial cell hypertrophy, colloid depletion, follicular atrophy and focal papillary formations present inconsistently at 5 ppm and more prominent at and above 50 ppm. This study identifies a NOAEL of 0.5 ppm (0.05 mg/kg-day) and a LOAEL of 5 ppm (0.5 mg/kg-day).

Groups of 40 male Sprague-Dawley rats (initial body weight 60-90 g) were fed diets containing 0, 5 or 50 ppm mirex (reported purity 98%) for 28 days and were evaluated for toxic effects at 28 days, or at 12, 24 or 48 weeks after exposure to mirex ended (Chu et al., 1981a). Estimated doses based on reported average food intakes and assumed average initial body weight of 75 g and reported final body weights were 0, 0.7 and 6.5 mg/kg-day. Toxicity was evaluated from complete hematologic analysis, serum chemistry, measurements of testicular sorbitol dehydrogenase and hepatic mixed function oxidase activity, serum T3 and T4 levels, and histologic examination of adrenal gland, bone marrow, brain, esophagus, heart, kidney, liver, lung, trachea and bronchi, lymph node (mesenteric and mediastinal), pancreas, parathyroid, pituitary, skeletal muscle, small and large intestine, spleen, stomach, testis and epididymis, thoracic aorta, thymus and thyroid. Histologic evaluations revealed lesions of the liver and thyroid in the 5 and 50 ppm dose groups. Liver lesions included fatty infiltration, cytoplasmic vacuolization, anisokaryosis and cellular necrosis. Thyroid lesions consisted of thickening of the follicular epithelium, loss of colloid and collapse of the follicles. Thyroid lesions regressed over the 48 week post-exposure observation period. Liver lesions persisted in the 50 ppm dose group. This study identifies a LOAEL of 5 ppm (0.7 mg/kg-day).

Groups of 10 male and 10 female Sherman rats (body weights not reported) were fed diets containing 0, 1, 5 or 25 ppm mirex (technical grade, reported purity 98%) for 166 days (Gaines and Kimbrough, 1970). Reported mirex doses were 0, 0.04-0.09, 0.21-0.48 and 1.3-3.1 mg/kg-day for males and 0, 0.06-0.10, 0.31-0.49 and 1.8-2.8 mg/kg-day for females. Toxicity was assessed from histologic examination (using light and electron microscopy) of the liver, which revealed dose-related hepatic cytomegaly in male and female rats. Incidences in male rats were: control, 0/10; 0.04-0.09 mg/kg-day, 2/10 (20%); 0.21-0.48 mg/kg-day, 5/10 (50%); and 1.3-3.1 mg/kg-day, 10/10 (100%). Incidences in females were: control, 0/10; 0.06-0.10 mg/kg-day, 0/10; 0.31- 0.49 mg/kg-day, 3/10 (30%); and 1.8-2.8 mg/kg-day, 5/10 (50%). This study identifies a LOAEL of 0.04-0.09 mg/kg-day.

In a series of subchronic studies, Larson et al. (1979) examined the effects of mirex in the diet of rats and beagle dogs. Groups of Charles River rats (10/sex/dose) were fed diets containing 0, 5, 20, 80, 320 or 1280 ppm mirex (reported purity 98%) for 13 weeks. Estimated mirex doses based on measured food consumption (the mean of food consumed at 4 and 13 weeks) were 0, 0.4, 1.3, 6.2, 24 and 96 mg/kg-day for males and 0, 0.3, 1.3, 5.8, 23 and 95 mg/kg-day for females.

