TECHNICAL REPORT DATA (Please read Instructions on the reverse before completing)		
1. REPORT NO. EPA/600/8-89/089	2.	3. RECIPIENT'S ACCESSION NO PB90-142415/AS
4. TITLE AND SUBTITLE Updated Health Effects Assessment for Chlordane		5. REPORT DATE 6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)		8. PERFORMING ORGANIZATION REPORT NO
9. PERFORMING ORGANIZATION NAME AND ADDRESS		10. PROGRAM ELEMENT NO. 11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268		13. TYPE OF REPORT AND PERIOD COVERED 14 SPONSORING AGENCY CODE EPA/600/22
15 SUPPLEMENTARY NOTES		

16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

17. KEY WORDS AND DOCUMENT ANALYSIS		
a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
18. DISTRIBUTION STATEMENT Public	19. SECURITY CLASS (This Report) Unclassified 20. SECURITY CLASS (This page) Unclassified	21. NO. OF PAGES 22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

EPA/600/8-89/089
July, 1988

HEALTH EFFECTS ASSESSMENT FOR CHLORDANE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
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This document has been reviewed in accordance with the U.S. Environmental Protection Agency's peer and administrative review policies and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with chlordane. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1987. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria for Chlordane. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-027. NTIS PB81-117384.

U.S. EPA. 1985a. Drinking Water Criteria Document on Heptachlor, Heptachlor Epoxide and Chlordane. Prepared by Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. Final Draft.

U.S. EPA. 1985b. Integrated Risk Information System (IRIS). Reference dose (RfD) for oral exposure for chlordane. On line. Verification date 12/18/85. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1986a. Carcinogenicity Assessment of Chlordane and Heptachlor/Heptachlor Epoxide. Prepared by the Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, DC. EPA-600/6-87-004. Final report.

U.S. EPA. 1987. Integrated Information System (IRIS). Risk estimate for carcinogenicity for chlordane. Online. Verification date 4/1/87. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RFD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1984).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Data concerning chlordane exposure and cancer in human populations are limited and equivocal. Data concerning carcinogenicity in experimental animals following inhalation exposure are lacking.

Three oral cancer bioassays have shown an increased incidence of hepatocellular carcinoma in chlordane-exposed mice and rats (IRDC, 1973; NCI, 1977; RIASBT, 1983a,b). U.S. EPA (1986a) calculated potency estimates for mice of each sex in the IRDC (1973) and NCI (1977) studies, and recommended using the geometric mean of these four values, 1.3 $(mg/kg/day)^{-1}$, as the human q_1^* for oral exposure to chlordane. U.S. EPA (1986a) also estimated unit risk for inhalation from the oral q_1^*, which suggests that carcinogenic potency is equivalent by both routes of exposure. Following the lead of U.S. EPA (1986a), the oral q_1^* of 1.3 $(mg/kg/day)^{-1}$ is also adopted as the estimate of carcinogenic potency for humans exposed by inhalation. These values have been verified by CRAVE and are available on IRIS (U.S. EPA, 1987).

ACKNOWLEDGEMENTS

TECHNICAL REVIEW

Scientists from the following U.S. EPA offices provided review comments for this document series:

Office of Air Quality Planning and Standards
Office of Solid Waste
Office of Pesticide Programs and Toxic Substances
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LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
bw	Body weight
CNS	Central nervous system
CS	Composite score
DNA	Deoxyribonucleic acid
K_{oc}	Soil sorption coefficient standardized with respect to organic carbon
K_{ow}	Octanol/water partition coefficient
LD_{50}	Median lethal dose
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect level
MED	Minimum effective dose
NOEL	No-observed-effect level
ppm	Parts per million
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_S	Subchronic reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
RNA	Ribonucleic acid
SGOT	Serum gutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of chlordane (CAS No. 57-74-9 for mixture; 5103-74-2 for cis isomer; 5103-71-9 for trans isomer) are as follows:

