Substance code
Chlordecone (Kepone); CASRN 143-50-0; 00/00/0000

Human health assessment information on a chemical substance is included in IRIS only after a comprehensive review of toxicity data by U.S. EPA health scientists from several program offices, regional offices, and the Office of Research and Development. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the positions that were reached during the review 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 at http://www.epa.gov/iris/backgr-d.htm.

STATUS OF DATA FOR CHLORDECONE (KEPONE)

File First On-Line 00/00/0000

Category (section)	Status	Last Revised
Chronic Oral RfD Assessment (I.A.)	on-line	00/00/0000
Chronic Inhalation RfC Assessment (I.B.)	discussion	00/00/0000
Carcinogenicity Assessment (II.)	on-line	00/00/0000

_I. HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

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

Substance Name -- Chlordecone (Kepone)
CASRN -- 143-50-0
Section I.A. Last Revised -- 00/00/0000

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (possibly threshold) mode of action. It is expressed in units of mg/kg-day. Please refer to the guidance documents at http://www.epa.gov/iris/backgr-d.htm for an elaboration of these concepts.

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

This is the first IRIS assessment for chlordecone. No oral RfD for chlordecone was previously available on IRIS.

___I.A.1. CHRONIC ORAL RfD SUMMARY

Critical Effect	Point of Departure*	UF	Chronic RfD
Renal lesions (glomerulosclerosis) in female Wistar rats 2-year feeding study Larson et al., 1979	$BMDL_{10}$[a]: 0.08 mg/kg-day	300	0.0003 mg/kg-day

*Conversion Factors and Assumptions -- The available models for quantal incidence data in the EPA Benchmark Dose Software (BMDS version 1.3.2) were fit to the female rat incidence data for histopathologic renal lesions (glomerulosclerosis) in female rats. The probit model provided the best fit to the female rat data. The BMD_{10} associated with a 10% extra risk for glomerulosclerosis in female rats was 0.12 mg/kg-day, and its lower 95% confidence limit ($BMDL_{10}$ shown above) was 0.08 mg/kg-day.
[a]BMD_{10} = benchmark dose for a 10% response; $BMDL_{10}$ = 95% lower bound on the BMD_{10}.

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES

Larson, PS; Egle, JL; Hennigar, GR; et al. (1979) Acute, subchronic, and chronic toxicity of chlordecone. Toxicol Appl Pharmacol 48(1):29–41.

Larson et al. (1979a) fed groups of Wistar rats (40/sex/group) diets estimated (based on graphically depicted food consumption and body weight data) to result in dose levels of 0, 0.06, 0.3, 0.5, 1.6, 3.9, or 7.0 mg/kg-day for up to two years. All rats in the highest two dose groups died within the first 6 months. Though the two highest dose groups were uninformative because of high mortality, four acceptable low-dose exposure groups exist. However due to serial sacrifices and early mortality in several dose groups, effective numbers of animals available for histological examination at the conclusion of the study were greatly reduced with only four animals per group available in the 1.6 mg/kg-day dose group. The most sensitive effects observed in this study include kidney lesions in female rats, testicular atrophy in males, and liver lesions in both sexes. The authors reported increased incidence of liver lesions and an increase in relative liver weights in female rats at 0.5 mg/kg-day and male rats at 1.6 mg/kg-day. The liver lesions observed were characterized primarily as fatty changes and hyperplasia.

In addition to liver lesions and testicular effects, Larson et al. (1979a) also observed a significant, dose-related increase in the incidence and severity of renal lesions in female Wistar rats in the

0.3, 0.5, and 1.6 mg/kg-day dose groups. The background incidence of renal lesions in male rats was high (56% as compared to 12% in female rats) and, as such, effects in dosed animals did not achieve statistical significance. An increase in proteinuria, a clinical sign of glomerular damage, was observed in female rats, starting at 0.3 mg/kg-day, though data from individual animals were not reported, precluding statistical analysis for this endpoint. Larson et al. (1979a) identified a LOAEL of 0.3 mg/kg-day for proteinuria and increased incidence of glomerulosclerosis in female Wistar rats with a corresponding NOAEL of 0.06 mg/kg-day.

Renal effects with chlordecone exposure were also reported in other studies. NCI (1976b) reported chronic kidney inflammation in male (at 0.6 mg/kg-day) and female Osborne-Mendel rats (at 2.0 mg/kg-day). Chu et al. (1980) reported that 28 days of dietary exposure to chlordecone (at 0.07 mg/kg-day) produced eosinophilic inclusions in proximal tubules in 2/10 male Sprague-Dawley rats. A 32-month oral exposure study in beagles (Larson et al., 1979a) reported increased relative kidney weights in the 0.5 mg/kg-day chlordecone exposure group, though renal histology findings were negative. Furthermore, a 3-month oral study observed increased relative kidney weight in female rats exposed to 1.6–1.7 mg/kg-day, though no histological findings were noted (Cannon and Kimbrough, 1978).

