# Chlordane (Technical); CASRN 12789-03-6

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 Chlordane

**File First On-Line 03/31/1987**

| Category (section) | Assessment Available? | Last Revised |
|---|---|---|
| **Oral RfD (I.A.)** | yes | 02/07/1998 |
| **Inhalation RfC (I.B.)** | yes | 02/07/1998 |
| **Carcinogenicity Assessment (II.)** | yes | 02/07/1998 |

## I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

### I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Chlordane (Technical)
CASRN — 12789-03-6
Last Revised — 02/07/1998

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 |
|---|---|---|---|---|
| **Hepatic Necrosis**<br><br>**Mouse 104-week oral study**<br><br>**Khasawinah and Grutsch, 1989a** | 0.15 mg/kg-day<br><br>NOAEL: 0.15 mg/kg-day<br>LOAEL: 0.75 mg/kg-day | 300 | 1 | 5E-4 mg/kg-day |

*Conversion Factors and Assumptions 1 ppm = 0.15 mg/kg Bw-day (assumed mouse food consumption).

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

Khasawinah, A.M. and J.F. Grutsch. 1989a. Chlordane: 24-month tumorigenicity and chronic toxicity test in mice. Reg. Toxicol. Pharmacol. 10: 244-254.

Velsicol Chemical Corporation. 1983. Twenty-four month chronic toxicity and tumorigenicity test in mice by chlordane technical. Unpublished study by Research Institute for Animal Science in Biochemistry and Toxicology, Japan. MRID No. 00144312, 00132566. Available from U.S. EPA.

ICR mice (80/sex/group) were fed 0, 1, 5, or 12.5 ppm technical chlordane in the diet for 104 weeks. The average doses corresponded to 0, 0.15, 0.75, and 1.875 mg/kg-day, respectively. Hematology, biochemistry, urinalysis, organ weights, and pathology of major tissues and organs were assessed on all animals that died during the study and on all survivors at week 104.

Exposure-related effects were restricted to the liver. Statistically significant increased absolute and relative liver weights were seen in high-dose males (200 and 203%) and females (144 and 129%) compared to control values at the end of the study. Absolute but not relative liver

weight also was elevated significantly ($p < 0.05$) in the females exposed to 1 (22%) and 5 ppm (14%). Statistically significant increased incidences over controls were found for hepatocellular swelling (hypertrophy) in 5- and 12.5-ppm males and females, and hepatic fatty degeneration was observed in 12.5-ppm males and 5- and 12.5-ppm females. Hepatic necrosis was noted in males only, including controls (7/80) and the 1-ppm (8/80), 5-ppm (25/80), and 12.5-ppm (27/80) groups. Male mice in only the 12.5-ppm group showed statistically significant elevated incidence of hepatocellular adenomas (also called hepatocellular nodules by the study authors) over controls. Hepatic necrosis is the most adverse lesion of those occurring at 5 ppm and is judged as the critical effect over both fatty degeneration and hepatocellular swelling (hypertrophy). Increased liver cell volume (hypertrophy) is commonly associated with ultrastructural cellular changes involving increased metabolic capacity resulting from the presence of the toxicant (Sipes and Gandolfi, 1991) and are considered more appropriately as nonadverse, adaptive changes. Based on the increased incidence of hepatic necrosis over controls, 1 ppm chlordane (0.15 mg/kg-day) was the NOAEL, and 5 ppm chlordane (0.75 mg/kg-day) was the LOAEL.

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

UF = 300. The following uncertainty factors are applied to the NOAEL derived from the principal study: 10 for consideration of intraspecies variation, 10 for consideration of interspecies extrapolation, and 3 for lack of any reproductive studies.

MF = 1.

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

The composition of mixtures called technical chlordane varies, as it does from mixtures labeled chlordane (CAS No. 57-74-9). The U.S. EPA (1979) recognizes a mixture composed of 60% octachloro-4, 7-methanotetraydroindane (the "cis" and "trans" isomers) and 40% related compounds as technical chlordane. Infante et al. (1978) reported on analysis of technical chlordane having 38-48% cis- and trans-chlordane, 3-7% or 7-13% heptachlor, 5-11% nonachlor, 17-25% other chlordane isomers, and a small amount of other compounds. Dearth and Hites (1991) identified 147 different compounds in a preparation of technical chlordane that included cis-chlordane (15%), trans-chlordane (15%), trans-nonachlor (15%), and heptachlor (3.8%). At least, the principal cis- and trans- isomers of chlordane and the component heptachlor may be metabolized to epoxides, oxychlordane and heptachlor epoxide, both of which have been detected in human tissues (reviewed in Nomeir and Hajjar, 1987). Unless otherwise indicated, all studies described in this document were carried out with technical grade chlordane; specific content will be given when available from the individual study.

Chlordane is extremely lipid soluble, and lipid partitioning of chlordane and its metabolites have been documented in both in humans and animals. Concentrations of chlordanes (cis-chlordane, trans-chlordane, oxychlordane, and trans-nonachlor) detected in human liver samples were 17-fold higher when expressed on a fat rather than a wet-weight basis (Mussalo-Rauhamaa, 1991). Unpublished work (cited in Adeshina and Todd, 1991) reports the mean fat/blood ratio of oxychlordane to be 290/1 among workers who had been exposed to technical grade chlordane. This value is concordant with the results of Khasawinah (1989), who reported this ratio to be 200-300/1 in rats and monkeys after 90-days of inhalation exposure to technical chlordane. Taguchi and Yakushiji (1988) measured chlordane residues (including the epoxide metabolites oxychlordane and hepatchlor epoxide) in the milk of 15 mothers who had lived in chlordane-treated residences for an average of 1.8 years, and the investigators evaluated these measurements with those for the milk of unexposed mothers. In a subgroup of these women who had been exposed for approximately 2 years in treated residences, the overall chlordane residues in milk (0.254 mg/kg milk fat) were similar to those of PCBs (0.389 mg/kg milk fat). Because of its long retention time in adipose tissue, oxychlordane is believed to be more toxic than its parent isomers, which are eliminated relatively rapidly from the body (Satoh and Kikawa, 1992) and, therefore, may be a major contributor to chlordane toxicity.

Available occupational studies, although limited, give no indication that the liver is a target organ in humans as a consequence of chronic exposure to low levels of chlordane. Alvarez and Hyman (1953) found no hepatic abnormalities after thorough physical examinations and liver function tests administered to 24 male workers who had worked for 2 months to 5 years at a chlordane manufacturing plant. Liver function tests were also normal in 15 workers at a chlordane manufacturing plant, 14 of whom had been employed 9-16 years (Fishbein et al., 1964). Air exposures of 0.0012-0.0017 mg/cu.m were cited in this report.

Recent epidemiological findings indicate that neurotoxicity may be a relevant human toxicological endpoint as a consequence of chronic as well as acute chlordane exposure. Neurotoxicity and possibly hematotoxicity (Fleming and Timmeny, 1993) are the principal endpoints of acute chlordane toxicity in both experimentally poisoned animals and accidentally poisoned humans, with tremors and convulsions being common interspecies symptoms (Grutsch and Khasawinah, 1991). IRIS chlordane RfC documentation (U.S. EPA, 1997) describes the study of Kilburn and Thornton (1995), in which adults (109 women and 97 men) who had been exposed to uncertain levels of chlordane via both air and oral routes were examined. Significant ($p < 0.05$) differences were observed with a battery of neurophysiological and neuropsychological function tests. Also, profiles of mood states (including tension, depression, anger, vigor, fatigue, and confusion) all were affected significantly ($p < 0.0005$), as compared to a referent population. These results indicate that neurological effects are a relevant endpoint in humans exposed to chlordane.

Other oral studies confirm the liver as the target organ of chlordane in rodents.

In a 30-month oral study (Khasawinah and Grutsch, 1989b), Fischer 344 rats (80/sex/group) were exposed to 0, 1, 5, or 25 ppm technical chlordane in the diet (0, 0.055, 0.273, or 1.409 mg/kg-day for females). Because symptoms of age-related leukemia (necrosis, swelling, hypertrophy, and fatty degeneration; Solleveld et al., 1984; Stromberg and Vogtsberger, 1983) confounded exposure-related liver lesions, incidence of nonneoplastic liver lesions only in nonleukemic rats were evaluated. A review of these data (ICF-Clement, 1987) indicated that exposure-related lesions were found only in the liver. Absolute liver weight was increased significantly ($p < 0.05$) in 5- and 25-ppm males at 130 weeks and in 25-ppm females at 26 and 52 weeks. The livers of nonleukemic female rats in the 25-ppm (15/44) and 5-ppm (9/40) groups [but not the livers of animals exposed to 1 ppm (4/43)] had statistically significant increases in regional hepatocellular hypertrophy relative to controls (2/37). No such effects were noted in the nonleukemic males, although group sizes were smaller (n = 16-23). Because of the confounding of leukemia and the nonadverse nature of hepatocellular hypertrophy, no effect levels were assigned to this study. The study indicates that rats may be more insensitive to the hepatotoxic effects of chlordane than are mice, which manifested adverse hepatic effects (necrosis and fatty degeneration) at comparable exposure levels.