Toxicity was assessed from a hematologic analysis (unspecified), urinalysis (unspecified), and histologic examination of adrenal gland, bone marrow, brain, cecum, gonad, heart, kidney, liver, lung, pancreas, pituitary, small and large intestine, spleen, stomach, urinary bladder and thyroid. Male rats in the 80 ppm dose group and female rats in the 320 ppm dose group had significantly enlarged livers (increased liver/body weight ratio, $p<0.05$). Histologic examination revealed vacuolization and cytomegaly in livers of males in the 80 ppm dose group. Survival of male rats in the 1280 ppm dose group was decreased relative to controls (0 vs. 100% in controls) as was survival of female rats in the 1280 ppm group (50% vs. 100% in controls). This study identifies a NOAEL of 20 ppm (1.3 mg/kg-day), a LOAEL of 80 ppm (6.2 mg/kg-day), and a FEL of 1280 ppm (95 mg/kg-day).

Larson et al. (1979) fed a diet containing 0, 4, 20 or 100 ppm mirex (reported purity 98%) to purebred beagle dogs (2/sex/dose) (7-12 kg initial body weight) for 13 weeks. Estimated mirex doses based on U.S. EPA (1987) and reported average body weights of 11 kg for males and 9 kg for females were 0, 1, 5 and 27 mg/kg-day for males and 0, 1, 5 and 24 mg/kg-day for females. Toxicity was assessed from hematologic analyses (unspecified), blood chemistry (glucose, urea nitrogen, glutamic oxaloacetic transaminase, alkaline phosphatase, cholinesterase), sulfobromophthalein retention, urinalyses (unspecified), and histologic examination of adrenal gland, bone marrow, brain, cecum, gonad, heart, kidney, liver, lung, pancreas, pituitary, small and large intestine, spleen, stomach, urinary bladder and thyroid. Male and female dogs in the 100 ppm dose groups gained less weight than controls and had elevated serum alkaline phosphate levels. One male and one female dog in these groups died (13 and 10 weeks, respectively); the male had increased sulfobromophthalein retention. Results of histologic examinations were reported as unremarkable. This study identifies a FEL of 100 ppm (24 mg/kg-day).

Fulfs et al. (1977) fed Sprague-Dawley rats (number, sex and initial body weights not specified) diets containing 0, 5 or 30 ppm mirex (purity not specified) for 12 or 8 months, respectively. Mirex doses based on U.S. EPA (1987) and assumed average body weights of 0.43 kg were 0, 0.4 and 2.2 mg/kg-day. Histochemical and histologic evaluations of the liver revealed "minimal" proliferation of smooth endoplasmic reticulum. This study identifies a NOAEL of 5 ppm (0.4 mg/kg-day).

Gaines and Kimbrough (1970) conducted a reproduction study of mirex (technical grade, reported purity 98%) in the diets of Sherman rats. Groups of 10 male rats (body weights not reported) were fed 0 or 25 ppm mirex for either 45 or 102 days. Groups of 10 female rats were fed 0 or 25 ppm mirex for 45 days or 0, 5 or 25 ppm mirex for 102 days. After the specified exposure period, rats fed mirex were mated with untreated rats. Females continued on their respective diets through gestation and lactation. Offspring from the rats exposed for 102 days were held after weaning and fed a nontreated diet until they were 90-100 days old. They were

pair-mated within respective groups and their offspring held until weaning and checked for abnormalities. Reported mirex doses for males were 0 and 1.3-3.1 mg/kg-day. Reported doses for females were 0, 0.31-0.49 and 1.8-2.8 mg/kg-day.

Females exposed to 25 ppm for 45 days prior to mating and through gestation and lactation had significantly smaller litters (8.5 vs. 12.0 pups per litter, $p<0.05$) and survival of pups to weaning was significantly decreased (53% vs. 89%, $p<0.05$). Pups born to these females had a 33% incidence of cataracts compared to 0% in controls. Survival to weaning of pups born to females treated with 25 ppm for 102 days prior to mating and through gestation and lactation was significantly decreased (61% vs. 94% survival, $p<0.05$) and pups born to these females had a 46.2% incidence of cataracts compared to 0% in controls. These parameters were not significantly affected in pups born to females treated with 5 ppm. Litters of pups born to females that had not been treated with mirex were transferred at birth to foster mothers that had been fed diets containing 0 or 5 ppm mirex for 73 days. Survival to weaning of pups transferred to treated females was significantly lower than pups transferred to untreated females (53.9% vs. 95.8%, $p<0.05$) and pups transferred to treated females had a significantly greater incidence of cataracts (37.5% vs. 0%, $p<0.05$). This study identifies a FEL of 5 ppm (0.31- 0.49 mg/kg-day).