Chemical class:	pesticide (insecticide)
Molecular weight:	410 (Windholz, 1983)
Vapor pressure:	1×10^{-5} mm Hg at 25°C (IARC, 1979)
Water solubility:	9 µg/ℓ at 25°C for technical grade and 56 µg/ℓ for cis:trans (75:25) chlordane (Verschueren, 1983; Deichmann, 1981)
Log K_{ow}:	3.32 (Rao and Davidson, 1982)
BCF:	4700 for aquatic organisms with 1% lipid content (U.S. EPA, 1980a)
K_{oc}:	1720 [estimated, based on log K_{ow} value and linear regression equation, log K_{oc} = 1.029 log K_{ow} -0.18 (Lyman et al., 1982)]
Half-life in soil:	2.5-17 years (Sanborn et al., 1977)

In the atmosphere, chlordane is expected to exist in both the particulate and vapor phases. It was estimated that 96% of the airborne reserve of chlordane exists in the sorbed state (Tucker and Preston, 1984). Detection of chlordane in rainwater (Sanborn et al., 1977) and on airborne particulate matter (Bidleman et al., 1986) indicates that this compound may be removed from the atmosphere by wet or dry deposition. Information in the literature is insufficient to estimate the overall half-life of chlordane in the atmosphere.

Processes likely to determine the fate of chlordane in aquatic media are volatilization, sorption to sediments and bioaccumulation. Based on measured chlordane to oxygen reaeration ratios in water (Atlas et al., 1982)

and typical oxygen reaeration coefficients for various water bodies (Lyman et al., 1982), the volatilization half-lives of chlordane from a pond (2 m deep), river (3 m deep) and lake (5 m deep) have been estimated to be 18-26, 3.6-5.2 and 14.4-20.6 days, respectively. Sorption to suspended solids and sediments may significantly diminish the importance of volatilization. The presence of chloroform in sediment core samples (Bopp et al., 1982) suggests that this compound will be very persistent in the adsorbed state in water.

Sanborn et al. (1977) reported that the mean degradation rate of chlordane in soil under field conditions ranges from 4.05-28.33%/year. Field tests, soil column leaching tests and K_{oc} estimations suggest that chlordane would be immobile or slightly mobile in soil (Wilson and Oloff, 1973). Detection of this compound in New Jersey groundwaters with a detection frequency of 40%, however, indicates that leaching can occur (Page, 1981).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Although quantitative data regarding the absorption of chlordane from the gastrointestinal tract of animals and humans are not available, the toxic effects observed after chlordane ingestion indicate that at least some absorption occurs. One male and one female Sprague-Dawley rat were given a single dose (0.05, 0.2 or 1.0 mg/kg) of [^{14}C]-HCS-3260, which is a highly purified chlordane preparation containing the cis- and trans-chlordane isomer in a 3:1 ratio (Barnett and Dorough, 1974). Within 7 days after treatment, 6% of the administered radioactive label was found in the urine of the female and 2% in the urine of the male. When cis- and trans-chlordane were given separately to female rats, 8.5 and 5%, respectively, of the administered radioactive label was eliminated in the urine; however, 33% of the administered radioactive label was excreted in the urine and 21% in the feces of a male rabbit within 2 days of receiving 25 ppm [^{14}C]-HCS-3260 in the diet. In cases where children (Curley and Garrettson, 1969; Aldrich and Holmes, 1969) have ingested chlordane, measurable quantities of chlordane have appeared in serum and fat several hours after the poisonings.

2.2. INHALATION

A peak concentration of radioactivity (~4% of the administered dose) appeared in the blood of Sprague-Dawley rats within 5 minutes of intratracheal administration of an unspecified amount of ^{14}C-chlordane (11,500 dpm/μg) in 20 μℓ ethanol as an aerosol spray (Nye and Dorough, 1976).

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. **Oral.** Ambrose et al. (1953a,b) fed groups of three to five rats food containing technical grade chlordane at levels from 10-1280 ppm for 400 days (Table 3-1). Increased mortality was observed in the 640 and 1280 ppm groups and retarded growth was observed in all animals at ≥320 ppm. Significantly enlarged livers and liver pathology were found in male and female rats fed chlordane at ≥80 ppm and liver pathology was occasionally found in male rats fed 40 ppm.