Groups of 100 male and 100 female CD-1 mice were fed diets containing analytical grade chlordane at concentrations of 0, 5, 25, or 50 ppm (approximately 0, 0.71, 3.57, or 7.14 mg/kg-day, respectively) for 18 months (IRDC, 1973). Mice were 6 weeks of age when exposure began, and the terminal sacrifice was at 19.5 months. Survival in the 50-ppm group was reduced greatly compared to controls. At the 5-ppm exposure level, which did not produce a carcinogenic response, hepatocyte hyperplasia was found, but not at an incidence that was significantly different from controls.

Groups of 50 male and 50 female Osborne-Mendel rats were fed low- or high-dose diets for 80 weeks and then observed for 29 weeks (NCI, 1977). Average doses were 10.2 and 20.4 mg/kg-day for male rats and 6.0 and 12.1 mg/kg-day for female rats. Surviving rats were sacrificed at 109 weeks. Statistically significant differences between exposed groups and control groups were restricted to observations that average body weight of high-dose male and female rats were consistently lower (by about 10%) than that of control rats throughout the study, and that obvious signs of toxicity (rough and discolored hair coats, palpable masses) occurred "frequently" in treated rats during the first year and increased in frequency during the second year. The lower dose (6-10.2 mg/kg-day) is a LOAEL for both sexes. This same study also reported cancer but no noncancer effects in the livers of B6C3F1 mice (50/sex/group) that were fed diets with analytical chlordane for 80 weeks and then observed for 10 weeks. Average doses were 4.3 and 8.0 mg/kg-day for male mice and 4.3 and 9.1 mg/kg-day for female mice. Surviving mice were sacrificed at 90-91 weeks. Survival of male mice in both

exposed groups was decreased significantly relative to control males. Neurotoxicity (tremors) was observed in high-dose males and females after 20 weeks (no further specifics given).

No multi-generational reproductive studies, by any route, exist for technical chlordane. Several items within the current chlordane database suggest that reproductive effects could be a relevant endpoint for chlordane. The study of Cassidy et al. (1994) indicates alterations in reproductive- related behavior in male rats as a consequence of chlordane exposure. Data on tissue distribution of chlordane or its metabolites also indicate the potential for reproductive consequences. Rani et al. (1992) reported accumulation of a major component of technical chlordane (heptachlor) in ovary, uterus, and adrenals in nonpregnant rats within 30 minutes after an oral dose of 120 mg/kg heptachlor. In pregnant rats, levels were markedly elevated in the uterus compared to nonpregnant rats; the higher accumulation is believed to be a result of a slower metabolic turnover of heptachlor. These results indicate that chlordane or some of its components/metabolites have an increased affinity towards reproductive organs during pregnancy and may have potential to adversely affect reproductive processes.

In contrast to the situation for reproductive effects, a number of studies have examined the potential of chlordane or its metabolites to affect developmental processes through investigations of a variety of endpoints.

Pregnant albino mice (6/group) were exposed orally by gavage to 0, 1, or 2.5 mg/kg-day technical grade chlordane dissolved in olive oil for 7 consecutive days during late gestation (i.e., gestational days 12 19) (Al-Hachim and Al-Baker, 1973). Each mouse received a total of 5 7 doses. It was not indicated whether animals were nursed or foster reared, and, thus, whether exposure also occurred through the milk. Groups of 10 randomly selected offspring were tested for conditioned avoidance response ( < 37 days of age), electroshock threshold (38 days of age), and response in open-field tests (6 weeks of age). Exposed animals exhibited depressed acquisition of avoidance response (mean responses 13.1, 9.7, and 9.7 in controls and low- and high-dose groups, respectively), increased seizure threshold (mean responses 90.1, 108.6 and 134.9 in controls and low- and high-dose groups, respectively), and increased exploratory activity (mean responses 93.9 and 88.4, and 137.7 in controls and low- and high-dose groups, respectively). Three-way ANOVA was performed and indicated significant differences between treatment groups ($p < 0.001$) that were dose-related. The lowest dose, 1 mg/kg-day, is a LOAEL.

Several investigations have assessed the effects of chlordane on the immunological system of offspring exposed during gestation and found that chlordane may affect cell-mediated immunity. Pregnant BALB/c mice (6/group) were fed 0, 0.16, or 8 mg/kg-day chlordane during the 19-day gestation period (Spyker-Cranmer et al., 1982). At birth, pups were randomized within treatment groups (45 pups/group), weaned at 28 days, and fed normal diets.

Immunological tests performed at 101 days of age showed a marked decrease ($p < 0.01$) in cell-mediated immune response (contact hypersensitivity assay) in the 8-mg/kg-day group. The lower dose of 0.16 mg/kg-day is a NOAEL for this endpoint. Barnett et al. (1985a) found that in utero exposure to either 8 or 16 mg/kg-day chlordane (in peanut butter) in pregnant BALB/c mice during gestational days 1-18 resulted in a significant decrease ($p < 0.05$) in virus-specific delayed-type hypersensitivity response in the offspring (degree of footpad swelling), but only at 48 hours post injection of an influenza type A virus. No differences were apparent at 72 hours postinjection. The LOAEL is 8 mg/kg-day. In another mice study by Barnett et al. (1985b), delayed hypersensitivity response in offspring, as well as depressed mixed lymphocyte reactivity of spleen cells in male offspring, occurred after in utero exposure to 4 or 16 mg/kg-day during gestational days 1-19. The LOAEL is 4 mg/kg-day. For both of these studies, offspring also were exposed to chlordane via milk.

Fleming and Timmeny (1993) reviewed case studies of aplastic anemia associated with acute exposure to chlordane and other chlorinated pesticides, implicating these pesticides in bone marrow toxicity. In an effort to understand the effects of prenatal chlordane exposure on adult bone marrow expansion potential, Barnett et al. (1990a) exposed female mice orally to chlordane at 0, 4, or 8 mg/kg-day for 18 days during pregnancy. Offspring were nursed, which would provide some postnatal chlordane exposure. Bone marrow hematopoietic activity, as measured by the ability of bone marrow cells to undergo clonal expansion in response to stimulating factors, and spleen colony forming units (after irradiation) both were evaluated in offspring of these mice at 100 and 200 days of age. Results showed a significant dose-related depression ($p < /= 0.05$) of both measures at both 100 and 200 days postexposure. In a subsequent study in which these same measures were evaluated at 18 days gestational age (and without chlordane exposure via milk), these results were confirmed, indicating that damage to stem cells occurred during the fetal period (Barnett et al., 1990b). A LOAEL of 4 mg/kg-day is indicated by these results.

Cassidy et al. (1994) tested the hypothesis that chlordane or its isomers/metabolities act to mimic sex steroids or change their concentrations to alter (in this case to masculinize) functions and behaviors. Pregnant Sprague-Dawley rats were dosed orally with 0, 0.1, 0.5, or 5 mg/kg-day technical grade chlordane from day 4 of gestation to day 21 of lactation, and offspring were dosed from postnatal day 22 to 80. A number of gender-related behavior patterns and effects were examined postnatally, including some aspects of male mating behavior. The authors claim the results from these tests demonstrate a consistent pattern of masculinization of male and female offspring. The lack of consistent dose-response relationships among the effects noted in this study, as well the uncertainty of their toxicological significance, preclude a clear interpretation of this study and assignment of any adverse effect levels. These observations show that, if testosterone or its receptors are

somehow involved in the effects of chlordane, the dose-response model (or mechanism) for the effects must be extremely complex and is in need of further clarification.

***For more details on other Hazard Identification Issues, exit to the toxicological review, Section 4.7 (PDF).***

### I.A.5. Confidence in the Oral RfD

Study — Medium
Database — Medium
RfD — Medium

The overall confidence for this RfD assessment is medium. The principal study, assigned a confidence of medium, is a rat chronic oral study performed with relatively large groups sizes, in which histopathological analyses on the known animal target tissue, the liver, were thoroughly performed. The confidence in the database for chlordane is rated medium. The critical effect of hepatic toxicity was consistent across routes of exposure (the inhalation RfC is also based on hepatic toxicity). Recent evidence, however, indicates that neurotoxicity, a known human endpoint in acute exposures, may be a relevant endpoint in chronic human exposures, and no chronic animals studies have examined neurotoxicity. Studies on pre-and postnatal animals indicating chlordane mimicry of sex-steroids raise reproductive concerns and no multigenerational reproductive studies, by any route, exist. Thus, there is some concern that the appropriate endpoints have not been examined adequately in the existing database. Despite this concern, the wide array of special studies (which may raise similar controversy for other chemicals having less data than does chlordane) and numerous chronic studies with consistent results are judged adequate information to rate the overall confidence in the database as medium.

