alpha-Hexachlorocyclohexane (alpha-HCH); CASRN 319-84-6

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 alpha-HCH

File First On-Line 03/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	03/31/1987

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — alpha-Hexachlorocyclohexane (alpha-HCH)
CASRN — 319-84-6

Not available at this time.

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

Substance Name — alpha-Hexachlorocyclohexane (alpha-HCH)
CASRN — 319-84-6

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — alpha-Hexachlorocyclohexane (alpha-HCH)
CASRN — 319-84-6
Last Revised — 03/31/1987

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 — Dietary alpha-HCH has been shown to cause increased incidence of liver tumors in five mouse strains and in Wistar rats.

II.A.2. Human Carcinogenicity Data

Inadequate. One case report of a Japanese sanitation employee with acute leukemia was associated with occupational exposure to HCH and DDT (Hoshizaki et al., 1970).

II.A.3. Animal Carcinogenicity Data

Dietary alpha-HCH has been shown to cause increased incidences of liver tumors in five mouse strains and in Wistar rats (Ito et al., 1973a,b, 1976; Nagasaki et al., 1972, 1975; Hanada et al., 1973; Goto et al., 1972; Schulte-Hermann and Parzefall, 1981).

Ito et al. (1973a) treated groups of 20-40 male dd mice with 100, 250, or 500 ppm alpha-HCH in the diet for 24 weeks. They observed liver nodules and hepatocellular carcinomas in the two upper dose groups. In a subsequent study, Ito et al. (1976) maintained male DDY mice on a diet containing 500 ppm alpha-HCH for 16, 20, 24, or 36 weeks. This was followed by basal diet for 4, 8, 12, 16, 24, or 36 weeks, respectively. Incidence of liver tumors increased with continuous alpha-HCH administration. Incidence decreased, however, with recovery time. At 24 weeks most lesions observed were nodules, but by 60 or 72 weeks the tumors were primarily hepatocellular carcinomas.

Schulte-Hermann and Parzefall (1981) noted an increased incidence of hepatic nodules and hepatocellular carcinomas in female Wistar rats treated with approximately 20 mg/kg/day alpha-HCH for their lifetime. Male Wistar rats (18-24 animals/group) were fed alpha-HCH in the diet at 500, 1000, or 1500 ppm for 24, 48, or 72 weeks. Liver nodules and carcinomas were observed in rats fed the two highest doses for 72 weeks. Liver nodules only developed in animals fed 1000 ppm for 48 weeks (Nagasaki et al., 1975). Nagasaki et al. (1972) observed liver nodules and tumor formation in male dd mice fed 250 or 500 ppm for 24 weeks, but not in those consuming 100 ppm alpha-HCH. Both males and females of the dd strain responded in a dose-dependent fashion with liver nodules and hepatomas when fed 100, 300, or 600 ppm dietary alpha-HCH for 32 weeks, followed by 5-6 weeks basal diet (Hanada et al., 1973). In a feeding study using male ICR-JCL mice, alpha-HCH produced hepatomas in 100% of the animals (Goto et al., 1972). Liver tumors have been observed as early as 24-26 weeks (Sugihara et al., 1975).

II.A.4. Supporting Data for Carcinogenicity

No data on the genetic toxicology of alpha-HCH are available. Alpha-HCH produces carcinogenic effects similar to that of t-HCH, which is 65% alpha- HCH. Shulte-Hermann and Parzefall (1981) reported that alpha-HCH may promote carcinogenic lesions initiated by diethylnitrosamine.

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

II.B.1. Summary of Risk Estimates

Oral Slope Factor — 6.3E+0 per (mg/kg)/day

Drinking Water Unit Risk — 1.8E-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)	6E-1 ug/L
E-5 (1 in 100,000)	6E-2 ug/L
E-6 (1 in 1,000,000)	6E-3 ug/L

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

Tumor Type: hepatic nodules and hepatocellular carcinomas
Test animals: mouse/dd, male
Route: diet
Reference: Ito et al., 1973a

Administered Dose		Human Equivalent Dose (mg/kg)/day	Tumor Incidence
ppm	**(mg/kg)/day**		
0	0	0	0/20
100	13.0	0.012	0/20

Administered Dose		Human Equivalent Dose (mg/kg)/day	Tumor Incidence
250	37.5	0.035	30/38
500	65.0	0.060	20/20

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

Animal doses were obtained by multiplying dietary ppm by a food consumption factor of 0.13. The authors classified 10/38 of the mid-dose tumors and 17/20 of the high-dose tumors as carcinomas. The slope factor includes an increase of (104/24)**-3 to adjust for the short duration of the experiment. The human equivalent dose was calculated by multiplying the transformed dose by (0.03/70)**1/3 for body weight adjustment and (24/104)**3 to adjust the length of the experiment to the lifespan of the animal. Mice dying during the experiment were excluded.