DeLong and Ludwig (1954) treated an unspecified number of male and female rats with technical grade chlordane administered in the diet. The dose level of chlordane, calculated from amount of food consumption, was 1.2 mg/kg/day. After 5 months, no histopathological damage to lungs, heart, stomach, liver, kidneys, spleen or testes was reported. One treated rat had a kidney adenocarcinoma believed to be unrelated to chlordane exposure.

Shain et al. (1977) fed 19.5 mg/kg/day of technical grade chlordane to male Sprague-Dawley rats for 90 days. A randomly selected subgroup of 12 rats had significantly depressed body weight gain; another subgroup of 24 rats did not have depressed body weight gain. The purpose of this study was to investigate the effects of chlordane on the prostate gland. Nuclear, but not cytoplasmic, androgen binding sites were significantly increased, and RNA and DNA content and ventral prostate protein content were significantly decreased in the chlordane-treated rats.

Benign proliferative lesions in the liver were reported in 2% of the low dose (25 ppm) and 7% of the higher dose (50 ppm) groups of mice fed dietary chlordane for at least 36 weeks (Becker and Sell, 1979).

TABLE 3-1

Effects of Subchronic Oral Chlordane Exposure

Dose or Exposure (mg/kg diet)	Duration of Treatment	Duration of Experiment	Species/ Strain	Sex	Number Treated	Effects	Reference
0 10 20 40 80 160 320 640 1280	400 days	400 days	rat/NR	M/F M/F M/F M/F M/F M/F M/F M/F M/F	3-5	Dose-related growth retardation; enlarged livers and liver pathology at ≥80 mg/kg; occasional liver pathology in males at 40 mg/kg; increased mortality at ≥640 mg/kg	Ambrose et al., 1953a,b
0 1.2 mg/kg bw	5 months	5 months	rat/NR	M/F M/F	NR	No effects were reported.	DeLong and Ludwig, 1954
0 19.5 mg/kg bw	90 days	90 days	rat/ Sprague-Dawley	M	42 42	Decreased body weight gain. No significant weight changes in testes or ventral prostate. See text for additional information.	Shain et al., 1977
0 25 50	≥36 weeks	≥36 weeks	mouse/ C57BC 6N	M	200 NR NR	Benign proliferative lesions were reported to occur in the liver in the low dose (2%) and high dose (7%) groups.	Becker and Sell, 1979

NR = Not reported

3.1.2. **Inhalation.** Velsicol Chemical Corporation (1984) exposed Wistar rats and cynomolgus monkeys to 0, 0.1, 1.0 or 10 mg/m³ chlordane for 90 days. The exposure schedule was not reported in the secondary source from which these data were taken. There were no effects on mortality, body weight, food consumption, pulmonary function, hematological parameters or urinalysis parameters in either species. Observed effects included increased organ weights (brain, liver, kidney and thyroid in rats) and adaptive liver changes in both rats and monkeys. U.S. EPA (1986a) concluded that this study defined a NOEL of 0.1 mg/m³ and a LOEL of 1.0 mg/m³ in rats and monkeys.

3.2. CHRONIC

3.2.1. Oral. Ingle (1952) treated groups of 20 rats/sex with chlordane (purity not specified) in their food at a dose range of 5-300 mg/kg diet for 2 years (Table 3-2). Extensive histological data were reported, but organ and body weight data were not included. After 80 weeks of exposure at a dose level of 30 mg/kg diet, the rats developed tremors and showed "slight" liver damage. At dose levels of $\geq$150 mg/kg diet, liver and kidney hypertrophy were detected, and histopathological lesions were reported in the liver, kidney, lung, myocardium, adrenal gland and spleen.

In the IRDC (1973) study reviewed by Epstein (1976), groups of 100 mice/sex were exposed to 5, 25 and 50 mg of analytical grade chlordane/kg diet for 18 months. The female mice appeared to be more sensitive than the male mice in this study, as indicated by the increased liver weights accompanied by hepatocytomegaly at a dose level of 5 mg/kg chlordane in the diet. Although hepatocytomegaly was present in male mice at this dose level, increased liver weight was not observed in males until they were exposed to the 25 mg/kg dose level. The highest dose level in this study (50 mg/kg diet) produced increased mortality in both sexes.

