Heptachlor; CASRN 76-44-8

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 Heptachlor

File First On-Line 09/30/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	09/30/1987
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	09/30/1987

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Heptachlor
CASRN — 76-44-8
Last Revised — 09/30/1987

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

information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Liver weight increases increases in males **2-Year Rat Feeding Study** **Velsicol Chemical, 1955a**	NOEL: 3 ppm diet (0.15 mg/kg/day) LEL: 5 ppm diet (0.25 mg/kg/day)	300	1	5E-4 mg/kg/day

*Conversion Factors -- 1 ppm = 0.05 mg/kg/day (assumed rat food consumption)

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

Velsicol Chemical Corporation. 1955a. MRID No. 00062599. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Six groups of CF strain white rats containing 20/sex were fed for 2 years with diets of 0, 1.5, 3, 5, 7, or 10 ppm of heptachlor. Lesions in the liver were limited to 7 ppm and above and were characteristic of chlorinated hydrocarbons (that is, hepatocellular swelling and peripheral arrangements of the cytoplasmic granules of cells of the central zone of the liver lobules). The NOEL for the lesions was 5 ppm and the LEL was 7 ppm. The NOEL for increased liver-to-body weight for males only was 3 ppm and the LEL was 5 ppm.

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

UF — Based on a chronic exposure study, an uncertainty factor of 100 was used to account for inter- and intraspecies differences. An additional factor of 3 was considered appropriate because of the lack of chronic toxicity data in a second species, for a total uncertainty factor of 300. The serious deficiencies in the toxicologic database would normally warrant a 10-fold factor for this area of uncertainty. However, toxicity data for other cyclodiene insecticides (aldrin, dieldrin, chlordane, and heptachlor epoxide) suggest that dogs and rats do not differ greatly in sensitivity

to the effects of this class of compounds. Furthermore, liver toxicity has been fairly well established as the most sensitive endpoint for this class of compounds, which reduces the uncertainty attributable to the lack of information on other toxic effects.

MF — None

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

Data Considered for Establishing the RfD:

1) 2-Year Feeding - rat: Principal study - see previous description; no core grade

2) 8-Month Feeding - rat: NOEL=none; LEL=5 ppm (0.25 mg/kg/day) (LDT) (swelling of cells); no core grade (Velsicol Chemical, 1964)

3) 1-Generation Reproduction - rat: NOEL=5 ppm (0.25 mg/kg/day); LEL=7 ppm (0.35 mg/kg/day) (increased pup death); no core grade (Velsicol Chemical, 1955b)

4) 3-Generation Reproduction - rat: NOEL=10 ppm (0.5 mg/kg/day) (HDT) (no adverse effects); no core grade (Velsicol Chemical, 1967)

Data Gap(s): Chronic Dog Feeding Study; Rat Teratology Study; Rabbit Teratology Study

I.A.5. Confidence in the Oral RfD

Study — Low
Database — Low
RfD — Low

The principal study is of low quality and is given a low confidence rating. Since ths database on chronic toxicity is incomplete, the database is given a low confidence rating. Low confidence in the RfD follows.

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

Pesticide Registration Standard, August 1986

Pesticide Registration Files

Agency Work Group Review — 05/20/1985, 12/18/1985, 02/26/1986, 09/16/1986, 04/16/1987

Verification Date — 04/16/1987

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 Heptachlor 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).

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

Substance Name — Heptachlor
CASRN — 76-44-8

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Heptachlor
CASRN — 76-44-8
Last Revised — 09/30/1987

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 is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) 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 I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — B2; probable human carcinogen

Basis — Inadequate human data, but sufficient evidence exist from studies in which benign and malignant liver tumors were induced in three strains of mice of both sexes. Several structurally related compounds are liver carcinogens.

II.A.2. Human Carcinogenicity Data

Inadequate. There were 11 case reports involving central nervous system effects, blood dyscrasias, and neuroblastomas in children with pre- or postnatal exposure to chlordane and heptachlor (Infante et al., 1978). Since no other information was available, no conclusions can be drawn.

There were three epidemiologic studies of workers exposed to chlordane and/or heptachlor. One retrospective cohort study of pesticide applicators was considered inadequate in sample size and duration of follow-up. This study showed marginal statistically significant increased mortality from bladder cancer (3 observed) (Wang and McMahon, 1979a). The other two studies were retrospective cohort studies of pesticide manufacturing workers. Neither of them showed any statistically significant increased cancer mortality (Wang and McMahon, 1979b; Ditraglia et al., 1981). Both these populations also had confounding exposures from other chemicals.