An area of scientific uncertainty in this assessment concerns the role of neurotoxicity, and possibly hematotoxicity, in chronic chlordane toxicity in humans. In acute chlordane exposures, neurotoxicity has been established as a common endpoint, with similar symptomatologies in both humans and animals (Grutsch and Khasawinah, 1991). Chronic studies with chlordane in animals have considered and found the liver to be the primary target organ, whereas occupational studies of workers with chronic chlordane exposure have not established any effect (neurological, hepatic, or hematotoxic). Recent epidemiology results from a nonoccupationally exposed cohort, however, do show strong evidence of neurotoxicity (Kilburn and Thornton, 1995). These findings could mean that, in rats, the liver is more sensitive to chlordane effects than is the nervous system. Some data do exist in rats (transient tremors in mice observed in NCI, 1977) indicating neurotoxicity to occur in chronic studies at levels higher than those eliciting liver effects. This possibility cannot be confirmed, however,

because no long-term, repeated-dose animal study has been conducted in which neurotoxicity has been evaluated specifically. These findings also could be a result of study design because the occupational studies were designed to elucidate hepatic effects; both Alvarez and Hyman (1953) and Fishbein et al. (1964) employed a number of liver function tests and addressed only neurological symptoms through a general physical exam and immunological effects not at all, although these protocols would probably have elucidated any hematotoxicity. The possibility exists that this assessment is based on studies that have not focused on the appropriate endpoints. Because of this circumstance, any future alteration of the RfC based on an improved database (such as the inclusion of chronic study) would have to be considered in light of what is made known about the neurotoxic potential of chlordane in both animals and humans.

Another area of scientific uncertainty in this assessment concerns the toxicological significance of endocrine mimicry effects of chlordane. Toxicity data for this chemical include a study demonstrating biochemical and behavioral alterations consistent with technical chlordane (or its metabolites) mimicking male sex-steroids (Cassidy et al., 1994). That these effects could include reproductive behaviors is suggested in this study. Tissue distribution data also offer evidence that developmental/reproductive toxicity could be a potential endpoint because technical chlordane (or its metabolites) appears to have an increased affinity toward reproductive organs during pregnancy. Evidence that these altered behaviors and circumstances would have functional consequences that could alter reproduction is, however, lacking because no multigenerational reproductive studies exist.

***For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF)***.

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

Source Document — Toxicological Review of Chlordane, U.S. EPA, 1997.

This assessment was peer reviewed by external scientists. Their comments have been evaluated and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to U.S. EPA, 1997. ***To review this appendix, exit to the toxicological review, Appendix B, Summary of and Response to External Peer Review Comments (PDF)***.

Other EPA Documentation — U.S. EPA, 1986.

Agency Consensus Date — 11/03/1997

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Chlordane (Technical) conducted in November 2001 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

### 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).

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

Substance Name — Chlordane (Technical)
CASRN — 12789-03-6
Last Revised — 02/07/1998

### I.B.1. Inhalation RfC Summary

| Critical Effect | Experimental Doses* | UF | MF | RfC |
|---|---|---|---|---|
| **Hepatic effects**<br><br>**Rat subchronic inhalation study**<br><br>**Khasawinah et al., 1989a** | 1.0 mg/cu.m<br><br>NOAEL 1.0 mg/cu m<br>NOAEL (ADJ) 0.24 mg./cu m<br>NOAEL (HEC) 0.65 mg/cu m | 1000 | 1 | 7E-4 mg/cu m |

* Conversion Factors and Assumptions — MW (general) = 409. NOAEL(ADJ) = 10 mg/cu.m x (8 hours/24 hours) x (5 days/7 days) = 0.24 mg/cu.m.

Scenario -- The NOAEL(HEC) is calculated for a particle: extra-respiratory effect (liver). The estimated RDDR(ER) is 2.7 for an MMAD of 1.8 um and sigma g of 3.1, based on dosimetric

modeling (U.S. EPA, 1994). NOAEL(HEC) = NOAEL(ADJ) x RDDR(ER) = 0.24 mg/cu.m x 2.7 = 0.65 mg/cu.m.

## I.B.2. Principal and Supporting Studies (Inhalation RfC)

Khasawinah, A., C. Hardy, and G. Clark. 1989a. Comparative inhalation toxicity of technical chlordane in rats and monkeys. J. Toxicol. Environ. Health 28(3): 327-347. (The 90-day rat study.)

Wistar rats (35 47/sex/group) were exposed to 0, 0.1, 1.0, or 10 mg/cu.m technical chlordane, 8 hours/day, 5 days/week, for 13 weeks, followed by a 13-week recovery period. The NOAEL(HEC) is calculated for a particle:extrarespiratory effect (liver). The estimated RDDR(ER) is 2.7, based on available information (MMAD of 1.8 um and sigma g of 3.1) and on dosimetric modeling (U.S. EPA, 1994). NOAEL(HEC) = NOAEL(ADJ) x RDDR(ER) = 0.24 mg/cu.m x 2.7 = 0.65 mg/cu.m. Blood chemistry and urinalysis were performed before and at 5 and 13 weeks of exposure. Histopathology was performed on all major tissues, including nasal passages. At the end of the exposure period, increased liver weights ($p < 0.01$) were observed for male and female rats exposed to 10 mg/cu.m at weeks 9 and 14. Analysis of blood chemistry results gave indications of hepatic functional alteration, but only among rats exposed to the highest concentration. Alterations included a significant decrease in glucose (83% of control for females), increased globulins (114% of control for males), increased total protein (104% of control for males), decreased albumin (95% of control for males), an increase in cholesterol (158% of control for females), and an altered albumin/globulin (A/G) ratio in males. This pattern of alterations in blood chemistry is indicative of changes in the functioning of the liver, the major site of synthesis of plasma proteins (Kaneko, 1989). In view of what is known about the progression of liver effects with increasing concentrations of chlordane (see discussion of 28-day inhalation study below), this pattern of changes is considered an adverse effect, with a LOAEL of 10 mg/cu.m and a NOAEL of 1 mg/cu.m.

Khasawinah, A., C. Hardy, and G. Clark. 1989b. Comparative inhalation toxicity of technical chlordane in rats and monkeys. J. Toxicol. Environ. Health 28(3): 327-347. (The 28-day rat study.)

In a 28-day range-finding study, Wistar (Crl:Cobs WI Br strain) rats (10/sex/group) inhaled 0, 5.8, 28.2, 154, or 413 mg/cu.m technical chlordane, 8 hours/day, 5 days/week. Body and organ weights and food and water consumption were measured, and hematology, urinalysis, and microscopic examination were performed. Deaths occurred in the 413- and 154-mg/cu.m groups. Livers were enlarged in the 154-mg/cu.m males and were discolored in the 413- and 154-mg/cu.m males. Hepatic necrosis, vacuolation, and hepatocellular hypertrophy were noted among rats exposed to 413 mg/cu.m. Hepatocellular hypertrophy, with or without vacuolation,

was observed among rats exposed to 154 mg/cu.m. Among rats exposed to 28.2 mg/cu.m, hepatocellular hypertrophy, increased kidney and thyroid weight, and decreased thymus weights were observed. At this concentration, there also were indications of hepatic function alteration from blood chemistry results, including a significant decrease in glucose (73% of control for males and 78% of control for females), increased globulins (116% of control for males and 119% of control for females), increased total protein (116% of control for females), increased albumin (117% of control for females), an increase in cholesterol (133% of control for females), and an altered albumin/globulin (A/G) ratio. The LOAEL was 28.2 mg/cu.m, based on the wide range of biochemical indicators demonstrating alteration of hepatic function at this concentration. The NOAEL was 5.8 mg/cu.m. The occurrence of these alterations in blood chemistry, as part of a toxicological progression of lesions, in this short-term study provides justification for the designation of these effects as a LOAEL in the subchronic study (Khasawinah et al., 1989a).

### I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF — 1000. The following uncertainty factors are applied to the NOAEL(ADJ): 10 for subchronic to chronic extrapolation; 10 for consideration of intraspecies variation. Partial uncertainty factors are used for interspecies extrapolation (which already has been addressed partially by calculation of an HEC) and for database deficiencies (lack of any reproductive studies).

MF — 1.

### I.B.4. Additional Studies/Comments (Inhalation RfC)

The composition of mixtures called technical chlordane varies, as does mixtures labeled chlordane (CAS No. 57-74-9). The U.S. EPA (1979) recognizes a mixture composed of 60% octachloro-4,7-methanotetraydroindane (the "cis" and "trans" isomers) and 40% related compounds as technical chlordane. Infante et al. (1978) reported on analysis of technical chlordane having 38-48% cis- and trans-chlordane, 3-7% or 7-13% heptachlor, 5-11% nonachlor, and 17-25% other chlordane isomers, and a small amount of other compounds. Dearth and Hites (1991) identified 147 different compounds in a preparation of technical chlordane that included cis-chlordane (15%), trans-chlordane (15%), trans-nonachlor (15%), and heptachlor (3.8%). At least the principal cis- and trans-isomers of chlordane and the component heptachlor may be metabolized to epoxides, oxychlordane and heptachlor epoxide, both of which have been detected in human tissues (reviewed in Nomeir and Hajjar, 1987). Unless otherwise indicated, all studies described in this document were carried out with technical grade chlordane; specific content will be given when available from the individual study.