In consideration of the available studies reporting effects of chronic and subchronic chlordecone exposure in humans and animals, Larson et al. (1979a) was chosen as the principal study. This study was adequately designed with several acceptable dose groups and adequate numbers of animals (though numbers of animals in high dose groups were greatly reduced following serial sacrifices and early mortality). Results were sufficiently reported for most endpoints. Sensitive endpoints identified in this study include glomerulosclerosis, liver lesions, and testicular atrophy. Though testicular atrophy was observed at 13 weeks, the only lesions observed chronically that were reported to be treatment related were in the liver and kidney. This observation coupled with the lack of support for testicular lesions in other studies in rats of similar dose and duration (Linder et al., 1983; Cannon and Kimbrough, 1978) decreases confidence in this endpoint. Additionally, the liver lesions observed in the principal study (characterized as fatty changes and hyperplasia) occurred at higher doses as compared with the observed kidney lesions. After consideration of all endpoints, the increased incidence of glomerulosclerosis in female rats was determined to be the most sensitive and biologically significant effect detected in this study. Furthermore, the chlordecone database contains additional support for the specific endpoint of glomerular damage (Sobel et al., 2006, 2005; Chetty et al., 1993) and general support for the kidney as a target organ as determined by increased kidney weights seen in studies in addition to the principal study (Cannon and Kimbrough, 1978; NCI, 1976a).

Glomerulosclerosis is believed to be an irreversible effect that can result in renal impairment (Medical College of Wisconsin, 1999). The mechanism by which chlordecone causes kidney lesions is not known; however, there is no indication that kidney lesions would not occur in humans chronically exposed to chlordecone. Therefore, for the above reasons, Larson et al. (1979a) was chosen as the principal study and renal lesions as the critical effect.

___I.A.3. UNCERTAINTY FACTORS

UF = 300

A total UF of 300 was applied to the POD of 0.08 mg/kg-day: 10 for interspecies extrapolation from animals to humans (UF_A); 10 for human intraspecies variability (UF_H); and 3 to account for database deficiencies (UF_D).

A 10-fold UF was used to account for uncertainties in extrapolating from laboratory rats to humans. Aside from a difference in metabolism (humans produce chlordecone alcohol, whereas rats do not), the available data do not suggest differential toxicity of these forms, nor do the toxicity data from various animal species provide marked evidence that rats or any other species are more sensitive to chlordecone than humans. Consequently, the default UF of 10 for extrapolating from laboratory animals to humans was applied.

A 10-fold UF was used to account for variation in susceptibility among members of the human population (i.e., interindividual variability). Insufficient information is available to predict potential variability in human susceptibility.

An UF of 3 was applied to account for deficiencies in the chlordecone toxicity database. The database includes limited human data from observational studies of occupationally exposed workers. The database also includes several studies in laboratory animals, including chronic and subchronic dietary exposure studies and several subchronic reproductive and developmental studies, as well as one specifically assessing developmental neurotoxicity. The chlordecone database does not have an appropriately designed multigenerational reproductive study, but includes approximately 10 oral repeat-exposure studies assessing reproductive and developmental toxicity, including several single-generation reproductive toxicity studies and three developmental studies in rats and mice (Linder et al., 1983; Squibb and Tilson, 1982; Cannon and Kimbrough, 1979; Chernoff and Rogers, 1976; Good et al., 1965; Huber et al., 1965). Several of these reproductive studies have indicated decreased reproductive success in chlordecone-treated animals (Cannon and Kimbrough, 1979; Good et al., 1965; Huber et al., 1965). The database also includes two nonstandard multigenerational studies that evaluate reproductive success of chlordecone-treated animals (Gellert and Wilson, 1979; Good et al., 1965). Due to limited scope and design, these studies are not considered adequate for the assessment of potential multigenerational reproductive toxicity.

Because the POD was selected from a dose associated with an endpoint identified by a chronic dietary study (Larson et al., 1979a), no uncertainty factor is needed for exposure duration (subchronic to chronic). An UF for LOAEL-to-NOAEL extrapolation was not used because the current approach is to address this factor as one of the considerations in selecting a BMR for BMD modeling. In this case, a BMR of a 10% increase in glomerulosclerosis was selected under an assumption that it represents a minimal biologically significant change.

The oral RfD for chlordecone was calculated as follows:

$$\begin{aligned} RfD &= BMDL_{10} \div UF \\ &= 0.08 \text{ mg/kg-day} \div 300 \\ &= 0.0003 \text{ or } 3E\text{-}4 \text{ mg/kg-day} \end{aligned}$$

___I.A.4. ADDITIONAL STUDIES/COMMENTS

The only available data concerning health effects of chlordecone in humans are derived from studies of a single group of 133 men exposed occupationally to chlordecone in the late 1970s at a chlordecone manufacturing facility in Hopewell, Virginia (Taylor, 1985, 1982; Guzelian, 1982a; Guzelian et al., 1980; Sanborn et al., 1979; Cannon et al., 1978; Martinez et al., 1978; Taylor et al., 1978). Due to inadequate industrial safety measures at the factory, substantial inhalation, dermal, and oral exposures likely occurred (Cannon et al., 1978). Toxicity observed in the exposed workers included effects on the nervous system, liver, and reproductive system. Of the 133 men, 76 experienced neurological symptoms, especially tremors, nervousness, and headaches, sometimes persistent for as long as 9–10 months after cessation of exposure and the start of treatment (Cannon et al., 1978). In addition, a subset of the men experienced reproductive effects, including oligospermia, reduced sperm motility, and decreased libido (Taylor, 1982). A subset of 32 of the occupationally exposed workers with clinical signs or symptoms of chlordecone toxicity and high chlordecone blood levels (>0.6 μg/mL at the time of diagnosis) were examined specifically for hepatotoxicity (Guzelian et al., 1980). Hepatomegaly was observed in 20 of 32 workers. Minimal elevation (less than two fold) of serum alkaline phosphatase (SALP) was noted in seven patients; however, other liver enzymes were normal including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyl transpeptidase (GGT) (Guzelian et al., 1980). Sulfobromophthalein retention, a measure of liver clearance, was normal in a subset of 18 workers tested (Guzelian et al., 1980). Upon biopsy of 12 workers with hepatomegaly, histological changes included proliferation of the smooth endoplasmic reticulum (SER) and cytoplasmic accumulation of lipofuscin. These changes in the liver were characterized by the authors as nonadverse in nature and were suggested to be adaptive changes rather than a reflection of hepatotoxicity (Guzelian, 1982a,b; Guzelian et al., 1980; Taylor et al., 1978). Upon follow-up of the exposed workers 2–3 years after exposure cessation, hepatomegaly had resolved in all workers and biopsies were negative for abnormal histopathological findings (Guzelian et al., 1980). Clinical indications of kidney dysfunction were not detected in workers. However, it is unclear, whether the relatively short average exposure duration of workers (5–6 months) would be sufficient for the development of detectable kidney impairment.