Groups of 10 male and 20 female Sprague-Dawley rats (92 g initial body weight) were fed diets containing mirex (reported purity >98%) at 0, 5, 10, 20 or 40 ppm for 13 weeks prior to mating, during a 2-week mating period and through gestation and lactation (Chu et al., 1981b). Mated pairs were exposed to the same dietary levels; males were discarded from the study after mating. Estimated mirex doses for females based on U.S. EPA (1987) and reported average initial body weight of 92 g and average weight gain of controls of 195 g were: 0.5, 1, 2 and 4 mg/kg-day. Toxicity in females was assessed from a complete hematologic analysis (hemoglobin, total and differential counts, bone marrow smear), serum chemistry (electrolytes, protein, enzymes, cholesterol, uric acid, bilirubin), measurements of liver aniline hydroxylase and aminopyrine demethylase activities; and histologic examination of adrenal gland, bone marrow, brain, bronchi, trachea and lungs, esophagus, eye, heart, kidney, liver, lymph nodes (mesenteric and mediastinal), ovaries, pancreas, parathyroid, peripheral nerves, pituitary, salivary glands, skeletal muscle, small and large intestine, skin, spleen, stomach, thoracic aorta, thymus, thyroid and uterus. The same histologic examinations (including prostrate, seminal vesicles and testes of males) and measurements of hepatic microsomal enzymes) were performed on pups that survived to 21 days. Histologic examinations revealed lesions of the liver and thyroid in adult females at all dose levels (at and above 5 ppm). Lesion incidences in the 5 ppm dose group were as follows: liver, 10/10 (100%) vs. 2/13 (15%) in controls; and thyroid, 6/10 (60%) vs. 2/13 (15%) in controls. Hepatic lesions included fatty infiltration and cytoplasmic vacuolization and anisokaryosis. Thyroid lesions included follicular epithelial thickening and collapse. Similar types of lesions of the liver and thyroid were observed in pups from treated females. Pups from treated females (at and above 5 ppm) had eye cataracts; incidences were 0/14 in controls and

4/10 (40%) in the 5 ppm group. Survival of pups to 21 days was significantly decreased (70% vs. 97% controls, $p<0.001$) in the 40 ppm dose group. This study identifies a LOAEL of 5 ppm (0.5 mg/kg-day) and a FEL of 40 ppm.

Chernoff et al. (1979a) fed diets containing 0 or 25 ppm mirex (reported purity >98%) to pregnant CD (Charles River) rats (numbers and initial weights not specified) from day 4 of gestation through day 34 post-parturition. Groups of 17-24 litters of pups were cross-fostered to yield four exposure groups: no exposure, prenatal exposure, postnatal exposure and perinatal exposure (prenatal and postnatal exposure). Estimated mirex doses based on U.S. EPA (1987) and assumed average body weight of 250 g were 0 and 2.2 mg/kg-day. Exposure to mirex during gestation resulted in a significant increase in the incidence of fetal mortality (14% vs. 3% in controls, $p<0.01$). Perinatal and postnatal exposure resulted in significantly decreased pup survival to 8 days (77% and 74%, respectively, vs. 94% in controls, $p<0.05$) and significantly increased incidence of cataracts and other lens changes (31% and 43%, respectively, vs. 0% in controls, $p<0.001$). Other studies by the same investigators have demonstrated cataractogenicity of postnatal exposure to mirex in Sherman and Long-Evans rats and CD-1 mice (Chernoff et al., 1979b; Scotti et al., 1981). This study (Chernoff et al., 1979a) identifies a FEL of 25 ppm (2.2 mg/kg-day).