Chlordane is extremely lipid soluble, and lipid partitioning of chlordane and its metabolites have been documented in both in humans and animals. Concentrations of chlordanes (cis-chlordane, trans-chlordane, oxychlordane, and trans-nonachlor) detected in human liver samples were 17-fold higher when expressed on a fat rather than a wet weight basis (Mussalo-Rauhamaa, 1991). Unpublished work (cited in Adeshina and Todd, 1991) reports the mean fat/blood ratio of oxychlordane to be 290/1 among workers that had been exposed to technical grade chlordane. This value is concordant with the results of Khasawinah (1989), who reported this ratio to be 200-300/1 in rats and monkeys after 90-days of inhalation exposure to technical chlordane. Taguchi and Yakushiji (1988) measured chlordane residues (including the epoxide metabolites oxychlordane and heptachlor epoxide) in the milk of 15 mothers who had lived in chlordane treated residences for an average of 1.8 years, and the investigators evaluated these measurements with those for the milk of unexposed mothers. In a subgroup of these women who had been exposed for approximately 2 years in treated residences, the overall chlordane residues in milk (0.254 mg/kg milk fat) were similar to those of PCBs (0.389 mg/kg milk fat). Because of long retention time in adipose tissue, oxychlordane is believed to be more toxic than its parent isomers, which are eliminated relatively rapidly from the body (Satoh and Kikawa, 1992) and, therefore, may be a major contributor to chlordane toxicity.

The relative contributions of particulate and vapor states of chlordane in inhalation experiments are unclear. The vapor pressure for pure chlordane has been reported as 1E-5 and, for technical grade chlordane, reported as 4.6E-4 mmHg at 25 degrees C (IARC, 1991). Based on these values (and a molecular weight of 409), a saturated vapor concentration for pure chlordane would be about 0.2 mg/cu.m; for technical chlordane, it would be approximately 10 mg/cu.m. Particle sizing measures performed in the Khasawinah et al., (1989a) study indicate that particulate chlordane was collected at the reported exposure levels of 1 and 10 mg/cu.m.

Other studies in rodents confirm the liver as the target organ for chlordane. The oral reference dose (RfD) currently on IRIS is based on hepatic necrosis observed in mice exposed orally to chlordane (Khasawinah and Grutsch, 1989; U.S. EPA, 1997).

Currently available occupational studies, although limited, give no indication that the liver is a target organ in humans as a consequence of chronic exposure to low levels of chlordane. Alvarez and Hyman (1953) found no hepatic abnormalities after thorough physical examinations and liver function tests administered to 24 male workers who had worked from 2 months to 5 years at a chlordane manufacturing plant. Liver function tests were also normal for 15 workers at a chlordane manufacturing plant, 14 of whom had been employed 9-16 years (Fishbein et al., 1964). Air exposures of 0.0012-0.0017 mg/cu.m were cited in this report.

Neurotoxicity [and possibly hematotoxicity (Fleming and Timmeny, 1993)] are the principal endpoints of acute chlordane toxicity in both experimentally poisoned animals and accidentally poisoned humans, with tremors and convulsions being common interspecies symptoms (Grutsch and Khasawinah, 1991). Recent epidemiological findings indicate that neurotoxicity may be a more relevant human toxicological endpoint as a consequence to chronic chlordane exposure. Kilburn and Thornton (1995) administered batteries of neurophysiological and neuropsychological tests to 216 adult occupants (109 women and 97 men) of an apartment complex, the exterior of which had been sprayed with an unknown concentration of chlordane 7 years prior to the administration of the tests. Chlordane levels were assayed for 3-4 years after the initial spraying and showed indoor concentrations of chlordane as high as 0.0136 mg/929 sq.cm (wipe samples) and indoor air levels reported as above 0.0005 mg/cu.m for 8-hour samples. The duration of the individuals residence at the complex was not reported. Blood and fat samples from eight of these residents (number actually tested not given) showed measurable and elevated levels of heptachlor, oxychlordane, and trans-nonachlor. The exposed group was compared with 174 unexposed referents matched on age and educational level. Significant ($p < 0.05$) differences found between the exposed and referent population included slowing of reaction times, balance dysfunction, and reductions in cognitive function and immediate and delayed recall. Profiles of mood states, including tension, depression, anger, vigor, fatigue, and confusion, were affected significantly ($p < 0.0005$), as compared to the referent population. Confounding factors that could affect the results, such as alcohol consumption, illicit drug use, neurological or psychiatric diseases, were addressed and dismissed as not having any influence on the results. These results show significant impairment of both neurophysiological and psychological functions in a nonoccupational population exposed to uncertain levels of chlordane, predominately through the inhalation route via indoor air. These results indicate that neurological effects are a relevant endpoint in humans exposed to airborne chlordane at air levels in the range of 0.0005 mg/cu.m. However, no dose-response information and no reliable exposure information, either levels or duration of exposure or information about co-exposure to other neurotoxicants such as lead, could be gleaned from this report, and no effect levels can be assigned to this study.

No multi-generational reproductive studies, by any route, exist for technical chlordane. Several items within the current chlordane database suggest that reproductive effects could be a relevant endpoint for chlordane. The study of Cassidy et al. (1994) indicates alterations in reproductive-related behavior in male rats as a consequence of chlordane exposure. Data on tissue distribution indicate the potential for reproductive consequences from exposure to chlordane or its metabolites. Rani et al. (1992) reported accumulation of a major component of technical chlordane (heptachlor) in ovary, uterus, and adrenals in nonpregnant rats within 30 minutes after an oral dose of 120 mg/kg heptachlor. In pregnant rats, levels were markedly elevated in the uterus compared to nonpregnant rats; the higher accumulation is believed to be a result of a slower metabolic turnover of heptachlor. These results indicate that chlordane or

some of its components/metabolites have an increased affinity toward reproductive organs during pregnancy and may have potential to adversely affect reproductive processes.

In contrast to the situation for reproductive effects, a number of studies have examined the potential of chlordane or its metabolites to affect developmental processes through investigations of a variety of endpoints. Prenatally treated mice exhibited altered behavioral responses at the lowest dose tested, 1 mg/kg-day (Al-Hachim and Al-Baker, 1973). Spyker-Cranmer et al. (1982) noted a marked decrease in cell-mediated immune responses among offspring exposed to chlordane during gestation at 8 mg/kg-day, but not at 0.16 mg/kg-day. Barnett et al. (1985) found a significant decrease in hypersensitivity response among offspring exposed in utero to chlordane at both levels tested, 8 or 16 mg/kg-day. Barnett et al. (1990a) noted a dose-related depression in bone marrow hematopoietic activity among offspring exposed in utero to chlordane at 4 or 8 mg/kg-day that apparently resulted from stem cell damage (Barnett et al., 1990b). Cassidy et al. (1994) tested the hypothesis that chlordane acted to mimic sex steroids among offspring exposed in utero to levels as low as 0.1 mg/kg-day with equivocal results. These studies are described more extensively in the IRIS RfD and U.S. EPA (1997).

***For more details on other Hazard Identification Issues, exit to the toxicological review, Section 4.7 (PDF).***

### I.B.5. Confidence in the Inhalation RfC

Study — Medium
Database — Low
RfC -- Low

The overall confidence in this RfC assessment is low. The principal study, rated as medium, is a rat subchronic inhalation study performed with relatively large group sizes in which histopathological analyses on the known animal target tissue, the liver, was thoroughly performed. There is a degree of technical uncertainty in the study about the particle distribution characteristics that were estimated from the available data. The confidence in the database for technical chlordane is rated low. In animal studies, the critical effect of hepatic toxicity was consistent across routes of exposure because oral studies also indicate hepatotoxicity as the critical endpoint of toxicity (Khasawinah and Grutsch, 1989). However, recent evidence indicates that neurotoxicity, a known human endpoint in acute exposures, may be a relevant endpoint in chronic human exposures, and no chronic animal studies have examined neurotoxicity. Studies on pre- and postnatal animals that indicate chlordane mimicry of sex steroids raise reproductive concerns, and no multigenerational reproductive studies, by any route, exist.

An area of scientific uncertainty in this assessment concerns the role of neurotoxicity in chronic chlordane toxicity in humans. In acute chlordane exposures, neurotoxicity has been established as a common endpoint with similar symptomatologies in both humans and animals (Grutsch and Khasawinah, 1991). Chronic studies with chlordane in animals have considered and found the liver to be the primary target organ, whereas occupational studies of workers with chronic chlordane exposure have not established any effect, either neurological or hepatic, although protocols in these studies should have elucidated any hematoxicity. Recent epidemiology results from a nonoccupationally exposed cohort, however, do show strong evidence of neurotoxicity (Kilburn and Thornton, 1995). These findings could mean that, in rats, the liver is more sensitive to chlordane effects than is the nervous system. Some data do exist in rats [transient tremors in rats observed in NCI (1977)] that indicate neurotoxicity to occur in chronic studies at levels higher than those eliciting liver effects. This possibility cannot be confirmed, however, as no long-term, repeated-dose animal study has been conducted in which neurotoxicity has been specifically evaluated. These findings could also be a result of study design, because the occupational studies available were designed to elucidate hepatic effects; both Alvarez and Hyman (1953) and Fishbein et al. (1964) employed a number of liver function tests and only addressed neurological symptoms through a general physical exam. The possibility exists that this assessment is based on studies flawed in design and endpoint assessment. Because of this circumstance, any future alteration of the RfC based on an improved database (such as a chronic study) would have to be considered in light of what is discovered about the neurotoxic potential of chlordane in both animals and humans.