Because of uncertainties regarding exposure routes and exposure levels at the facility, NOAELs or LOAELs could not be established for the observed neurological, liver, and reproductive effects in the occupationally exposed workers. Additionally, workers may have had concomitant exposure to the chemical precursors used to manufacture chlordecone. Because of these major uncertainties, health effects data in these workers are unsuitable for derivation of an RfD.

The toxicity database for oral exposure in laboratory animals includes a few chronic duration studies (Chu et al., 1981a; Larson et al., 1979; NCI, 1976a,b) and several reproductive and developmental toxicity studies (see Section 4.5 and Table 4-18 of the *Toxicological Review* [U.S. EPA, 2009]).

Chu et al. (1981a) fed rats (10/group) chlordecone at 0.07 mg/kg-day for 21 months. The authors reported an increase in liver lesions (described as pericentral cytoplasmic vacuolation with mild anisokaryosis) compared to the control group (5/6 compared to 3/7). Chu et al. (1981a) also reported an increase in thyroid lesions (described as mild degenerative and proliferative changes

in the epithelium). However, because of small study size and high incidence of effects in the controls, these increases were not statistically significant (Chu et al. 1981a). Thus, due to limited study size, dosing regimen, and high incidence of effects in the control group, this study was not selected as the principal study.

NCI (1976a,b) conducted a 20-month feeding study in B6C3F1 mice and Osborne-Mendel rats. Though treatment groups consisted of 50/sex/group for both rats and mice, only 10 (19 for male mice) matched controls per sex were used. Pooled control groups (from the same laboratory with birth dates within 3–4 months of the treatment groups) contained about 100/sex/group. During the course of the study, toxicity and mortality in the high-dose groups prompted the investigators to reduce dietary chlordecone concentrations to one-half to one-sixth of the previous levels. The resulting time-weighted-average dietary concentrations were 0, 8, or 24 ppm (0, 0.6, or 1.7 mg/kg-day) for male rats and 0, 18, or 26 ppm (0, 1.4, or 2.0 mg/kg-day) for female rats. In mice, time-weighted-average dietary concentrations were 0, 20, or 23 ppm (0, 3.4, or 3.9 mg/kg-day) for male mice and 0, 20, or 40 ppm (0, 3.5, or 7.0 mg/kg-day) for female mice. Noncancer effects reported in response to chlordecone treatment included tremors, dermatologic changes, and liver lesions.The observed liver lesions were characterized as extensive hyperplasia and atypia in both male and female mice in both dose groups. However, due to the lack of incidence data or statistical testing of non-cancer effects, this study was not selected as the principal study.

Support in the chlordecone database exists for a variety of reproductive effects with chlordecone exposure. Larson et al. (1979a) observed testicular atrophy in male rats treated with chlordecone for 13 weeks at dose levels of ≥1.6 mg/kg-day. The incidence of testicular atrophy at 13 weeks was reported as 1/10, 0/5, 1/5, 4/5, 4/5, and 5/5 at 0, 0.3, 0.5, 1.6, 3.9, and 7.0 mg/kg-day. Testicular effects were not noted for the longer exposure durations (1–2 years) in the same study. Other animal studies have shown male reproductive effects, such as decreased sperm viability, motility, and concentration, following exposure to chlordecone (US EPA, 1986; Linder et al., 1983). EPA (1986c) reported decreased sperm concentration in male rats treated orally for 10 days with 0.625 mg/kg-day chlordecone. Linder et al. (1983) saw sperm effects (decreased viability, motility, and concentration) in rats at 0.83 and 1.67 mg/kg-day (90 days of treatment); however, the authors did not see any treatment-related histological lesions or an effect on reproductive performance (number of pregnant females, number of live litters, average live litter size, number of implants, percentage of resorptions, and fetal weight) when treated males were mated to untreated females. This study and a study by Cannon and Kimbrough (1979) indicate that decreased reproductive success in experimental animals may not be solely attributable to male reproductive effects. Cannon and Kimbrough (1979) reported that treated female rats (1.6–1.7 mg/kg-day for 3 months) mated to control rats failed to produce litters, whereas treated males (1.2–1.6 mg/kg-day for 3 months) mated to control females had reproductive success similar to controls. Good et al. (1965) reported in a continuous breeding study that male and female mice treated with 0.94 mg/kg-day for 1 month prior to mating and 5 months during mating had impaired reproductive success; reduced production of litters was seen in treated mice and the mated offspring of treated mice. However, the general confidence in this study is limited by incomplete reporting of the variance of reproductive parameters and decreased fertility of the control mice one generation apart. Two other reproductive studies (Good et al., 1965; Huber et al., 1965) treated outbred mice in the diet for 1 month prior to mating and 3–5 months during the mating period with doses of chlordecone starting at 1.9 mg/kg-day and did not see a depression of reproductive parameters until doses of 3.3 or 5.6 mg/kg-day (Good et al., 1965, and Huber et

al., 1965, respectively). Additional studies have reported reproductive toxicity, but at higher doses (Swartz and Mall, 1989; Swartz et al., 1988; Gellert and Wilson, 1979; Huber, 1965).