TABLE 3-2

Effects of Chronic Oral Chlordane Exposure

Dose or Exposure (ppm)	Duration of Treatment	Length of Experiment	Species/ Strain	Sex	Number Treated	Effects	Reference
5 10 30 150 300	up to 2 years	2 years	rat/ Osborne-Mendel	M/F M/F M/F M/F M/F	20/20 20/20 20/20 20/20 20/20	Occasional hypertrophy of hepatocytes occurred at 5 mg/kg diet, but no other effects were observed. Slight tremors were present after 80 weeks at 30 mg/kg diet. Decreased growth rate, anorexia and tremors were seen in animals treated with 150 mg/kg diet; liver and kidney hypertrophy was present, as well as moderate to marked kidney, lung, myocardial, adrenal and spleen damage. At 300 mg/kg diet the animals died earlier and had severe liver, kidney, heart, adrenal, lung, myocardial and spleen damage.	Ingle, 1952
0 5 25 50	18 months	18 months	mouse/ CD-1	M/F M/F M/F M/F	33/45 55/61 52/50 39/37	Increased liver weight was significant at all dose levels for females and at 25 and 50 mg/kg diet for the males after 18 months of exposure. Survival was decreased for both males and females at 50 mg/kg diet. Hepatocytomegaly was observed in all treatment groups in both sexes.	Epstein, 1976
0 29.9 56.2	80 weeks	91 weeks	mouse/ B6C3F1	M M M	18 48 49	High-dose males and females had tremors at 20 weeks. Male mortality rate was significantly increased compared with controls in both the high- and low-dose treatment groups. No effect on mortality was seen in the females.	NCI, 1977
0 30.1 63.8	80 weeks	91 weeks	mouse/ B6C3F1	F F F	19 47 49		
0 203.5 407.0	80 weeks	109 weeks	rat/ Osborne-Mendel	M M M	6 34 31	Decreased body weights were seen in high-dose males and both dose levels of females. Tremors occurred in the high-dose females at 44 weeks. Dose-related increased mortality occurred in the females but not males.	NCI, 1977
0 120.8 241.5	80 weeks	109 weeks	rat/ Osborne-Mendel	F F F	10 43 32		
0 1 5 12.5	2 years	2 years	mouse/ICR	M/F	NR	Hepatocellular swelling and necrosis, increased liver weight, increased SGOT and SGPT at 5 and 12.5 ppm. No effects at 1 ppm.	Velsicol Chemical Corporation, 1983a

TABLE 3-2 (cont.)

)ose or :xposure (ppm)	Duration of Treatment	Length of Experiment	Species/ Strain	Sex	Number Treated	Effects	Reference
0 1 5 25	130 weeks	130 weeks	rat/ Fischer 344	M/F	NR	Increased incidence of hepatocellular swelling in treated males at all doses.	Velsicol Chemical Corporation, 1983b
0.3 3.0 15.0 30.5	2 years	NR	dog	NR	NR	A review panel for WHO/FAO indicated that 3 mg/kg diet was a NOEL.	Wazeter, 1968

R = Not reported

In the NCI (1977) study, both rats (50/sex/group) and mice (50/sex/group) were maintained on diets containing chlordane (71.7% cis, 23.1% trans, 0.3% heptachlor, 0.6% nonachlor, 1.1% hexachlorocyclopentadiene and 0.28% chlordene) for 80 weeks, followed by an observation period. Because the dose levels were changed during the experiment, the dosage listed in Table 3-2 is a TWA as calculated by the NCI (1977). Rats received higher dose levels in mg/kg bw than mice in this study. Female rats appeared to be more sensitive than male rats, as evidenced by increased mortality in females in both treated groups. High-dose females, but not males, had tremors after 44 weeks of treatment. In mice, a dose-related significant increase in mortality occurred in both treated groups of males.

Velsicol Chemical Corporation (1983a) fed ICR mice diets containing 0, 1, 5 or 12.5 ppm technical grade chlordane, resulting in approximate dosages of 0, 0.15, 0.71 or 1.79 mg/kg bw/day for 2 years. Liver effects, including increased SGOT and SGPT, hepatocellular swelling and necrosis, and increased liver weight occurred in the 5 and 12.5 ppm groups. No effects were observed at 1 ppm.