Another area of scientific uncertainty in this assessment concerns the toxicological significance of endocrine mimicry effects of chlordane. Toxicity data for this chemical include a study demonstrating biochemical and behavioral alterations consistent with technical chlordane (or its metabolites) mimicking male sex steroids (Cassidy et al., 1994). That these alterations could include effects on reproductive behavior is suggested in this study. Tissue distribution data also offer evidence that developmental/reproductive toxicity could be a potential endpoint because technical chlordane (or its metabolites) appears to have an increased affinity toward reproductive organs during pregnancy. Evidence that these altered behaviors and circumstances would have functional consequences that could alter reproduction is, however, lacking because no multi-generational reproductive studies exist.

***For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).***

### I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — Toxicological Review of Chlordane, U.S. EPA, 1997.

This assessment was peer reviewed by external scientists. Their comments have been evaluated and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to U.S. EPA, 1997. ***To review this appendix, exit to the toxicological review, Appendix B, Summary of and Response to External Peer Review Comments (PDF)***.

Other EPA Documentation — U.S. EPA, 1986. Carcinogenicity Assessment of Chlordane and Heptachlor/Heptachlor Epoxide. Washington, DC: Office of Health and Environmental Assessment. NTIS PB87-208757.

Agency Consensus Date — 11/03/1997

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for Chlordane (Technical) conducted in November 2001 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

### I.B.7. EPA Contacts (Inhalation RfC)

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).

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## II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Chlordane (Technical)
CASRN — 12789-03-6
Last Revised — 02/07/1998

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 ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented in a

concentration of the chemical in drinking water or air providing cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 100,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section 1 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

Chlordane is classified as B2; probable human carcinogen, using the 1986 Guidelines for Carcinogen Risk Assessment. Under the 1996 Proposed Guidelines, it would be characterized as a likely carcinogen by all routes of exposure. These characterizations are based on the following summaries of the evidence available: (1) human epidemiology studies showing non-Hodgkin's lymphoma in farmers exposed to chlordane and case reports of aplastic anemia, chlordane associated with home use are inadequate to demonstrate carcinogenicity; (2) animal studies in which benign and malignant liver tumors were induced in both sexes of four strains of mice and occurred with an elevated, but not statistically significant, incidence in a fifth strain, as well as liver toxicity but no tumors in rats of two strains; and (3) structural similarity to other rodent liver carcinogens.

***For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF)***.

***For more details on other Hazard Identification Issues, exit to the toxicological review, Section 4.7 (PDF)***.

### II.A.2. Human Carcinogenicity Data

Inadequate evidence. Three types of studies have been reported: (1) Case- control studies of non-Hodgkin's lymphoma among farmers, (2) occupational cohort studies in a chlordane manufacturing plant and of professional pesticide applicators, and (3) individual case reports of disease in people exposed to chlordane in home situations.

Case-Control Studies:

Cantor et al. (1992) compared 622 white men newly diagnosed with non-Hodgkin's lymphoma in Iowa and Minnesota with 1245 population-based controls, matched with respect to age, vital status at the time of interview, and state of residence. Detailed interviews elicited information about their pesticide handling practices on farms. Chlordane was one of 12 chemicals evaluated as animal (livestock) insecticides and one of 15 chemicals evaluated as crop insecticides. The investigators found that the odds of chlordane use as an animal insecticide were significantly greater among cases than among controls (OR = 1.7, 95% CI = 1.0-2.9). The odds of chlordane use as both an animal and a crop insecticide were also significant (OR = 1.8, 95% CI = 1.1-3.1). The pattern of odds ratios for other chemicals studied was similar, in that livestock use had greater odds ratios than crop use; this consistency indicated to the authors that the increased odds ratios resulted from greater exposure with livestock than crops, rather than some random error. In discussing the limitations of their study, the authors point out the difficulty of attributing the results to individual pesticides when the exposures were multiple, and they also point out the possibility that important associations may have been missed because of non-differential exposure mis-classification resulting from the difficulties in accurate recall of past pesticide exposures. They concluded that chlordane (as well as some other specifically mentioned pesticides) has an important role in the etiology of non-Hodgkin's lymphoma among farmers.

In a study of similar design to that of Cantor et al. (1992), Brown et al. (1990) conducted a population-based case-control study of leukemia among 578 white men with leukemia and 1245 controls living in Iowa and Minnesota. No significantly elevated odds ratios for leukemia were associated with chlordane exposures. Chlordane was one of 17 crop insecticide exposures and one of 16 animal insecticide exposures evaluated.

Woods et al. (1987) published a population-based case-control study of 128 soft-tissue sarcomas and 576 non-Hodgkin's lymphomas among men in western Washington state, where phenoxy herbicides and chlorinated phenols are used widely in the agricultural, forestry, and wood products industries. They investigated other chemical handling practices, including the use of chlordane, that potentially could modify or independently affect the risk of these diseases. Although their main interests were herbicides and phenols, one of their findings was an elevated, but not statistically significant, odds ratio of non-Hodgkin's lymphoma among farmers who worked with chlordane (OR = 1.46, CI = 0.8-2.8). This study is mentioned here in connection with chlordane use by farmers, not because it is strong evidence of chlordane risk, but because it supports the findings of Cantor et al. (1992) that are discussed above.

Brown et al. (1993) published a population-based case-control study of multiple myeloma among 173 white men in Iowa, compared with 650 controls to evaluate possible contribution of agricultural risk factors and exposure to individual pesticides. They found no statistically

significant odds ratios associated with the handling of pesticide classes or individual compounds. Chlordane was one of seven animal insecticides evaluated.

Pesatori et al. (1994) updated an earlier study of licensed structural pest control workers in Florida (Blair et al., 1983). The original cohort of 3827 men was begun in 1965 and followed until 1977, and the 1994 study updated the follow-up period to 1982. In view of the elevated lung cancer mortality found in the original study, the investigators conducted a nested case-control study of 65 lung cancer cases. Two hundred and ninety-four controls were interviewed; these interviews gathered information on tobacco use, occupation, work practices, and dietary habits. The authors found, in the case-control study, that tobacco use, diet, and other occupations had little effect on the excess lung cancer associated with occupational pesticide exposure. This excess was larger among those licensed before the age of 40 and those licensed for more than 20 years. Because of the small sample size, the use of individual pesticides could not be evaluated, but carbamates and phenoxyacetic acids were elevated significantly and use of inorganics, organobromides, organochlorines, and organophosphates were elevated non-significantly in these lung cancer cases. Use of chlordane specifically was not associated with lung cancer.

Occupational Cohort Studies:

Wang and MacMahon (1979) studied the mortality patterns of male workers in two plants, one in Illinois that manufactured chlordane, and the other in Tennessee, which manufactured heptachlor and endrin. The authors did not have a measure of exposure to chlordane. The employees working from the start-up of the plants (1946 for the chlordane plant and 1952 for the other plant) until 1976 were eligible for the study. In the 113 deaths at the two plants, including 13 deaths in the chlordane plant, there was no statistically significant excess of deaths from cancer, even in those followed for more than 20 years after the beginning of employment. The study is too small to conclude that there is negligible risk.

Brown (1992) reported follow-up data through 1987 of a cohort mortality study of white male workers employed at four organochlorine pesticide manufacturing plants, two of which were the same plants studied by Wang and MacMahon (1979). The original study, Ditraglia et al. (1981), included all employees who worked at least 6 months prior to 1964, and vital statistics were followed until 1976. There was no excess cancer mortality in either the original study or in Brown's follow-up study. The small number of deaths in the chlordane plant workers (159) available for analysis precludes the ability to arrive at definitive conclusions about the effects of chlordane exposure.

Shindell and Ulrich (1986) published a retrospective mortality study of workers in the same plant. Their population was employees who worked for more than 3 months from 1946

through June 1985. No excess cancer rates were found in this study (based on 37 cancer deaths analyzed), but the authors presented no information about expected rates. In a letter, the editors, Infante and Freeman (1987), challenged these results by calculating expected rates based on other studies of this cohort and asserted that there was an increasing trend of the SMR with increasing duration of employment. Shindell responded in the same 1987 publication with a table showing the expected rates and stated that there was no trend in mortality rates with respect to length of employment.

Wang and MacMahon (1979) studied the prospective mortality of male pesticide applicators employed by three nationwide companies between 1967 and 1976. In the 16,126 men in the study, there were 311 deaths with no statistically significant excess cancer mortality. A follow-up of this cohort to 1984 was published by MacMahon et al. (1988); it showed no statistically significant excess mortality for any cancer except for lung, and that was for employment for less than 5 years. Attributing that finding to chlordane exposure is unlikely, because there was no increase in lung cancer among termite control operators, the group most likely to be exposed. A maximum latent time of 17 years may not have been long enough to observe cases that could have been induced by chlordane exposure.

Case Reports:

Epstein and Ozonoff (1987) presented 25 new cases (cases not previously reported to EPA) of blood dyscrasias (thrombocytopenic purpura, aplastic anemia, and leukemia) following exposure to chlordane and heptachlor; four of these were leukemia cases. In 16 of the 25 cases, no exposure other than to chlordane or heptachlor was reported, and over 75% of these cases involved homeowners following termite treatment or garden and lawn applications.