Several studies described above demonstrate reproductive effects following chlordecone exposure at levels slightly higher than the level reported to cause renal lesions in chronically treated rats (Linder et al., 1983; Cannon and Kimbrough, 1979; Larson et al., 1979a; Good et al., 1965; Huber et al., 1965). Therefore, reproductive effects were not selected as the critical effect of chlordecone exposure. Nevertheless, potential points of departure (PODs) for reproductive endpoints from Linder et al. (1983), Squibb and Tilson (1982), Larson et al. (1979a), and Good et al. (1965) were considered in the derivation of a RfD (see Section 5.1.2 and Appendix B).

___I.A.5. CONFIDENCE IN THE CHRONIC ORAL RfD

Study -- Medium
Data Base -- Medium
RfD -- Medium

The overall confidence in the RfD and the principal study (Larson et al., 1979a) is medium. The principal study involves a sufficient number of animals per group, several acceptable dose levels, and a wide range of tissues and endpoints assessed. Confidence in the database is medium. The chlordecone database includes case studies of occupationally exposed workers, chronic and subchronic dietary exposure studies in laboratory animals, and several subchronic reproductive and developmental studies, including one developmental neurotoxicity study. However, the database is lacking a multigenerational reproductive toxicity study. Therefore, reflecting medium confidence in both the database and the principal study, confidence in the RfD is medium.

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

Source Document -- U.S. EPA (2009)

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Chlordecone* (U.S. EPA, 2009).

Agency Completion Date -- __/__/__

___I.A.7. EPA CONTACTS

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 (email address).

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

EXPOSURE

Substance Name -- Chlordecone (Kepone)
CASRN -- 143-50-0
Section I.B. Last Revised -- 00/00/0000

The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfC considers toxic effects for both the respiratory system (portal of entry) and for effects peripheral to the respiratory system (extrarespiratory effects). The inhalation RfC (generally expressed in units of mg/m^3) is analogous to the oral RfD and is similarly intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (possibly threshold) mode of action.

Inhalation RfCs are derived according to *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). Because RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical 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.B.1. CHRONIC INHALATION RfC SUMMARY

No inhalation RfC is derived for chlordecone due to the lack of appropriate inhalation exposure toxicity data for humans or animals and the lack of rat and human PBPK models for chlordecone that would permit route-to-route extrapolation from the oral dose-response data. Although adverse health effects from an occupational exposure incident may have resulted from inhalation exposure (in combination with oral and dermal exposures), the data do not identify doses at which effects occur (Taylor, 1985, 1982; Guzelian, 1982a; Guzelian et al., 1980; Sanborn et al., 1979; Cannon et al., 1978; Martinez et al., 1978; Taylor et al., 1978). Consequently, the human data cannot be used to define a dose-response relationship for inhalation exposure to chlordecone. No studies on the toxicity of chlordecone following inhalation exposure in laboratory animals were located. This lack of data precludes the derivation of an RfC.

___I.B.2. PRINCIPAL AND SUPPORTING STUDIES

Not applicable.

___I.B.3. UNCERTAINTY FACTORS

Not applicable.

___I.B.4. ADDITIONAL STUDIES/COMMENTS

Not applicable.

___I.B.5. CONFIDENCE IN THE CHRONIC INHALATION RfC

Not applicable.

___I.B.6. EPA DOCUMENTATION AND REVIEW OF THE CHRONIC INHALATION RfC

Source Document -- U.S. EPA (2009)

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Chlordecone* (U.S. EPA, 2009).

Agency Completion Date -- __/__/__

___I.B.7. EPA CONTACTS

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 (email address).

_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Chlordecone (Kepone)
CASRN -- 143-50-0
Section II. Last Revised -- 00/00/0000

This section 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 and inhalation exposure. Users are referred to Section I of this file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS are described in the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) and the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b). The quantitative risk estimates are derived from the application of a low-dose extrapolation procedure, and are presented in two ways to better facilitate their use. First, route-specific risk values are presented. The "oral slope factor" is a plausable upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a "unit risk" is a plausible upper bound on the estimate of risk per unit of concentration, either per μg/L drinking water (see Section II.B.1.) or per $\mu g/m^3$ air breathed (see Section II.C.1.). Second, the estimated

concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000 is also provided.