Groups of 10-37 pregnant female CD rats were administered mirex (technical grade, reported purity >98%) in corn oil by oral gavage; doses were 0, 5, 7, 9.5, 19 or 38 mg/kg-day on days 7-16 of gestation (Chernoff et al., 1979b). Animals were killed on day 21 of gestation, resorption sites and live fetuses were recorded, and live fetuses were examined for external and skeletal abnormalities. The incidence of edematous live fetuses was significantly elevated at doses at and above 7 mg/kg-day ($p<0.05$); incidences were as follows: control, 0%; 5 mg/kg-day, 5.8%; 7 mg/kg-day, 27.3%; 9.5 mg/kg-day, 22.9%; 19 mg/kg-day, 74.7%; and the number of sternal ossification centers was significantly decreased at doses at and above 7 mg/kg-day ($p<0.05$). Fetal mortality was significantly increased at doses at and above 19 mg/kg-day ($p<0.001$); control, 4%; 19 mg/kg-day, 65.1%; and 38 mg/kg-day, 100%. Maternal weight gain was significantly decreased at doses at and above 9.5 mg/kg-day, and maternal liver/body weight ratios were significantly increased at doses at and above 7 mg/kg-day. This study identifies a NOAEL of 5 mg/kg-day, a LOAEL of 7 mg/kg-day, and an FEL of 19 mg/kg-day.

Groups of 5 or 6 pregnant CD rats were administered 0, 6 or 12 mg/kg-day mirex (purity not specified) by oral gavage on days 7-16 of gestation (Kavlock et al., 1982). Dams were killed on day 21 of gestation and fetuses examined for external abnormalities. The following evaluations were made on fetuses that had no external abnormalities: body, brain, kidney, liver and lung weights; total DNA and protein in brain; total dipalmitoyl phosphatidylcholine and sphingomyelin in lung; total glycogen in liver; and total protein and alkaline phosphatase in kidney. External abnormalities observed at and above 6 mg/kg-day included edema, ectopic

gonads and hydrocephaly. Brain and liver weights adjusted for fetal body weight were significantly decreased in the 6 and 12 mg/kg-day dose groups. Total liver glycogen, total kidney protein and total kidney alkaline phosphatase, all adjusted for fetal body weight, were significantly decreased in the 6 and 12 mg/kg-day groups ($p<0.05$). This study identifies a LOAEL of 6 mg/kg-day.

Groups of 20 mated female Wistar rats were administered mirex (reported purity 98%) in corn oil by oral gavage on days 6-15 of gestation; doses were 0, 1.5, 3, 6 or 12.5 mg/kg-day (Khera et al., 1976). Rats were killed on day 22 of gestation and fetuses were examined for external and skeletal abnormalities. Doses at and above 3 mg/kg-day increased the incidence of resorptions (7.4 vs. 3.7% in controls). Doses at and above 6 mg/kg-day significantly increased fetal mortality and the incidence of visceral anomalies ($p<0.05$). These included edema, scoliosis, runts and short tail at 6 mg/kg-day; and these anomalies in addition to cleft palate and heart defects at 12.5 mg/kg-day. Doses at and above 3 mg/kg-day decreased the incidence of pregnancy of survivors 22 days after mating. Doses at and above 6 mg/kg-day increased maternal mortality. This study identifies a NOAEL of 1.5 mg/kg-day, a LOAEL 3 mg/kg-day and an FEL of 6 mg/kg-day.

Groups of 20 male Wistar rats were administered mirex (reported purity 98%) in corn oil by oral gavage for 10 consecutive days; doses were 0, 1.5, 3 or 6 mg/kg-day (Khera et al., 1976). Following dosing, 14 mating trials were conducted in which each treated male was paired with two untreated virgin females for 5 days. Females were killed 13-15 days after pairing and viable embryos, deciduomas and corpora lutea were recorded. At a dose of 6 mg/kg-day, weight gain in the male rats was decreased and one male rat died, and the incidence of pregnancies (% of matings) resulting from the first trial (but not subsequent trials) was significantly decreased ($p<0.05$). This study identifies a 6 mg/kg-day LOAEL.