In a Velsicol Chemical Corporation (1983b) study, Fischer 344 rats were fed diets containing 0, 1, 5 or 25 ppm chlordane (isomers not specified) (~0, 0.05, 0.25 or 1.25 mg/kg bw/day) for 130 weeks. Liver weights of females receiving 5 or 25 ppm were increased at 26 and 52 weeks but not at 130 weeks. Male liver weights were increased at 130 weeks but not at 26 and 52 weeks. There was an increased incidence of hepatocellular swelling and necrosis in treated males. The 1 ppm level was considered a LOEL for liver effects in male rats.

In a study by Wazeter (1968), dogs exposed orally to chlordane (type not specified) developed enlarged livers with histopathological changes.

A scientific review panel of WHO/FAO examined this study and concluded that a dose of 3 mg/kg diet was a NOEL (Vettorazzi, 1975). No further information was available.

3.2.2. Inhalation. Pertinent data regarding the chronic toxicity of inhaled chlordane were not located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Ingle (1952) investigated the effect of chlordane-contaminated diets at dose levels of 5, 10, 30, 150 and 300 ppm on the fetus in utero and on the newborn while nursing. Two female Osborne-Mendel rats from each dose level were mated after 24 and 48 weeks of chlordane exposure. No effect on fetal mortality and health or on litter size was reported. After birth, three pups remained with their chlordane-treated dams, while three others were placed with foster dams that had not been exposed to chlordane. Pups nursed by dams exposed to chlordane levels of 150 and 300 mg/kg diet developed toxic effects, such as hyperexcitability, tremors, decreased body weight and death. Toxic effects developed in the pups that were nursed by dams treated with chlordane-contaminated ($\geq$150 ppm) diets, whether or not they had been exposed in utero; however, the pups whose mothers were exposed to high levels of chlordane ($\geq$150 ppm) during pregnancy did not develop toxic effects when they were nursed by foster dams exposed to low levels (5, 10 and 30 ppm) of chlordane.

Deichmann and Keplinger (1966) reported decreased viability of offspring of mice that ate a diet containing 100 ppm chlordane for 4 months. Chlordane was also found to decrease fertility in male and female rats (Ambrose et al., 1953a) and in female mice (Welch et al., 1971). There was decreased survival among offspring of rats fed 640 and 1280 ppm chlordane (Ambrose et al., 1953b).

3.3.2. Inhalation. Pertinent data regarding the teratogenicity or fetotoxicity of chlordane inhalation were not located in the available literature.

3.4. TOXICANT INTERACTIONS

Intraperitoneal injection of phenobarbital in neonatal Sprague-Dawley rats reduced the LD_{50} of chlordane injected intraperitoneally (Harbison, 1975). Pretreatment of rats with chlordane potentiated the hepatocellular necrosis produced by carbon tetrachloride (Stenger et al., 1975). Male weanling Wistar rats (Boyd and Taylor, 1969) on a low-protein diet (3.5%) for 28 days had a much lower LD_{50} (137 ± 30 mg/kg bw) than a group of weanling rats that ate commercial rodent food (LD_{50}=311 mg/kg bw).

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. No data were located in the literature search conducted for purposes of this document.

4.1.2. Inhalation. Most inhalation exposure to chlordane occurs as work-related exposure either in the manufacturing or application of chlordane. Exposure to several chemicals in addition to chlordane often confounds evaluation of the human data. Aplastic and refractory megoblastic anemia, as well as acute stem cell, acute lymphoblastic and acute myelomonocytic leukemia, have been reported to result from chlordane exposure, primarily through inhalation (Infante et al., 1978; Klemmer et al., 1977; Furie and Trubowitz, 1976). A retrospective mortality study of 1403 white male workers employed for >3 months in the manufacture of chlordane and heptachlor indicated that the observed incidences of all types of cancer except lung cancer were less than expected (Wang and MacMahon, 1979). The increased incidence of lung cancer was not statistically significant. U.S. EPA (1986a) concluded that insufficient population size, exposure duration and follow-up periods, exposure characterization, confounding factors such as other chemical exposures and smoking in this and other studies (Alvarez and Hyman, 1953; Ditraglia et al., 1981; Fishbein et al., 1964; Princi and Spurbeck, 1951; Klemmer et al., 1977) preclude definitive conclusions regarding the effects of human occupational exposure. The studies as a group were considered inadequate epidemiologic evidence.