__II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

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

Under the U.S. EPA Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005a), chlordecone is likely to be carcinogenic to humans based on data from an oral cancer bioassay in rats and mice demonstrating an increase in the incidence of hepatocellular carcinomas in both sexes of both species (NCI, 1976 a,b). NCI (1976 a,b) demonstrated a statistically significant increase in hepatocellular carcinomas in both sexes of mice. Male and female rats exhibited increased incidences of hepatocellular carcinomas at high doses that were statistically significant when compared with pooled controls. The incidence of hepatocellular carcinomas was not statistically significant in comparison with matched controls for rats of either sex. The tumor response was particularly robust in male and female mice at the highest doses. NCI (1976 a,b) also demonstrated a decrease in the time to tumor in both sexes of both species. No other tumor types were significantly increased in either rats or mice in this study.

There are no studies in humans that assess the carcinogenic potential of chlordecone. Other chronic animal studies of chlordecone, Chu et al. (1981a) and Larson et al. (1976a), lacked adequate power to detect carcinogenicity. Chu et al. (1981a) included only one dose group of 10 animals per sex and did not use an adequately high dose (0.07 mg/kg-day). The study by Larson et al (1979a) also was limited in power. Specifically, only 4 animals per sex were examined in the highest dose group (1.6 mg/kg-day) at the termination of the 1-2 year study.

The mode of carcinogenic action of chlordecone in the livers of rats and mice is unknown. Most genotoxicity tests for chlordecone are negative. For the liver tumors in rats and mice, some data suggest that chlordecone may induce cell proliferation and lead to a promotion in the growth of preinitiated cells. However, key precursor events linked to observed cell proliferation have not been identified. In the absence of any information indicating otherwise, the liver tumors observed in the NCI cancer bioassay in rats and mice were considered relevant to the assessment of the human carcinogenic potential of chlordecone.

No animal cancer bioassay data following inhalation exposure to chlordecone are available. However, EPA's *Guidelines for Carcinogen Risk Assessment* (2005a) indicate that, for tumors occurring at a site other than the initial point of contact, the carcinogenic potential may apply to all routes of exposure that have not been adequately tested at sufficient doses. Thus, chlordecone is *likely* to be carcinogenic to humans by any route of exposure.

___II.A.2. HUMAN CARCINOGENICITY DATA

There are no human studies that assess carcinogenic potential of chlordecone. Human case reports and clinical observations of occupational chlordecone exposure lack sufficient design, power, and follow-up to determine carcinogenic potential of chlordecone in humans. A review of biological and epidemiological evidence of cancer found no population-based studies on cancer in humans related to chlordecone exposure (Ahlborg et al., 1995).

___II.A.3. ANIMAL CARCINOGENICITY DATA

Chlordecone has been shown to induce liver tumors in Osborne-Mendel rats and B6C3F1 mice in a single study performed by the National Cancer Institute (NCI, 1976a,b). B6C3F1 mice (50/sex/group) and Osborne-Mendel rats (50/sex/group) were exposed to chlordecone in the diet for 20 months. Dietary concentrations of chlordecone began at 0, 15, 30, or 60 ppm for male rats and 0, 30, or 60 ppm for female rats. In mice, dietary concentrations of chlordecone began at 0 or 40 ppm (two groups at this concentration) for males and 0, 40 or 80 ppm for females. During the course of the study, concentrations were reduced at least once in each treatment group due to toxicity. Time-weighted-average dietary concentrations were 0, 8, or 24 ppm (0, 0.6, or 1.7 mg/kg-day) for male rats and 0, 18, or 26 ppm (0, 1.4, or 2.0 mg/kg-day) for female rats. In mice, time-weighted-average dietary concentrations were 0, 20, or 23 ppm (0, 3.4, or 3.9 mg/kg-day) for male mice and 0, 20, or 40 ppm (0, 3.5, or 7.0 mg/kg-day) for female mice. Liver tumors described as hepatocellular carcinomas were observed in high-dose female rats at an incidence that was significantly elevated compared with the pooled control incidence (0/100, 0/10, 1/49, and 10/45 in the pooled control, matched control, and low-dose and high-dose groups, respectively). Incidences of male rats with hepatocellular carcinomas were lower at 0/105, 0/10, 1/50, and 3/44, respectively. The incidence of carcinomas in high-dose males was significant (p = 0.049) in comparison with pooled controls. The incidence of hepatocellular carcinomas was not statistically significant in comparison with matched controls (n=10) for rats of either sex. A significant dose-response trend was observed for the incidence of hepatocellular carcinoma in both male and female rats (Cochran-Armitage test conducted for this review). In mice, statistically significant elevated incidences of hepatocellular carcinomas were found in both exposed groups compared with matched and pooled control incidences (NCI, 1976a). Incidences for matched control, low-, and high-dose groups were 6/19, 39/48, and 43/49 for male mice and 0/10, 26/50, and 23/49 for female mice. No other tumor types in rats or mice were found to be significantly elevated in this study.

Other chronic animal studies of chlordecone, Chu et al. (1981a) and Larson et al. (1976a), lacked adequate power to detect carcinogenicity. Chu et al. (1981a) included only one dose group of 10 animals per sex and did not use an adequately high dose (0.07 mg/kg-day). The study by Larson et al (1979a) also was limited in power. Specifically, only 4 animals per sex were examined in the highest dose group (1.6 mg/kg-day) at the termination of the study.

