

Heptachlor epoxide; CASRN 1024-57-3

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 epoxide

File First On-Line 03/31/1987

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 epoxide

CASRN — 1024-57-3

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
Increased liver-to-body weight ratio in both males and females 60-Week Dog Feeding Study Dow Chemical Co., 1958	NOEL: none LEL: 0.5 ppm (diet) (0.0125 mg/kg/day)	1000	1	1.3E-5 mg/kg/day

* Conversion Factors: 1 ppm = 0.025 mg/kg/day (assumed dog food consumption)

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

Dow Chemical Company. 1958. MRID No. 00061912. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Beagle dogs from 23 to 27 weeks of age were divided into five groups (3 females and 2 males) and given diets containing 0, 0.5, 2.5, 5 or 7.5 ppm of heptachlor epoxide for 60 weeks. Liver-to-body weight ratios were significantly increased in a treatment-related fashion. Effects were noted for both males and females at the LEL of 0.5 ppm. A NOEL was not established.

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

UF — Based on a chronic exposure study, an uncertainty factor of 1000 was used to account for inter- and intraspecies differences and to account for the fact that a NOEL was not attained.

MF — None

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

None.

Data Considered for Establishing the RfD:

- 1) 60-Week Feeding - dog: Principal study - see previous description; no core grade
- 2) 2-Generation Reproduction - dog: NOEL=1 ppm (0.025 mg/kg/day); LEL=3 ppm (0.075 mg/kg/day) (liver lesions in pups); Reproductive NOEL=5 ppm (0.125 mg/kg/day); Reproductive LEL=7 ppm (0.175 mg/kg/day) (pup survival); no core grade (Velsicol Chemical, 1973a)
- 3) 3-Generation Reproduction - rat: NOEL=5 ppm (0.25 mg/kg/day); LEL=10 ppm (0.5 mg/kg/day) (pup mortality); no core grade (Velsicol Chemical, 1959a)
- 4) 2-Year Feeding - rat: LEL=0.5 ppm (0.025 mg/kg/day) (LDT) (females - vacuolar changes in central hepatic lobule); NOEL not established; no core grade (Velsicol Chemical, 1959b)

Other Data Reviewed:

- 1) Chronic Feeding Study - mouse: Heptachlor/Heptachlor Epoxide (1:3): NOEL=none; LEL=1 ppm (LDT) (vacuolation, enlarged nucleus, hepatocytomegaly); no core grade (Velsicol Chemical, 1973b)
- 2) Chronic Feeding Study - rat: Heptachlor/Heptachlor Epoxide (3:1): NOEL=none; LEL=5 ppm (LDT) (liver-to-body weight increase in females); no core grade (Velsicol Chemical, 1966)
- 3) 3-Generation Reproduction - rat: Heptachlor/Heptachlor Epoxide (3:1): NOEL=7 ppm (HDT); LEL=none; no core grade (Velsicol Chemical, 1967)

Data Gap(s): Rat Teratology Study; Rabbit Teratology

I.A.5. Confidence in the Oral RfD

Study — Low
Database — Medium
RfD — Low

The principal study is of low quality and is given a low confidence rating. Since the database on chronic toxicity is complete but consists of low- quality studies, the database is given a medium to 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

Agency Work Group Review — 12/18/1985, 09/16/1986

Verification Date — 09/16/1986

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 epoxide conducted in August 2003 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 epoxide

CASRN — 1024-57-3

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Heptachlor epoxide

CASRN — 1024-57-3

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 — Sufficient evidence exists from rodent studies in which liver carcinomas were induced in two strains of mice of both sexes and in CFN female rats. Several structurally related compounds are liver carcinogens.

II.A.2. Human Carcinogenicity Data

Inadequate. There are no published epidemiologic evaluations of heptachlor epoxide. It is not commercially available in the United States, but is a product of heptachlor oxidation.

There were 11 case reports involving central nervous system effects, blood dyscrasias and neuroblastomas in children with pre-/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). Two other retrospective cohort studies were 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. Four long-term carcinogenesis bioassays of heptachlor epoxide have been reported. The major finding in mice has been an increased incidence of liver carcinomas. Davis (1965) fed groups of 100 male and 100 female C3H mice 0 or 10 ppm heptachlor epoxide for 2 years. Survival was generally low, with 50% of controls and 9.5% of treated mice living 2 years. A 2-fold increase in benign liver lesions (hepatic hyperplasia and benign tumors) over the controls was reported. Reevaluation by Reuber (1977b) revealed a significant increase in liver carcinomas in the dosed group (77/81 in females and 73/79 in males) over the controls (2/53 in females and 22/73 in males). The Velsicol Chemical Co. (1973) tested a 75:25 mixture of heptachlor epoxide:heptachlor in groups of 100 male and 100 female CD-1 mice. The mice were fed 0, 1, 5, and 10 ppm for 18 months. A statistically significant increase of hyperplasia was observed in the 5, and 10 ppm dose groups in both sexes; Reuber's reevaluation (U.S. EPA, 1985) resulted in a change in diagnosis for benign to liver carcinomas, thereby increasing the incidence of hepatic carcinomas ($p < 0.01$). Four independent pathologists concurred with Reuber's reevaluation.

The earliest bioassay with rats (Witherup et al., 1959) tested 25 male and 25 female CFN rats each at 0.5, 2.5, 5.0, 7.5, and 10 ppm for 108 weeks. The authors observed malignant and benign tumors randomly among test groups and controls. Reuber's reevaluation (1985) reported a significant increase of hepatic carcinomas above the controls at 5 and 10 ppm in the female rats. A reevaluation by Williams (1985) reported a significant increase of hepatic nodules at the 10 ppm level in the males over the controls. The Kettering Laboratory (Jolley et al., 1966) tested a mixture of 75:25 heptachlor:heptachlor epoxide in the diet of 25 female CD rats at 5, 7.5, 10, and 12.5 ppm for 2 years. Although no malignant lesions of the liver were observed, hepatocytomegaly was increased at 7.5, 10, and 12.5 ppm.