Infante et al. (1978) presented 11 clinical cases of blood dyscrasias associated with chlordane exposure. There were five cases of neuroblastoma in children exposed to chlordane, three of which were prenatal exposures to the mother during pregnancy. They also discussed three cases of aplastic anemia, two of which reported chlordane-only exposure, and three cases of leukemia, two of which also reported chlordane-only exposure. They also reviewed 25 cases of blood dyscrasias previously reported to be associated with chlordane and heptachlor exposure.

Three studies of cancer patients [Caldwell et al., 1981; (colon cancer in adolescents living on farms where pesticides were used); Teufel et al., 1990 (eight different childhood cancers); and Falck et al., 1992 (breast cancer)] reported no differences in tissue levels of chlordane between controls and cancer patients. These studies were done to test the hypothesis that chlordane is a risk factor for these populations.

## II.A.3. Animal Carcinogenicity Data

Sufficient. Chlordane treatment has induced benign or malignant liver tumors in each of the five strains of mice in which bioassays have been reported [CD-1 (IRDC, 1973), B6C3F1 (NCI, 1977), ICR (Khasawinah and Grutsch, 1989a), C57Bl/10J (Barrass et al., 1993), and B6D2F1 (Malarkey et al., 1995)]. In rats, no tumors were induced in two strains [Osborne-Mendel (NCI, 1977), and Fischer 344 (Khasawinah and Grutsch 1989b)].

Mouse Studies:

Groups of 100 male and 100 female CD-1 mice were fed diets containing analytical grade chlordane at concentrations of 0, 5, 25, or 50 ppm (approximately 0, 0.71, 3.57, or 7.14 mg/kg-day, respectively) for 18 months (IRDC, 1973; U.S. EPA, 1986). At the 19.5-month terminal sacrifice, no exposure-related changes in body weight gain or food consumption were observed, but survival in the 50-ppm group was greatly reduced compared to controls (only 39 males and 37 females were examined histologically). Many mice were lost because of autolysis, so that only about half of the mice were examined histologically. EPA-sponsored examination of the liver histological slides found statistically significant increased incidence of hepatic carcinomas in males and females in the 25- and 50-ppm groups.

Groups of 50 male and 50 female B6C3F1 mice were fed diets with low and high concentrations of analytical chlordane for 80 weeks and then were observed for 10 weeks (NCI, 1977). Time-weighted average concentrations were 29.9 and 56.2 ppm for male mice and 30.1 and 63.8 ppm for female mice and correspond to approximate average doses of 4.3 and 8.0 mg/kg-day for male and 4.3 and 9.1 mg/kg-day for female mice for low and high doses, respectively. Matched controls consisted of 10 male and 10 female untreated mice. A pooled control group consisted of the matched control mice and 70 male and 80 female untreated mice from similar bioassays conducted during periods that overlapped with the chlordane bioassay by at least a year. Surviving mice were sacrificed at 90-91 weeks. Major organs and tissues from sacrificed mice and from mice found dead were examined grossly and microscopically.

No significant exposure-related changes in average body weight were found in male or female mice (NCI, 1977). Survival of exposed female mice was essentially the same as control female mice, but survival of male mice in both exposed groups (60%) was significantly decreased relative to control males (100%).

Exposure-related neoplastic or nonneoplastic lesions in mice were restricted to the liver (NCI, 1977). Hepatocytomegaly, nodular hyperplasia, and diffuse hyperplasia were found in exposed male and female mice, but not at incidences that were statistically significantly different from

controls. Statistically significant elevated incidences for hepatocellular carcinomas, relative to controls, were found in low- and high-dose male mice and in high-dose female mice. Tumor incidence data are presented in Section II.B.2.

ICR mice (80/sex/group) were fed 0, 1, 5, or 12.5 ppm technical chlordane in the diet for 104 weeks (Khasawinah and Grutsch, 1989a; Velsicol Chemical Corporation, 1983). The study authors reported that average doses corresponded to 0, 0.15, 0.75, or 1.875 mg/kg-day, respectively, based on food consumption and body weight data. Hematology, biochemistry, urinalysis, organ weights, and pathology (of major tissues and organs) were assessed at week 52 (8 males and 8 females/group), on all animals that died during the study, and on all survivors at week 104.

When male mice were analyzed without regard to the presence or absence of tumors, no consistent, exposure-related changes were found, except that 12.5-ppm male mice showed a statistically significant elevation in serum alanine transferase activity (SGPT or ALT) at week 104. However, when animals with adenocarcinomas were compared with those without adenomas or adenocarcinomas, the animals with malignant tumors had statistically significant elevations of all blood biochemistry measurements made (SGOT, SGPT, glucose, urea nitrogen, cholesterol, and protein). The authors concluded that the presence of the malignant tumors, and not the exposure to chlordane, altered the blood biochemistry parameters. Statistically significant increased relative and absolute liver weights were seen in high-dose males ($p < 0.0001$) and females ($p < 0.01$), compared to control values at the end of the study. No consistent changes in other organ weights were found (Khasawinah and Grutsch, 1989a; Velsicol Chemical Corporation, 1983).

Exposure-related neoplastic and nonneoplastic lesions were restricted to the liver. Statistically significant increased incidences, relative to controls, were found for the following nonneoplastic lesions: hepatocellular swelling in male and female mice in the 5- and 12.5-ppm groups, hepatic fatty degeneration in 12.5-ppm males, and hepatic necrosis in 5- and 12.5-ppm male mice. Male mice in the 12.5-ppm group showed statistically significant elevated incidence of hepatocellular adenomas (also called hepatocellular nodules by the study authors) and hepatic hemangiomas compared with controls. The hepatic hemangiomas were described as benign tumors of capillary cells associated with the hepatocellular adenomas. The 1989 report mentions the occurrence of liver adenocarcinomas but does not present incidence data. However, the earlier report of this assay (Velsicol Chemical Corporation, 1983, cited by U.S. EPA, 1986) shows that the hepatocellular carcinoma incidence in males in the 0-, 1-, 5-, and 12.5-ppm groups is 3/71, 3/71, 7/72, and 8/72, respectively. These data are used for the quantitative cancer risk estimates in Section II.B.2. No other statistically significant differences between control and exposed groups of mice were found for incidences of nonneoplastic or neoplastic lesions (Khasawinah and Grutsch, 1989a).

Barrass et al. (1993) carried out two assays in which chlordane with a concentration of 50 ppm was fed to C57Bl/10J mice. The first was a 24-month bioassay of chlordane in a group of 100 male mice, with histopathological analysis of liver sections. The authors found that, in the animals surviving after 2 years of treatment, the incidences of hepatocellular adenomas and carcinomas were 15/39 and 5/39, respectively. In the animals with unscheduled deaths during the assay, the incidences of adenomas and carcinomas were 1/40 and 2/40, respectively. The incidence of total liver tumors in a concurrent colony control group was 8/400. Therefore, the incidence of adenomas and carcinomas combined was 23/79, which is statistically significant relative to controls. However, because the incidence of carcinomas alone in the control group was not given, the statistical significance of the carcinomas alone can not be calculated, nor can the risk of carcinoma alone be determined.

The second assay was a 6-month cell proliferation study with nine serial sacrifices, in which replicating cells were labeled by infusing BrdU via subcutaneous mini-osmotic pumps 3 days before sacrifice. Thyroid and liver cell replication and histopathology were measured. In this assay, there were no morphological thyroid abnormalities; the thyroid labeling index reached a peak after 5 days and reached control levels after 99 days. Centrilobular hepatocellular hypertrophy was seen early and became more severe throughout the experiment. The liver-labeling index showed an initial peak phase lasting 4 weeks and a sustained elevated phase lasting for the entire 200-day period, but gradually declining by day 200.

Malarkey et al. (1995) reported on the age-specific prevalence of malignant and benign tumors in male mice of two strains [B6C3F1 (210 treated animals) and B6D2F1 (160 treated animals)] fed 55 ppm of chlordane continuously for 18 and 22 months, respectively. Groups of 100 B6C3F1 mice and 50 B6D2F1 mice served as controls. The investigators also measured the time course of two measures of liver toxicity (centrilobular hypertrophy and "toxic change", defined as cellular necrosis and vacuolization and tissue inflammation). They found that all the mice of both strains eventually had tumors, and that the onset was more rapid in B6C3F1 mice by about 100 days. After 72 weeks of treatment (568 days of age), which was about 8 weeks less than the duration of the NCI (1977) test, the prevalence of carcinomas in B6C3F1 mice was about 88%, as determined from the prevalence vs. time graphs in the Malarkey et al. paper. This is the same as the incidence of tumors in the NCI bioassay, which was 43/49 = 88% after 80 weeks of treatment. Therefore, the incidence of carcinomas in the current study closely matches the experiment done under similar conditions 18 years earlier in mice of a different strain. The multiplicity of adenomas (tumors per tumor-bearing animal) increased over time, whereas that of carcinomas was constant. Centrilobular hypertrophy preceded the development of tumors by over 100 days, whereas the toxic change occurred at about the same time as the development of tumors. In one group of B1C3F1 mice in which the chlordane was withdrawn from the diet after 14 months, there was a partial regression (reduction in prevalence) of both adenomas and carcinomas, as well as a reduction of adenoma

multiplicity. There were no mutations of H-ras or K-ras oncogenes in tumors of treated animals of either strain, whereas H-ras mutations occurred in 4 of 10 spontaneous tumors in control animals. The authors also observed that the proliferative lesions preceding tumor formation in treated animals consisted of large hepatocytes with acidophilic cytoplasm, whereas, in control animals, they were of normal size, with basophilic staining. The authors postulate a progression of tumors from a dependent stage, where growth is dependent on the presence of chlordane, to an autonomous stage that does not regress after its withdrawal.