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Similarities in the tumor profile of chlordecone and mirex, a structurally related chemical, have been observed in animals. Mirex has been shown to induce hepatocellular adenomas or carcinomans in both sexes of rats and mice (PWG, 1992; NTP, 1990; Ulland et al., 1977; NCI, 1976a,b; Innes et al., 1969). A statistically significantly increased incidence of liver tumors in F344/N and CD rats and B6C3F1 and B6AKF1 mice has been observed following chronic oral exposure to mirex at similar dose levels as chlordecone. The liver tumors resulting from exposure to mirex, similar to chlordecone, are described as predominantly well-differentiated masses without vascular invasion or metastases (PWG, 1992; NTP, 1990; Ulland et al., 1977; NCI, 1976a,b; Innes et al., 1969). In vivo and in vitro genotoxicity studies for mirex and chlordecone are generally negative. However, the available evidence for chlordecone and mirex is inadequate to establish a mode of action by which these chemicals induce liver tumors in rats and mice. It should be noted that, though chlordecone and mirex appear to have closely related biological activity and carcinogenicity in the liver at similar dose levels (though the mode of action for each is unknown), several noncancer effects reported following exposure to mirex and

chlordecone are dissimilar.

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

___II.B.1. SUMMARY OF RISK ESTIMATES

____II.B.1.1. Oral Slope Factor = 10 per mg/kg-day

The oral slope factor is derived from the $BMDL_{10}$, the 95% lower bound on the dose associated with a 10% extra cancer risk of hepatocellular carcinoma in male $B6C3F_1$ mice, by dividing the BMR (0.10) by the $BMDL_{10}$, and represents an upper bound, continuous lifetime exposure estimate of cancer potency:

$BMDL_{10}$, lower 95% bound on exposure at 10% extra risk, is 1.01×10^{-2} mg/kg-day. The slope of the linear extrapolation from the $BMDL_{10}$ to 0 = $0.10/1.01 \times 10^{-2} = 10$ per mg/kg-day.

BMD_{10}, central estimate of exposure at 10% extra risk, is 1.5×10^{-2} mg/kg-day. The slope of the linear extrapolation from the BMD_{10} to 0 = $0.10/1.5 \times 10^{-2} = 6.6$ per mg/kg-day.

This slope factor should not be used with chlordecone exposures greater than the POD (0.01 mg/kg/day) because the observed dose-response relationship may not continue linearly above this dose level.

____II.B.1.2. Drinking Water Unit Risk = 3×10^{-4} per µg/L*

Drinking Water Concentrations at Specified Risk Levels

Risk Level	Lower Bound on Concentration Estimate*
E-4 (1 in 10,000)	0.33 µg/L
E-5 (1 in 100,000)	0.033 µg/L
E-6 (1 in 1,000,000)	0.0033 µg/L

* The unit risk and concentration estimates assume water consumption of 2 L/day by a 70 kg human.

____II.B.1.3. Extrapolation Method

Multistage-Weibull model (implemented in TOX_RISK) with linear extrapolation from the POD ($BMDL_{10}$).

___II.B.2. DOSE-RESPONSE DATA

Tumor Type- liver hepatocellular carcinoma
Test Species- $B6C3F_1$ mice
Route- oral, dietary
Reference- NCI (1976a)

	Matched Control	Pooled Control	Low Dose mg/kg-day	High Dose mg/kg-day
Hepatocellular Carcinoma	6/19 (31%)	8/49 (16%)	39/48 (81%) [b]	43/49 (88%) [ab]
Time to first tumor (weeks)	87	87	70	62

[a] Statistically significant dose response trend ($p < 0.05$) by Cochran-Armitage trend test;
[b] Statistically significant increase in incidence, as compared with matched or pooled controls, using one-tailed ($p < 0.05$) Fisher's exact test for 2 × 2 contingency table;

___II.B.3. ADDITIONAL COMMENTS

Due to the earlier occurrence of tumors with increasing exposure and the mortality observed (especially in the high-dose groups in the second year of the study), dose-response methodologies which account for the influence of competing risks and intercurrent mortality on site-specific tumor incidence were used. The EPA has generally used a model which incorporates the time at which death-with-tumor occurred as well as the dose, such as the multistage-Weibull model implemented through the TOX_RISK dose-response software program TOX_RISK estimates time-weighted average continuous lifetime exposures, as well as converts these time-weighted exposures to human equivalents using EPA's accepted cross-species scaling methodology of $(\text{body weight})^{3/4}$ (U.S. EPA, 1992).
See the *Toxicological Review of Chlordecone (Kepone)* for more information (U.S. EPA, 2009).

___II.B.4. DISCUSSION OF CONFIDENCE

Due to the early mortality in some dose groups, methods which can reflect the influence of intercurrent mortality on tumor incidence rates are preferred. EPA has generally used the multistage-Weibull model in this type of situation, because it incorporates the time at which death-with-tumor occurred; however, it is unknown how well this model or the linear low-dose

extrapolation predicts low-dose risks for chlordecone. The selected model does not represent all possible models one might fit, and other models could conceivably be selected to yield more extreme results consistent with the observed data, both higher and lower than those included in this assessment. The human equivalent oral slope factors estimated from the statistically significant increase in liver tumors ranged from 1 per mg/kg-day in female mice to 10 per mg/kg-day in male mice, a range of one order of magnitude.

The oral slope factor for chlordecone was quantified using the tumor incidence data for male mice, which were found to be more sensitive than female mice or female rats to the carcinogenicity of chlordecone. The oral slope factor calculated from male mice was 6-7 times higher than the slope factors calculated from female mice and female rats. Liver tumor incidence in the high dose group of male rats was far less robust (7%) than the high dose groups of female rats, female mice, or male mice, which had liver tumor incidences of 22%, 47% and 88%, respectively. As there is no information to inform which species or gender of animals would be most applicable to humans, the most sensitive group was selected for the basis of the oral slope factor.