4.2. BIOASSAYS

4.2.1. Oral. In the unpublished report by the IRDC (1973) reviewed by Epstein (1976), the liver lesions produced during chlordane treatment were originally diagnosed as preneoplastic lesions. A subsequent rediagnosis of

hepatocellular carcinoma was made by Reuber (1978) and other pathologists (Epstein, 1976). The results of this reevaluation are presented in Table 4-1.

In the NCI (1977) study, the dose levels were changed during the experiment for both mice and rats. The TWA dose levels calculated by the NCI (1977) are given in Table 4-1. Mice in the NCI (1977) study developed a dose-related increase in the incidence of hepatocellular carcinoma. As in the IRDC study (Epstein, 1976), the male mice appeared more sensitive. Rats in the NCI (1977) study developed miscellaneous neoplasms; these occurred spontaneously in the control groups as well as in the treated rats. The only significant dose-related increase in tumors was in fibrous histiocytomas in male rats. These tumors were discounted as biologically significant since the incidence is known to vary greatly. The incidence of thyroid tumors was not consistently significant or dose-related. One of the two hepatocellular carcinomas occurred in a low-dose male; the other occurred in one of the pooled control animals.

In what appears to be another reporting of the Velsicol Chemical Corporation (1983a) study, RIASBT (1983a) described a study in which groups of 80 male and 80 female ICR mice were fed diets containing 0, 1, 5 or 12.5 ppm technical grade chlordane for 24 months. There was a significant ($p<0.001$) increase in the incidence of hepatocellular adenoma and hemangioma of the liver in 12.5 ppm males dying between 19 and 24 months or at terminal sacrifice. There were no other treatment-related effects on tumor incidence.

In what appears to be another reporting of the Velsicol Chemical Corporation (1983b) study, RIASBT (1983b) described a study in which groups of 80 male and 80 female Fischer 344 rats were fed diets containing 0, 1, 5 or 25 ppm chlordane for 130 weeks. The incidence of hepatic adenomas was

TABLE 4-1

Carcinogenicity of Chlordane by Ingestion

Dose or Exposure (ppm)	Duration of Treatment	Length of Experiment	Species/ Strain	Sex	Number Examined	Target Organ	Tumor Incidence	Comments	Reference
0	550 days	550 days	mouse/	M	33	liver	3/33	Male mice appeared more	Epstein, 1976
5			CD-1	M	55		5/55	sensitive to the carcinogenic	
25				M	52		41/52	effects of chlordane in the	
50				M	39		32/39	liver.	
0	550 days	550 days	mouse/	F	45	liver	0/45		
5			CD-1	F	61		0/61		
25				F	50		32/50		
50				F	37		26/37		
0	80 weeks	91 weeks	mouse/	M	18	liver	2/18	Dose-related increase in the	NCI, 1977
29.9			B6C3F1	M	48		16/48	incidence of hepatocellular	
56.2				M	49		43/49	carcinoma was highly signifi-	
0	80 weeks	91 weeks	mouse/	F	19	liver	0/19	cant ($p<0.0001$) for both	
30.1			B6C3F1	F	47		3/47	males and females.	
63.8				F	49		34/49		
0	18 months	18 months	mouse/	NR	NR	liver	NR	Hepatocellular carcinomas in	Becker and
25			C57B1/6N				NR	27% of survivors (16 mice).	Sell, 1979
50							NR		
0	24 months	24 months	mouse/ICR	M	71	liver	20/71	Significant ($p<0.001$) increase	RIASBT, 1983a
1					71		17/71	in hepatocellular adenoma and	
5					72		30/72	hemangioma in the high-dose	
12.5					72		51/72	group.	
0	24 months	24 months	mouse/ICR	F	72	liver	1/72	No increase in hepatic tumors	RIASBT, 1983a
1					72		3/72	tumors among female mice.	
5					71		4/71		
12.5					72		2/72		
0	80 weeks	109 weeks	rat/	M	6	thyroid	0/6	Thyroid tumors included	NCI, 1977
203.5			Osborne-	M	34		6/34	follicular cell adenoma and	
407.0			Mendel	M	31		11/31	carcinoma as well as C-cell	
0	80 weeks	109 weeks	rat/	F	10	thyroid	3/10	adenoma and carcinoma. Only	
120.8			Osborne-	F	43		7/43	two hepatocellular carcinomas	
241.5			Mendel	F	32		16/32	were observed.	