Rat Studies:

Groups of 50 male and 50 female Osborne-Mendel rats were fed low- or high-dose diets containing analytical grade chlordane for 80 weeks and then observed for 29 weeks (NCI, 1977). The test material contained 71.7% cis-chlordane, 23.1% trans-chlordane, 0.3% heptachlor, 0.6% nonachlor, 1.1% hexachlorocyclopentadiene, and 0.25% chlordane isomers. Time-weighted average concentrations were 203.5 and 407 ppm for males and 120.8 and 241.5 ppm for females, respectively. These concentrations correspond to approximate average doses of 10.2 and 20.4 mg/kg-day for male and 6.0 and 12.1 mg/kg-day for female rats, respectively. Matched controls consisted of 10 male and 10 female rats. A pooled control group consisted of the matched-control rats and 50 male and 50 female untreated rats from similar bioassays conducted during periods that overlapped the chlordane bioassay by at least a year. Surviving rats were sacrificed at 109 weeks. Major organs and tissues from sacrificed rats and from rats found dead, were examined grossly and microscopically.

Obvious clinical signs of toxicity (rough and discolored hair coats and palpable masses) occurred "frequently" in treated rats during the first year and increased in frequency during the second year. No statistically significant differences in survival were found for exposed male rats compared with control rats, but there was a significant dose-related trend for decreased survival in exposed female rats. No statistically significant increased incidence of liver tumors or liver nonneoplastic lesions was found in exposed rats compared with control rats. Statistically significant increased incidences of proliferative lesions of follicular cells of the thyroid and of malignant fibrous histiocytoma were found in exposed male rats compared with controls. The study authors concluded, however, that these differences were not biologically significant, because the incidences were within the range of incidence for control rat populations. No other exposure-related neoplastic or nonneoplastic lesions were found in rats in this study.

In a 30-month oral study, Fischer 344 rats (80/sex/group) were exposed to 0, 1, 5, or 25 ppm technical chlordane in the diet (Khasawinah and Grutsch, 1989b; Velsicol Chemical Corporation, 1983; ICF-Clement, 1987; U.S. EPA, 1988). Based on food consumption and body weight data, the study authors calculated the doses to be 0, 0.045, 0.229, or 1.175 mg/kg-

day for males and 0.055, 0.273, and 1.409 mg/kg-day for females, respectively. Because the original 1983 pathology report was completed before the publication of NTP's diagnostic criteria for proliferative liver lesions, and diagnostic discrepancies were found in the original pathology report, the sponsor of the study (Velsicol Chemical Corporation) convened a pathology working group (PWG) of six U.S. pathologists to review the liver histopathological slides. The PWG's liver pathology findings are reported herein.

No treatment-related clinical signs, deaths, or biochemical and hematological parameters were observed (Khasawinah and Grutsch, 1989b). The original pathologist noted that exposure-related lesions were found only in the liver. Absolute liver weight was increased significantly ($p < 0.05$) in 5- and 25-ppm male rats at 130 weeks and in 25-ppm female rats at 26 and 52 weeks. Large granular lymphocyte leukemia was found at a high incidence in all groups of female and male rats, including controls. Elevated incidence of leukemia in control F344 rats living beyond 104 weeks, relative to rats sacrificed at 104 weeks, was reported as a common, age-related occurrence that is accompanied by nonneoplastic liver lesions, including necrosis, cytomegaly (i.e., swelling or hypertrophy), and fatty degeneration (Solleveld et al., 1984; Stromberg and Vogtsberger, 1983). Because age-related leukemia confounded exposure-related liver lesions, the PWG examined incidence of nonneoplastic liver lesions in rats without leukemia. Nonleukemic female rats in the 5- and 25-ppm groups had statistically significant increases in hepatocellular hypertrophy relative to controls, whereas nonleukemic females in the 1-ppm group and nonleukemic males in the 1-, 5- and 25-ppm groups had no significant increases. Overall incidence for hepatocellular adenomas in 25-ppm male rats (not including interim-kill rats) was increased by a marginally statistical significance relative to controls (7/64 vs. 2/64). Incidences for hepatic neoplasms in other exposed groups were not increased. According to the authors, no increased incidence of foci of cellular alteration in nonleukemic livers (the first stage of rat liver carcinogenesis) was found in exposed groups relative to controls.

Incidences for hepatocellular adenomas in the concurrent F344 rat controls (3.1% in males and 0% in females) were below historical values for control F344 rats in U.S. (range 0-17%) and Japanese laboratories (2.5% for males dying before 104 weeks and 9.6% for males in studies of longer duration). In consideration of this and the marginal significance of the observed increased incidence of hepatocellular adenomas in 25-ppm males compared with controls ($p = 0.08$), the PWG concluded that chlordane treatment in this study did not produce a tumorigenic response in male or female F344 rats. The Toxicology Branch of EPA's Office of Pesticides and Toxic Substances concurred with this conclusion (U.S. EPA. 1988).

### II.A.4. Supporting Data for Carcinogenicity

U.S. EPA (1986) evaluated genotoxicity studies on chlordane and concluded that the available genotoxicity data did not provide a fully comprehensive data set on which to definitively assess the mutagenic potential of chlordane.

In a more recent review of chlordane genotoxicity studies, Jackson et al. (1993) concluded that three studies provided sufficient evidence to classify chlordane as having "limited evidence of mutagenicity". These studies found weakly positive results for gene mutation in V-79 cells (Ahmed et al., 1977), positive results in the mouse lymphoma assay (McGregor et al., 1988), and positive results for the induction of sister chromatid exchanges in cultured human lymphocytes (Sobti et al., 1983).

In general, chlordane has been classified as a "non-genotoxic murine hepatocarcinogen", but the mechanisms whereby it produces cancer in rodents are uncertain (see, for example, Malarkey et al., 1995). Whereas the evidence of mutagenicity for chlordane is limited, several toxicological properties have been described that may play roles in the expression of chlordane carcinogenicity in rodents, including chlordane induction of hair follicle nuclear aberrations in CD-1 mice (Schop et al., 1990); irreversible binding of chlordane metabolites to intracellular macromolecules, including DNA and RNA (Brimfield and Street, 1981); chlordane inhibition of intercellular communication (Telang et al., 1982; Ruch et al., 1990; Bessi et al., 1995); chlordane stimulation of protein kinase C activity (Moser and Smart, 1989); chlordane induction of in vitro hepatic lipid peroxidation and DNA single-strand breaks (Hassoun et al., 1993); and chlordane suppression of in vitro immune responses (Johnson et al., 1987; Chuang et al., 1992).

Malarkey et al. (1995) found no H- or K-ras mutations in hepatocellular tumors from chlordane-exposed B6C3F1 or B6D2F1 mice, whereas H-ras mutations were found in 4/10 spontaneous hepatocellular tumors examined from control B6C3F1 mice and in 6/15 liver tumors from control B6D2F1 mice. This observation of lower H-ras mutation frequency in tumors from exposed mice than spontaneous tumors from control mice has been observed for other nongenotoxic agents that cause liver tumors in mice, including dieldrin, Aroclor, phenobarbital, and chloroform. The majority of neoplastic hepatocytes and altered hepatocellular foci in exposed mice had acidophilic cytoplasm, whereas neoplastic hepatocytes and altered hepatocellular foci in controls had basophilic cytoplasm. Therefore, spontaneous tumors are different than chlordane-induced tumors in two respects: (1) the occurrence of H-ras gene mutations and (2) histochemical staining.

Five compounds structurally related to chlordane (aldrin, dieldrin, heptachlor, heptachlor epoxide, and chlorendic acid) have produced liver tumors in mice. Chlorendic acid also has produced liver tumors in rats.