The unit risk should not be used if the water concentration exceeds 60 ug/L, since above this concentration the unit risk may not be appropriate.

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

Relatively few animals were treated, and the treatment time was not considered adequate for the development of spontaneous tumors. A slope factor based on data of Nagasaki et al. (1972) was calculated to be 4.7 per (mg/kg)/day, and one based on Schulte-Hermann and Parzefall was determined to be 1.3 per (mg/kg)/day. An estimate based on the Ito et al. (1976) data was calculated to be 2.7 per (mg/kg)/day (U.S. EPA, 1980). A slope factor for t- HCH, which contains 65% alpha-HCH, was calculated to be 1.8 per (mg/kg)/day based on data of Munir et al., 1983. These estimates are supportive of the slope factor based on the Ito et al. (1973a) study.

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

II.C.1. Summary of Risk Estimates

Inhalation Unit Risk — 1.8E-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)	6E-2 ug/cu.m
E-5 (1 in 100,000)	6E-3 ug/cu.m
E-6 (1 in 1,000,000)	6E-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 unit risk should not be used if the air concentration exceeds 6 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 1986 Health and Environmental Effects Profile received Agency Review.

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

Agency Work Group Review — 12/17/1986

Verification Date — 12/17/1986

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 alpha-Hexachlorocyclohexane (alpha-HCH) conducted in September 2002 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 — alpha-Hexachlorocyclohexane (alpha-HCH)
CASRN — 319-84-6

VI.A. Oral RfD References

None

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

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Nagasaki, H., H. Kawabata, Y. Miyata, et al. 1975. Effect of various factors on induction of liver tumors in animals by the alpha-isomer of benzene hexachloride. Gann. 66(2): 185-191.

Schulte-Hermann, R. and W. Parzefall. 1981. Failure to determine initiation from promotion of liver tumors in a long-term study with the phenobarbital- type inducer alpha-hexachlorocyclohexane and the role of sustained stimulation of hepatic growth and monooxygenases. Cancer Res. 41: 4140-4146.

Sugihara, S., K. Hirao, M. Hananouchi and N. Ito. 1975. Ultrastructural studies on hepatoma induced by benzene hexachloride (BHC). J. Electron. MIcrosc. 24: 192.

U.S. EPA. 1986. Health and Environmental Effects Profile for Hexachloro- cyclohexanes. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

VII. Revision History

Substance Name — alpha-Hexachlorocyclohexane (alpha-HCH)
CASRN — 319-84-6

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

VIII. Synonyms

Substance Name — alpha-Hexachlorocyclohexane (alpha-HCH)
CASRN — 319-84-6
Last Revised — 03/31/1987

- 319-84-6
- alpha-BENZENEHEXACHLORIDE
- BENZENE HEXACHLORIDE-alpha-isomer
- alpha-BHC
- CYCLOHEXANE, 1,2,3,4,5,6-HEXACHLORO-, alpha-
- CYCLOHEXANE, alpha-1,2,3,4,5,6-HEXACHLORO-
- CYCLOHEXANE, 1,2,3,4,5,6-HEXACHLORO-, alpha-isomer
- ENT 9,232
- alpha-HCH
- alpha-HEXACHLORAN
- alpha-HEXACHLORANE
- HEXACHLORCYCLOHEXAN
- alpha-HEXACHLORCYCLOHEXANE
- 1-alpha,2-alpha,3-beta,4-alpha,5-beta,6-beta-HEXACHLOROCYCLOHEXANE
- Hexachlorocyclohexane, alpha-
- alpha-1,2,3,4,5,6-HEXACHLOROCYCLOHEXANE
- alpha-LINDANE