TABLE 4-1 (cont.)

Dose or Exposure (ppm)	Duration of Treatment	Length of Experiment	Species/ Strain	Sex	Number Examined	Target Organ	Tumor Incidence	Comments	Reference
0	130 weeks	130 weeks	rat/ Fischer 344	M	64	liver	1/64	Increased incidence of hepato- cellular adenomas in high-dose males. Nonneoplastic lesions of liver at all doses.	RIASBT, 1983b
1					64		1/64		
5					64		3/64		
25					64		9/64		
0	130 weeks	130 weeks	rat/ Fischer 344	F	64	liver	0/64	Nonneoplastic liver lesions at high dose.	RIASBT, 1983b
1					64		2/64		
5					64		0/64		
24					64		0/64		

reported to be significantly ($p<0.001$) increased in males given 25 ppm (9/64 vs. 1/64 in controls). No other significant treatment-related effects on tumor incidence were found.

Becker and Sell (1979) correlated elevated levels of alpha-fetoprotein with primary hepatocellular carcinoma in mice exposed for 36 weeks to diets containing 25 or 50 ppm of chlordane. Hepatocellular carcinomas were found in 27% of the survivors.

Ambrose et al. (1953a) did not observe treatment-related tumors in groups of 3-5 rats fed diets containing 10-1280 ppm chlordane for 400 days. Liver lesions occurred at ≥80 ppm. Ingle (1952) exposed groups of 20 male and female Osborne-Mendel rats to diets containing 0, 5, 10, 30, 150 or 300 ppm chlordane for 2 years. "High toxicity" occurred at 150 and 300 ppm, but no treatment-related tumors were observed.

4.2.2. Inhalation. Pertinent data regarding the inhalation carcinogenicity of chlordane were not located in the available literature.

4.3. OTHER RELEVANT DATA

Chlordane did not cause reverse mutations in nine strains of Salmonella typhimurium or in two strains of Escherichia coli with or without metabolic activation (Probst et al., 1981; Gentile et al., 1982); unscheduled DNA synthesis in rat, mouse or hamster primary hepatocyte cultures (Probst et al., 1981; Maslansky and Williams, 1981); or dominant lethal mutations in CD-1 mice following intragastric or intraperitoneal administration (Arnold et al., 1977). Positive results were obtained for mitotic gene conversion assays in Saccharomyces cerevisiae only after metabolic activation (Gentile et al., 1982), and for unscheduled DNA synthesis in SV-40 transformed human fibroblasts only in the absence of metabolic activation (Ahmed et al., 1977).

U.S. EPA (1986a) summarized the available mutagenicity data for chlordane and concluded that chlordane is apparently not mutagenic in bacterial assays, in *in vitro* DNA repair assays and in mouse dominant lethal assays. Positive results were obtained in some but not all mammalian cell assays. The available data were insufficient, however, to assess definitively the mutagenic potential of chlordane.

4.4. WEIGHT OF EVIDENCE

U.S. EPA (1986a) reviewed the available information concerning chlordane carcinogenicity and concluded that a number of independent laboratory animal studies demonstrated that oral exposure to chlordane causes liver cancer in mice and rats. U.S. EPA (1986a) classified chlordane as a probable human carcinogen, Group B2, using the Agency's guidelines for carcinogen risk assessment (U.S. EPA, 1986b).