II.A.3. Animal Carcinogenicity Data

Sufficient. Long-term carcinogenicity bioassays with heptachlor have been performed in rats and mice, with the latter showing a carcinogenic response. Davis (1965) fed groups of 100 male and 100 female C3H mice diets with 0 or 10 ppm heptachlor (purity not specified) for 2 years. Survival was low, with 50% of the controls and 30% of the treated mice surviving until the end of the experiment. A 2-fold increase in benign liver lesions over the controls was reported. After a histologic reevaluation, Reuber (as cited in Epstein, 1976), as well as four other pathologists, remarked a statistically significant increase in liver carcinomas in the treated male (64/87) and female (57/78) groups by comparison to controls (22/73 and 2/53 for males and females, respectively).

The NCI (1977) reported a significant dose-related increase of hepatocellular carcinomas in male and female B6C3F1 mice. Fifty male and 50 female mice were fed diets delivering technical-grade heptachlor at TWA concentrations of 6.1 and 13.8 ppm and 9 and 18 ppm, respectively. Treatment was for 80 weeks, followed by 10 weeks of observation. The authors also reported a statistically significant increase of hepatocellular carcinomas in high-dose males and females over the controls.

No indication of treatment-related increase of tumors has been reported in chronic studies with rats. In an early experiment, Witherup et al. (1955) fed 20 male and 20 female CFN rats each at 1.5, 3.5, 7.0, and 10.0 ppm in the diet for 110 weeks. Although no increase in tumors was found, liver lesions, described as the "chlorinated hydrocarbon" type, were observed at 7 and 10 ppm. Using 25 female CD rats, Jolley et al. (1966) also observed no malignant lesions of the liver but did find hepatocytomegaly when the rats were fed 7.5, 10, and 12.5 ppm heptachlor:heptachlor epoxide (mixture of 75:25). Over the 2 years of the experiment, a dose-related increase in mortality was observed. Two additional experiments, Cabral et al. (1972) and NCI (1977), found no increased incidence of hepatocellular carcinomas when the mixture was administered to Wistar rats by gavage or to Osborne-Mendel rats by diet.

II.A.4. Supporting Data for Carcinogenicity

Gene mutation assays indicate that heptachlor is not mutagenic in bacteria (Probst et al., 1981; Shirasu et al., 1976; Moriya et al., 1983) or mammalian liver cells (Telang et al., 1982). Negative results were reported in two dominant lethal assays using male germinal cells (Epstein et al., 1972; Arnold et al., 1977). DNA repair assays indicate that heptachlor is not genotoxic in rodent hepatocytes (Maslansky and Williams, 1981; Probst et al., 1981) but showed qualitative evidence of unscheduled DNA synthesis in human fibroblasts (Ahmed et al., 1977).

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

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

II.B.1. Summary of Risk Estimates

Oral Slope Factor — 4.5E+0 per (mg/kg)/day

Drinking Water Unit Risk — 1.3E-4 per (ug/L)

Extrapolation Method — Linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	8E-1 ug/L
E-5 (1 in 100,000)	8E-2 ug/L
E-6 (1 in 1,000,000)	8E-3 ug/L

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

Tumor Type: hepatocellular carcinomas
Test animals: mouse/C3H; mouse/B6C3F1
Route: diet
Reference: Davis, 1965; NCI, 1977

Administered Dose (ppm)	Human Equivalent Dose (mg/kg)/day	Tumor Incidence	Reference
Mouse/C3H, male			
0	0.000	22/73	Davis, 1965 as evaluated by Reuber,cited in Epstein, 1976
10	0.108	64/87	
Mouse/C3H, female			
0	0.000	2/53	

Administered Dose (ppm)	Human Equivalent Dose (mg/kg)/day	Tumor Incidence	Reference
10	0.108	57/78	
Mouse/B6C3F1, male (matched controls)			
0	0.000	5/19	NCI, 1977
6.1	0.063	11/46	
13.8	0.140	34/47	
Mouse/B56C3F1, female (matched controls)			
0.0	0.000	2/10	
9.0	0.094	3/47	

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

Four data sets showed a significant increase in hepatocellular carcinomas in treatment groups compared with controls in mice. The quantitative estimate is the geometric mean of the slope factors from the four mouse data sets. The slope factors for each set are: 12.4 per (mg/kg)/day for C3H male mice, 14.9 per (mg/kg)/day for C3H female mice, 2.79 per (mg/kg)/day for B6C3F1 male mice, and 0.83 per (mg/kg)/day for B6C3F1 female mice. Although the magnitude of the responses differed somewhat, a combined risk estimate was chosen because the two strains are related and so that relevant data will not be discarded.

The above unit risk should not be used if the water concentration exceeds 80 ug/L, since above this concentration the unit risk may not be appropriate.

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

Adequate numbers of animals were treated and observed for the majority of their expected lifetime. The incidences of malignant lesions were significantly increased in all four data sets, and dose-response effects were observed in the NCI (1977) study.

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

II.C.1. Summary of Risk Estimates

Inhalation Unit Risk — 1.3E-3 per (ug/cu.m)

Extrapolation Method — Linearized multistage procedure, extra risk

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	8E-2 ug/cu.m
E-5 (1 in 100,000)	8E-3 ug/cu.m
E-6 (1 in 1,000,000)	8E-4 ug/cu.m

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

The risk estimates were calculated from the oral data presented in II.B.2.