II.A.4. Supporting Data for Carcinogenicity

Gene mutation assays indicate that heptachlor epoxide is not mutagenic in bacteria (Moriya et al., 1983). In two mouse dominant lethal assays, heptachlor epoxide did not induce major chromosomal aberrations in male germinal cells (Arnold et al., 1977; Epstein et al., 1972). Ahmed et al. (1977) reported qualitative evidence of uncheduled DNA synthesis response in SV40 transformed human fibroblasts in the presence of hepatic homogenates and heptachlor epoxide.

Five compounds structurally related to heptachlor epoxide (chlordane, aldrin, dieldrin, heptachlor 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 — 9.1E+0 per (mg/kg)/day

Drinking Water Unit Risk — 2.6E-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)	4E-1 ug/L
E-5 (1 in 100,000)	4E-2 ug/L
E-6 (1 in 1,000,000)	4E-3 ug/L

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

Tumor Type — hepatocellular carcinomas

Test animals — mouse/C3H (Davis); mouse/CD1 (Velsicol)

Route — diet

Reference — Davis, 1965; Velsicol, 1973 (see table)

Administered Dose (ppm)	Human Equivalent Dose (mg/kg/day)	Tumor Incidence	Reference
male			
0	0.0	22/73	Davis, 1965 as diagnosed by Reuber, 1977 (cited in Epstein, 1976)
10	0.108	73/79	
female			
0	0.000	2/53	
10	0.108	77/81	
female			
0	0.00	6/76	Velsicol, 1973 as evaluated by Reuber, 1977
1	0.01	1/70	
5	0.052	6/65	
10	0.10	30/57	
male			
0	0.00	0/62	
1	0.01	2/68	
5	0.052	18/68	
10	0.10	52/80	

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

The Davis (1965) study was designed to be for lifetime exposure. Thus, although survival was low, no correction for duration of experiment was made. Five data sets (four in mice and one in rats) show an increased incidence of hepatocellular carcinomas in treated groups compared with controls. There are four slope factors, 27.7 per (mg/kg)/day for C3H male mice, 36.2 per (mg/kg)/day for C3H female mice, 1.04 per (mg/kg)/day for CD-1 female mice, and 6.48 per (mg/kg)/day for CD-1 male mice. Since mice were the more sensitive species tested and to avoid discarding relevant data, the quantitative estimate is based on the geometric mean of 9.1 per (mg/kg)/day. This geometric mean is consistent with the potency estimate from rats of 5.8 per (mg/kg)/day (CFN females).

The above unit risk should not be used if the water concentration exceeds 40 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 in both studies, but survival in the Davis (1985) study was low. A dose-related increase in tumor incidence was observed in CD-1 mice. Slope factors were consistent in two species of rodents.

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

II.C.1. Summary of Risk Estimates

Inhalation Unit Risk — 2.6E-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)	4E-2 ug/cu.m
E-5 (1 in 100,000)	4E-3 ug/cu.m
E-6 (1 in 1,000,000)	4E-4 ug/cu.m

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

The inhalation 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 4 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, 1985, 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 epoxide conducted in August 2003 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 epoxide
CASRN — 1024-57-3

VI.A. Oral RfD References

Dow Chemical Company. 1958. MRID No. 00061912. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Dow Chemical Company. 1959a. MRID No. 00062676. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Dow Chemical Company. 1959b. MRID No. 00061911. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Dow Chemical Company. 1966. MRID No. 00086208. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Dow Chemical Company. 1967. MRID No. 00147057. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Dow Chemical Company. 1973a. MRID No. 00050058. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Dow Chemical Company. 1973b. MRID No. 000523262, 00062678, 00064943. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

Davis, K.J. 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.

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. 1985. Hearing Files on Chlordane, Heptachlor Suspension (unpublished draft). Available for inspection at: U.S. EPA, Washington, DC.

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

Velsicol Chemical Corporation. 1973. MRID No. 00062678. Available from EPA. Write to FOI, EPA, Washington, D.C. 20460.

VII. Revision History

Substance Name — Heptachlor epoxide

CASRN — 1024-57-3

Date	Section	Description
09/30/1987	I., II.	RfD & Carcinogen summary on-line
10/28/2003	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Heptachlor epoxide

CASRN — 1024-57-3

Last Revised —03/31/1987

- 1024-57-3
- ENT 25,584
- EPOXYHEPTACHLOR
- HCE
- Heptachlor Epoxide
- 1,4,5,6,7,8,8-HEPTACHLORO-2,3-EPOXY-2,3,3a,4,7,7a-HEXAHYDRO-4,7-METHANOINDENE
- 1,4,5,6,7,8,8-HEPTACHLORO-2,3-EPOXY-3a,4,7,7a-TETRAHYDRO-4,7-METHANOINDAN
- 2,3,4,5,6,7,7-HEPTACHLORO-1a,1b,5,5a,6,6a-HEXAHYDRO-2,5-METHANO-2H-INDENO(1,2-b)OXIRENE
- HIPTACHLOR EPOXIDE
- 4,7-METHANOINDAN, 1,4,5,6,7,8,8-HEPTACHLORO-2,3-EPOXY-3a,4,7,7a-TETRAHYDRO-
- 2,5-METHANO-2H-OXIRENO(a)INDENE, 2,3,4,5,6,7,7-HEPTACHLORO-1a,1b,5,5a,6,6a-HEXAHYDRO-
- VELSICOL 53-CS-17