5. REGULATORY STANDARDS AND CRITERIA

A tolerance of 0.3 mg/kg has been established by the U.S. EPA (1976) for residues of chlordane in or on ~50 fruit and vegetable crops. The ACGIH (1986) has adopted a TLV of 0.5 mg/m^3 and an STEL of 2 mg/m^3. OSHA (1985) lists a PEL of 0.5 mg/m^3. U.S. EPA (1985b) calculated an RfD for oral exposure for chlordane based on the Velsicol Chemical Corporation (1983b) 30-month study in rats. The RfD was calculated from the LOAEL of 1 ppm in the diet (0.045 mg/kg/day), which caused a significant increase in incidence of hepatocellular necrosis in males. U.S. EPA (1985b) applied an uncertainty factor of 1000 to this LOAEL to derive an RfD of 5×10^{-5} mg/kg/day.

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

Chlordane is a chemical for which a carcinogenic potency has been calculated and that may be carcinogenic in humans. Based upon the guidelines for this document series, it is inappropriate to calculate an oral or inhalation RfD_S for chlordane.

6.2. REFERENCE DOSE (RfD)

Chlordane is a chemical for which a carcinogenic potency has been calculated and that may be carcinogenic in humans. Calculation of an RfD is therefore outside the scope of this document series. Existing approaches are described in Chapter 5.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. Chlordane treatment was associated with significant increases in hepatocellular carcinomas in treated mice of both sexes in the IRDC (1973) and NCI (1977) studies. The RIASBT (1983b) study also showed a significant increase in liver tumors in treated male rats compared with controls. The Office of Pesticide Programs is currently in the process of reevaluating this study. U.S. EPA (1986a) fitted the linearized multistage model to each of these data sets to obtain estimates of carcinogenic potency. These potency estimates (human q_1^* values) are presented in Table 6-1. The geometric mean of the potency estimates for mice was 1.3 $(mg/kg/day)^{-1}$, which was consistent with the potency estimate from the single rat data set, 1.1 $(mg/kg/day)^{-1}$. U.S. EPA (1986a) concluded that mice were the more sensitive tested species, and because humans may be as sensitive as the most sensitive animal species, adopted 1.3 $(mg/kg/day)^{-1}$ as the potency estimate for the general population. This value has been verified by CRAVE and is available on IRIS (U.S. EPA, 1987).

TABLE 6-1

Human Potency Estimates for Chlordane*

Species/Strain	Sex	Tumor Site/Type	Potency $(mg/kg/day)^{-1}$	Reference
Mice/CD-1	M	liver, carcinoma	4.74	IRCD, 1973
Mice/CD-1	F	liver, carcinoma	2.98	IRDC, 1973
Mice/B6C3F1	M	liver, carcinoma	0.76	NCI, 1977
Mice/B6C3F1	F	liver, carcinoma	0.25	NCI, 1977
Rats/F344	M	liver, adenoma and carcinoma	1.11	RIASBT, 1983b

*Source: U.S. EPA, 1986a

6.3.2. Inhalation. Inhalation data were not available for estimation of carcinogenic potency; however, U.S. EPA (1986a) used the potency estimate for oral exposure to calculate a unit risk in air. Thus, U.S. EPA (1986a) supports the position that chlordane is equally carcinogenic by either the oral or inhalation routes. Therefore, the oral q_1^* of 1.3 $(mg/kg/day)^{-1}$ is adopted as the inhalation q_1^* for the purposes of this document. This value has been verified by CRAVE and is available on IRIS (U.S. EPA, 1987).

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APPENDIX

Summary Table for Chlordane

	Species	Experimental Dose/Exposure	Effect	q_1^*	Reference
Inhalation					
RfD_S (formerly AIS)				ND	
RfD (formerly AIC)				ND	
Carcinogenic potency	mice	several oral studies	hepatocellular carcinoma	1.3 $(mg/kg/day)^{-1}$	IRDC, 1973; NCI, 1977; U.S. EPA, 1986a
Oral					
RfD_S (formerly AIS)				ND	
RfD (formerly AIC)				ND	
Carcinogenic potency	mice	several oral studies	hepatocellular carcinoma	1.3 $(mg/kg/day)^{-1}$	IRDC, 1973; NCI, 1977; U.S. EPA, 1986a

ND = Not derived