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

The above unit risk should not be used if the air concentration exceeds 8 ug/cu.m, since above this concentration the unit risk may not be appropriate.

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

See II.B.4.

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

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1986

The values in the 1986 Carcinogenicity Assessment for Chlordane and Heptachlor/Heptachlor Epoxide have been reviewed by the Carcinogen Assessment Group.

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

Agency Work Group Review — 04/01/1987

Verification Date — 04/01/1987

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 Heptachlor 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).

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

VI. Bibliography

Substance Name — Heptachlor
CASRN — 76-44-8

VI.A. Oral RfD References

Velsicol Chemical Corporation. 1955a. MRID No. 00062599. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Velsicol Chemical Corporation. 1955b. MRID No. 00062599. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Velsicol Chemical Corporation. 1964. MRID No. 00086210. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Velsicol Chemical Corporation. 1967. MRID No. 00147058. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

Davis, K. 1965. Pathology Report on Mice Fed Aldrin, Dieldrin, Heptachlor and Heptachlor Epoxide for Two Years. Internal FDA memorandum to Dr. A.J. Lehman, July 19.

Epstein, S.S. 1976. Carcinogenicity of heptachlor and chlordane. Sci. Total Environ. 6: 103-154.

NCI (National Cancer Institute). 1977. Bioassay of Heptachlor for Possible Carcinogenicity. NCI Carcinogenesis Tech. Rep. Ser. No. 9. (Also published as DHEW Publication No. [NIH] 77-809).

Reuber, M.D. 1977. Histopathology of Carcinomas of the Liver in Mice Ingesting Heptachlor or Heptachlor Epoxide. Exp. Cell Biol. 45: 147-157.

U.S. EPA. 1986. Carcinogenicity Assessment of Chlordane and Hepta- chlor/Heptachlor Epoxide. Prepared by the Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, DC. OHEA-C-204.

VII. Revision History

Substance Name — Heptachlor
CASRN — 76-44-8

Date	Section	Description
12/03/2002	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Heptachlor
CASRN — 76-44-8
Last Revised — 09/30/1987

- 76-44-8
- AGROCERES
- 3-CHLOROCHLORDENE
- DICYCLOPENTADIENE, 3,4,5,6,7,8,8a-HEPTACHLORO-
- DRINOX
- DRINOX H-34
- E 3314
- ENT 15,152
- EPTACLORO
- 1,4,5,6,7,8,8-EPTACLORO-3a,4,7,7a-TETRAIDRO-4,7-endo-METANO-INDENE
- GPKh
- H
- H-34
- HEPTACHLOOR
- 1,4,5,6,7,8,8-HEPTACHLOOR-3a,4,7,7a-TETRAHYDRO-4,7-endo-METHANO-INDEEN
- Heptachlor
- HEPTACHLORE
- 1(3a),4,5,6,7,8,8-HEPTACHLORO-3a(1),4,7,7a-TETRAHYDRO-4,7-METHANOINDENE

- 3,4,5,6,7,8,8-HEPTACHLORODICYCLOPENTADIENE
- 3,4,5,6,7,8,8a-HEPTACHLORODICYCLOPENTADIENE
- 1,4,5,6,7,8,8-HEPTACHLORO-3a,4,7,7a-TETRAHYDRO-4,7-ENDOMETHANOINDENE
- 1,4,5,6,7,10,10-HEPTACHLORO-4,7,8,9-TETRAHYDRO-4,7-ENDOMETHYLENEINDENE
- 1,4,5,6,7,8,8a-HEPTACHLORO-3a,4,7,7a-TETRAHYDRO-4,7-METHANOINDANE
- 1,4,5,6,7,8,8-HEPTACHLORO-3a,4,7,7a-TETRAHYDRO-4,7-METHANOINDENE
- 1,4,5,6,7,8,8-HEPTACHLORO-3a,4,7,7a-TETRAHYDRO-4,7-METHANOL-1H-INDENE
- 1,4,5,6,7,10,10-HEPTACHLORO-4,7,8,9-TETRAHYDRO-4,7-METHYLENEINDENE
- 1,4,5,6,7,8,8-HEPTACHLORO-3a,4,7,7,7a-TETRAHYDRO-4,7-METHYLENE INDENE
- 1,4,5,6,7,8,8-HEPTACHLOR-3a,4,7,7,7a-TETRAHYDRO-4,7-endo-METHANO-INDEN
- HEPTAGRAN
- HEPTAMUL
- 4,7-METHANOINDENE, 1,4,5,6,7,8,8-HEPTACHLORO-3a,4,7,7a-TETRAHYDRO-
- NA 2761
- NCI-C00180
- RCRA WASTE NUMBER P059
- RHODIACHLOR
- VELSICOL 104