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

No inhalation unit risk for chlordecone was derived. Cancer bioassays involving inhalation exposure to chlordecone are not available, and a route-to-route extrapolation is not recommended at this time. A physiologically based toxicokinetic model, which could assist in route-to-route extrapolation, has not been developed for chlordecone.

___II.C.1. SUMMARY OF RISK ESTIMATES

Not applicable.

____II.C.1.1. Inhalation Unit Risk

Not applicable.

____II.C.1.2. Extrapolation Method

Not applicable.

___II.C.2. DOSE-RESPONSE DATA

Not applicable.

___II.C.3. ADDITIONAL COMMENTS

Not applicable.

___II.C.4. DISCUSSION OF CONFIDENCE

Not applicable.

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

___II.D.1. EPA DOCUMENTATION

Source Document -- U.S. EPA (2009)

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Chlordecone* (U.S. EPA, 2009).

___II.D.2. EPA REVIEW

Agency Completion Date -- __/__/__

___II.D.3. EPA CONTACTS

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 (email address).

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

_VI. BIBLIOGRAPHY

Substance Name -- Chlordecone (Kepone)
CASRN -- 143-50-0
Section VI. Last Revised -- 00/00/0000

__VI.A. ORAL RfD REFERENCES

Cannon, SB; Kimbrough, RD. (1979) Short-term chlordecone toxicity in rats including effects on reproduction, pathological organ changes, and their reversibility. Toxicol Pharmacol 47:469–

476.

Cannon, SB; Veazey, JM; Jackson, RS; et al. (1978) Epidemic Kepone poisoning in chemical workers. Am J Epidemiol 107:529–537.

Chernoff, N; Rogers, EH. (1976) Fetal toxicity of Kepone in rats and mice. Toxicol Appl Pharmacol 38:189–194.

Chetty, KN; Walker, J; Brown, K; et al. (1993) Influence of dietary calcium on chlordecone-induced biochemical changes in serum of rat. Ecotoxicol Environ Saf 26(2):248–252.

Chu, I; Villeneuve, DC; Becking, GC; et al. (1980) Short-term study of the combined effects of mirex, photomirex, and Kepone with halogenated biphenyls in rats. J Toxicol Environ Health 6:421–432.

Chu, I; Villeneuve, DC; Valli, VE; et al. (1981a) Chronic toxicity of photomirex in the rat. Toxicol Appl Pharmacol 59:268–278.

Gellert, RJ; Wilson, C. (1979) Reproductive function in rats exposed prenatally to pesticides and polychlorinated biphenyls (PCB). Environ Res 18:437–443.

Good, EE; Ware, GW; Miller, DF. (1965) Effects of insecticides on reproduction in the laboratory mouse: I. Kepone. J Econ Entomol 58(4):754–757.

Guzelian, PS. (1982a) Chlordecone poisoning: a case study in approaches for the detoxification of humans exposed to environmental chemicals. Drug Metab Rev 13:663–679.

Guzelian, PS. (1982b) Comparative toxicology of chlordecone (Kepone) in humans and experimental animals. Ann Rev Pharmacol Toxicol 22:89–113.

Guzelian, PS; Vranian, G; Boylan, JJ; et al. (1980) Liver structure and function in patients poisoned with chlordecone (Kepone). Gastroenterology 78(2):206–213.

Huber, JJ. (1965) Some physiological effects of the insecticide Kepone in the laboratory mouse. Toxicol Appl Pharmacol 7:516–524.

Larson, PS; Egle, JL, Jr; Hennigar, GR. (1979) Acute, subchronic, and chronic toxicity of chlordecone. Toxicol Appl Pharmacol 48:29–41.

Linder, RE; Scotti, TM; McElroy, WK; et al. (1983) Spermotoxicity and tissue accumulation of chlordecone (Kepone) in male rats. J Toxicol Environ Health 12:183–192.

Martinez, AJ; Taylor, JR; Dyck, PJ; et al. (1978) Chlordecone intoxication in man: II. Ultrastructure of peripheral nerves and skeletal muscle. Neurology 28:631–635.

Medical College of Wisconsin. 1999. Glomerulosclerosis, *In Healthlink*. Accessed online at: http://healthlink.mcw.edu/article/943054092.html

NCI. (1976b) Carcinogenesis bioassay of technical grade chlordecone (Kepone) (CAS No. 143-50-0). Project # 455-5224. [unpublished raw data].

Sanborn, GE; Selhorst, JB; Calabrese, VP; et al. (1979) *Pseudotumor cerebri* and insecticide intoxication. Neurology 29(9 Pt. 1):1222–1227.

Sobel, ES; Gianini, J; Butfiloski, EJ; et al. (2005) Acceleration of autoimmunity by organochlorine pesticides in (NZB × NZW)F_1 mice. Environ Health Perspect 113(3):323–328.

Sobel, ES; Wang, F; Butfiloski, EJ; et al. (2006) Comparison of chlordecone effects on autoimmunity in (NZB × NZW) F(1) and BALB/c mice. Toxicology 218(2–3):81–89.

Squibb, RE; Tilson, HA. (1982) Effects of gestational and perinatal exposure to chlordecone (Kepone) on the neurobehavioral development of Fischer-344 rats. Neurotoxicology 3(2):17–26.