## II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

### II.B.1. Summary of Risk Estimates

### II.B.1.1. Oral Slope Factor — 3.5E-1 per mg/(kg-day)

### II.B.1.2. Drinking Water Unit Risk — 1E-5 per (ug/L)

### II.B.1.3. Extrapolation Method — Linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

| Risk Level | Concentration |
|---|---|
| **E-4 (1 in 10,000)** | 1E+1 ug/L |
| **E-5 (1 in 100,000)** | 1E+0 ug/L |
| **E-6 (1 in 1,000,000)** | 1E-1 ug/L |

### II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

**Tumor Type:** Hepatocellular carcinoma
**Test animals:** Mouse/CD-1 (IRDC), Mouse/B6C3F1 (NCI), Mouse/ICR (Khasawinah and Grutsch)
**Route:** Diet

| Administered Dose (ppm) | Human Equivalent Dose (mg/kg-day) | Carcinoma Incidence | Reference |
|---|---|---|---|
| **Male** | | | IRDC(1973) |

| Administered Dose (ppm) | Human Equivalent Dose (mg/kg-day) | Carcinoma Incidence | Reference |
|---|---|---|---|
| **0** | 0 | 3/33 | |
| **5** | 0.1022 | 5/55 | |
| **25** | 0.5137 | 41/52 | |
| **50** | 1.0273 | 32/39 | |
| **Female** | | | IRDC(1973) |
| **0** | 0 | 0/45 | |
| **5** | 0.1022 | 0/61 | |
| **25** | 0.5137 | 32/50 | |
| **50** | 1.027 | 26/37 | |
| **Male** | | | NCI(1977) |
| **0** | 0 | 17/92 | |
| **29.9** | 0.65187 | 16/48 | |
| **56.2** | 1.1511 | 43/49 | |
| **Female** | | | NCI(1977) |
| **0** | 0 | 3/78 | |

| Administered Dose (ppm) | Human Equivalent Dose (mg/kg-day) | Carcinoma Incidence | Reference |
|---|---|---|---|
| **30.1** | 0.6187 | 3/47 | |
| **63.8** | 1.3093 | 33/49 | |
| **Male** | | | Khasawinah and |
| **0** | 0 | 3/71 | Grutsch (1989b) |
| **1** | 0.0216 | 3/71 | |
| **5** | 0.1079 | 7/72 | |
| **12.5** | 0.2698 | 9/72 | |

### II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

The quantitative estimate is based on the geometric mean of the five data sets, all hepatocellular carcinomas in mice. The slope factors [units of mg per (kg/day)] for the individual data sets are as follows: CD-1 males, 0.858; CD-1 females, 0.217; B6C3F1 males, 0.345; B6C3F1 females, 0.114; and ICR males, 0.710. In the calculation of human equivalent dose from the dietary concentrations, data in the publications were used (where given) to arrive at the animal dose in mg/kg-day units, and the human equivalent dose was calculated from the animal dose using the following equation: human dose = animal dose x (w/70)E1/4, where w is the adult body weight of the mice. The animal weights were assumed to be 30 g in the absence of data in the publications; however, the NCI study stated that males weighed 35 g, and females weighed 30 g, so the actual weights were used rather than the 30-g default value. In the NCI study, the animal dose was assumed to be 0.13 times the concentration in the feed (the default assumption in the absence of animal dose values in the report). Also in the NCI study, the pooled control tumor incidence data were used instead of the matched control (not given above) data. None of the studies presented above, except Khasawinah and Grutsch, reported hepatocellular adenomas, and the above data are for carcinomas alone. The only other study showing adenomas is the Barrass et al. (1993) study (not presented here), and that was

for only one dose group. These two studies are not considered extensive or reliable enough to derive a human estimate of carcinogenic risk. Neither the male nor the female IRDC data could be fit to the multistage model, and the procedure of deleting the high-dose group was used to get an adequate fit. In the case of the females, the best fit was obtained by a polynomial with all terms zero except Q(6), the sixth degree in powers of dose. Because the low-dose slope determination for the IRDC data was judged to be unreliable, the effect of deleting the IRDC data from the geometric mean was evaluated; the resulting geometric mean was 0.303 per mg/kg-day, which was close enough to the geometric mean of all five data sets (0.35 per mg/kg-day) so that this difficult data affected the result to only an insignificant extent. The earlier IRIS Summary of the IRDC data sets used a version of the multistage model in which the degree of the polynomial was fixed at 3; because that model did not adequately fit the data, it was not used here.

The 1996 proposed cancer guidelines propose an alternate method of low-dose extrapolation in which a linear extrapolation to small doses is done based on the lower 95% confidence limit of the dose giving a 10% incidence of tumors. Linear extrapolation from this point to zero dose is then performed. Using this method, the five data sets would have the following slope values: CD-1 males, 1.136; CD-1 females, 0.699; B6C3F1 males, 0.502; B6C3F1 females, 0.218; and ICR males, 0.676. The geometric mean of these values is 0.567, compared with 0.349, the mean of the slopes from the linearized multistage model. The higher slope values derived from the alternate method, compared with the low-dose slope estimates derived from the linear multistage procedure, is a reflection of the positive curvature (concave upwards) of all of the animal dose-response curves except the ICR mice data set. The alternate method is not used because the proposed guidelines are not yet in effect.

The unit risk should not be used if the water concentration exceeds 1000 ug/L, because, above this concentration, the unit risk may not be appropriate.

### II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

Hepatocellular carcinomas were induced by dietary chlordane of comparable concentrations in five mice strains and in both sexes. The liver is also the target organ for toxicity in rats. There were an adequate number of animals in these assays, and the slope values are similar. Therefore, the confidence is high that chlordane is a mouse liver carcinogen at dietary concentrations above 10 ppm. Although there is indication that the dose-response curve is sublinear in the dose region between 5 and 60 ppm, linearity at low doses cannot be ruled out on theoretical grounds. Although the evidence for chlordane exposure leading to cancer in humans is tentative at best, it indicates that the target is the hematopoietic system rather than the liver. Therefore, it is prudent to regard mice liver cancer as an indicator of human hazard,

and to regard the extrapolated linear no-threshold dose-response curve as a health-protective estimate of the doses at which human Hazards could occur.

## II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

### II.C.1. Summary of Risk Estimates

#### II.C.1.1. Air Unit Risk — 1E-4 per (ug/cu.m)

#### II.C.1.2. Extrapolation Method — Linearized multistage procedure, extra risk

Air Concentrations at Specified Risk Levels:

| Risk Level | Concentration |
|---|---|
| **E-4 (1 in 10,000)** | 1E+0 ug/cu.m |
| **E-5 (1 in 100,000)** | 1E-1 ug/cu.m |
| **E-6 (1 in 1,000,000)** | 1E-2 ug/cu.m |

### II.C.2. Dose-Response Data for Carcinogenicity, Inhalation Exposure

The air unit risk estimate was derived from the oral slope factor (Section II.B.1) because no chronic bioassays have been done via the inhalation route. As discussed in Section 5.3.3 of the toxicological review (U.S. EPA, 1997), the human air unit risk is estimated assuming 100% absorption of inhaled chlordane and assuming a breathing rate of 20 cu.m/day.

### II.C.3. Additional Comments (Carcinogenicity, Inhalation Exposure)

The inhalation toxicity data indicate that inhaled chlordane causes systemic effects similar to effects via ingestion exposure. Therefore, there is no reason to expect effects unique to inhalation, and estimates for inhalation risk are justified. The unit risk should not be used if the air concentration exceeds 100 ug/cu.m because above this concentration, the unit risk may not be appropriate.

### II.C.4. Discussion of Confidence (Carcinogenicity, Inhalation Exposure)

See oral quantitative estimate.

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## II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

### II.D.1. EPA Documentation

Source Document — U.S. EPA, 1986; Toxicological Review of Chlordane, U.S. EPA, 1997.

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 (U.S. EPA 1997). ***To review this appendix, exit to the toxicological review, Appendix B, Summary of and Response to External Peer Review Comments (PDF)***.

### II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Consensus Review Date -- 11/03/1997.

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Chlordane (Technical) conducted in November 2001 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

### II.D.3. EPA Contacts (Carcinogenicity Assessment)

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).

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

## VI. Bibliography

Substance Name — Chlordane (Technical)
CASRN — 12789-03-6

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## VII. Revision History

Substance Name — Chlordane (Technical)
CASRN — 12789-03-6

| Date | Section | Description |
|---|---|---|
| **09/30/1987** | II. | Carcinogenicity section added |
| **04/01/1989** | I.A. | Withdrawn, new RfD verified (in preparation) |
| **06/01/1989** | I.A. | Revised oral RfD summary added |
| **02/07/1998** | I.A., I.B., II., VI. | Revised RfD and cancer assessments, new RfC added |
| **12/03/2002** | I.A.6., I.B.6., II.D.2. | Screening-Level Literature Review Findings message has been added. |

## VIII. Synonyms

Substance Name — Chlordane (Technical)
CASRN — 12789-03-6
Last Revised — 02/07/1998

- 57-74-9
- Belt
- CD 68
- Chlordane
- Chlorindan
- Chlor Kil
- Corodan
- Dowchlor
- ENT 9, 932
- HCS 3260
- Kypchlor
- M 140

- M 410
- 4,7-Methanoindan, 1,2,4,5,6,7,8,8-Octachloro-3a,4,7,7a-Tetrahydro-
- 4,7-Methano-1H-Indene, 1,2,4,5,6,7,8,8-Octachloro-2,3,3a,4,7,7a-Hexahydro-
- NCI-C00099
- Niran
- Octachlorodihydrodicyclopentadiene
- 1,2,4,5,6,7,8,8-Octachloro-2,3,3a,4,7,7a-Hexahydro-4, 7-Methano-indene
- 1,2,4,5,6,7,8,8-Octachloro-3a,4,7,7a-Hexahydro-4,7-Methylene Indane
- Octachloro-4, 7-Methanohydroindane
- Octachloro-4, 7-Methanotetrahydroindane
- Octa-Klor
- Oktaterr
- Ortho-Klor
- Synklor
- TAT Chlor 4
- Topiclor
- Toxichlor
- Velsicol 1068