Groups of pregnant Long-Evans rats (group size not specified) were administered mirex (commercial grade, purity not specified) in peanut oil by oral gavage at doses of 0 or 0.25 mg/kg-day on days 15.5-21.5 of gestation (Grabowski, 1983). Pups from dams exposed to mirex had abnormal electrocardiograms, including significantly prolonged PR and QT intervals ($p<0.03$). In other studies with doses at and above 5 mg/kg-day, prolongation of the PR interval correlated with edema and progressed to first and second degree heart block (missed ventricular beat) (Grabowski and Payne, 1980; 1983a,b). This study (Grabowski, 1983) identifies a LOAEL of 0.25 mg/kg-day.

Groups of 100-108 male and female Swiss Balb/c and CFW mice were fed diets containing 0 or 5 ppm technical grade mirex (reported purity 99%) for 30 days prior to pairing and for 90 days after pairing (Ware and Good, 1967). The study of Balb/c mice was repeated. Estimated mirex doses based on U.S. EPA (1987) and assumed average body weight of 0.038 kg were 0 and 0.84 mg/kg-day. Numbers of litters, litter size, sex ratio and mortality were assessed. Mirex

significantly increased parent mortality of Balb/c mice ($p<0.05$) but not CFW mice. Fecundity (young per producing pair) was significantly less in CFW mice exposed to mirex compared to controls ($p<0.05$). Fecundity and litter size were significantly less in Balb/c mice compared with controls ($p<0.05$) in one study; however, these effects were not corroborated in a duplication of the study. This study identifies an FEL of 0.84 mg/kg-day.

Groups of 24 or 25 pregnant CD-1 mice were administered 0 or 7.5 mg/kg-day mirex (in corn oil, purity not specified) by oral gavage on days 8-12 of gestation (Chernoff and Kavlock, 1982). Dams were allowed to give birth and litters were counted and weighed on postnatal days 1 and 3. Body weights and survival of pups in the mirex group were significantly decreased on postnatal days 1 and 3 compared to the control group ($p<0.05$). This study identifies an FEL of 7.5 mg/kg-day.

I.A.5. Confidence in the Oral RfD

Study — High
Database — High
RfD — High

Confidence in the study can be considered high to medium. NTP (1990) used an adequate number of animals and examined all tissues identified as potential targets in other studies. Confidence in the database can be considered is high to medium. Several good quality chronic, subchronic and developmental/reproductive studies have been conducted, although the database is lacking a rodent multi-generation study. Reflecting high to medium confidence in the study and the database, confidence in the RfD can be considered high to medium.

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — This assessment is not presented in any existing U.S. EPA documentation.

Other EPA Documentation — U.S. EPA, 1987

Agency Work Group Review — 06/24/1986, 04/15/1987, 06/24/1992

Verification Date — 06/24/1992

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Mirex
CASRN — 2385-85-5

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Mirex
CASRN — 2385-85-5

Not available at this time.

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Mirex
CASRN — 2385-85-5

VI.A. Oral RfD References

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VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — Mirex
CASRN — 2385-85-5

Date	Section	Description
08/01/1992	I.A.	Withdrawn; new oral RfD verified (in preparation)
10/01/1992	I.A.	Oral RfD summary replaced; RfD changed

VIII. Synonyms

Substance Name — Mirex
CASRN — 2385-85-5
Last Revised — 09/30/1987

- 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-
- Mirex
- NCI-C06428
- PERCHLORODIHOMOCUBANE
- PERCHLOROPENTACYCLO(5.2.1.0(sup 2,6).0(sup 3,9).0(sup 5,8))DECANE
- PERCHLOROPENTACYCLODECANE