Swartz, WJ; Mall, GM. (1989) Chlordecone-induced follicular toxicity in mouse ovaries. Reprod Toxicol 3:203–206.

Swartz, WJ; Eroschenko, VP; Schutzmann, RL. (1988) Ovulatory response of chlordecone (Kepone)-exposed mice to exogenous gonadotropins. Toxicology 51(2–3):147–153.

Taylor, JR. (1982) Neurological manifestations in humans exposed to chlordecone and follow-up results. Neurotoxicology 3(2):9–16.

Taylor, JR. (1985) Neurological manifestations in humans exposed to chlordecone: follow-up results. Neurotoxicology 6(1):231–236.

Taylor, JR; Selhorst, JB; Houff, SA; et al. (1978) Chlordecone intoxication in man: I. Clinical observations. Neurology 28:626–630.

U.S. EPA. (1986) Final report on the evaluation of four toxic chemicals in an in vivo/in vitro toxicological screen: Acrylamide, chlordecone, cyclophosphamide, and diethylstilbestrol. EPA/600/1-86/002.

U.S. EPA (Environmental Protection Agency). (1988) Recommendations for and documentation of biological values for use in risk assessment. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Cincinnati, OH; EPA/600/6-87/008. Available from the National Technical Information Service, Springfield, VA; PB88-179874/AS, and online at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855.

U.S. EPA. (2009) Toxicological review of chlordecone (Kepone). Integrated Risk Information System (IRIS), National Center for Environmental Assessment, Washington, DC. Available online at http://www.epa.gov/iris.

__VI.B. INHALATION RfC REFERENCES

U.S. EPA. (1994) Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Cincinnati, OH; EPA/600/8-90/066F. Available from the National Technical Information Service, Springfield, VA, PB2000-500023, and online at http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=71993.

U.S. EPA. (2009) Toxicological review of chlordecone (Kepone). Integrated Risk Information System (IRIS), National Center for Environmental Assessment, Washington, DC. Available online at http://www.epa.gov/iris.

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Ahlborg, UG; Lipworth, L; Titus-Ernstoff, L; et al. (1995) Organochlorine compounds in relation to breast cancer, endometrial cancer, and endometriosis: an assessment of the biological and epidemiological evidence. CRC Crit Rev Toxicol 25(6):463–531.

Chu, I; Villeneuve, DC; Valli, VE; et al. (1981a) Chronic toxicity of photomirex in the rat. Toxicol Appl Pharmacol 59:268–278.

Innes, JRM; Ulland, BM; Valerio, MG; et al. (1969) Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: a preliminary note. J Natl Cancer Inst 42(6):1101–1114.

Larson, PS; Egle, JL, Jr; Hennigar, GR. (1979) Acute, subchronic, and chronic toxicity of chlordecone. Toxicol Appl Pharmacol 48:29–41.

NCI. (1976a) Report on carcinogenesis bioassay of technical grade chlordecone (Kepone) (CAS No. 143-50-0). Carcinogenesis Program, Division of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services, Bethesda, MD; DHEW Publication No. (NIH) 76-1278. Available from the National Technical Information Service, Springfield, VA; PB-264041 and online at http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/trchlordecone(kepone).pdf.

NCI. (1976b) Carcinogenesis bioassay of technical grade chlordecone (Kepone) (CAS No. 143-50-0). Project # 455-5224. [unpublished raw data].

NTP (National Toxicology Program). (1990) Toxicology and carcinogenesis studies of mirex (CAS No. 2385-85-5) in F344/N rats (feed studies). Public Health Service, U.S. Department of Health and Human Services; NTP TR313; NIH Publ. No. 90-2569. Available online at http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr313.pdf.

PWG (Pathology Working Group). (1992) Pathology Working Group report on mirex chronic toxicity/carcinogenicity study in F344 rats. Prepared by R.M. Sauer, PATHCO, Inc., Ijamsville, MD. (Unpublished report)

Ulland, BM; Page, NP; Squire, RL; et al. (1977) A carcinogenicity assay of mirex in Charles River CD rats. J Natl Cancer Inst 58:133–140.

U.S. EPA. (2002) A review of the reference dose concentration and reference concentration processess. Risk Assessment Forum, Washington, DC; EPA/630/P-02/002F. Available online at http://cfpub.epa.gov/ncea/raf/raf_pubtitles.cfm?detype=document&excCol=archive.

U.S. EPA. (2005a) Guidelines for carcinogen risk assessment. Federal Register 70(66):17765–18717. Available online at http://www.epa.gov/cancerguidelines.

U.S. EPA. (2005b) Supplemental guidance for assessing susceptibility from early-life exposure to carcinogens. Risk Assessment Forum, Washington, DC; EPA/630/R-03/003F. Available online at http://www.epa.gov/cancerguidelines.

U.S. EPA. (2009) Toxicological review of chlordecone (Kepone). Integrated Risk Information System (IRIS), National Center for Environmental Assessment, Washington, DC. Available online at http://www.epa.gov/iris.

_VII. REVISION HISTORY

Substance Name -- Chlordecone (Kepone)
CASRN -- 143-50-0
File First On-Line 00/00/0000

_VIII. SYNONYMS

Substance Name -- Chlordecone (Kepone)
CASRN -- 143-50-0
Section VIII. Last Revised -- 00/00/0000

decachlorooctahydro-1,3,4-metheno-2H-cyclobuta[cd]-pentalen-2-one
GC-1189