Hexachlorodibenzo-p-dioxin (HxCDD), mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD; CASRN 57653-85-7 and 19408-74-3

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 HxCDD, mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD

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 — Hexachlorodibenzo-p-dioxin (HxCDD), mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD
CASRN — 57653-85-7
CASRN — 19408-74-3

Not available at this time.

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

Substance Name — Hexachlorodibenzo-p-dioxin (HxCDD), mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD
CASRN — 57653-85-7
CASRN — 19408-74-3

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Hexachlorodibenzo-p-dioxin (HxCDD), mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD
CASRN — 57653-85-7
CASRN — 19408-74-3
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 — Hepatic tumors in mice and rats by gavage

II.A.2. Human Carcinogenicity Data

None. There are no published epidemiologic evaluations of hexachlorodibenzo-p-dioxin, a contaminant in chlorinated phenols.

II.A.3. Animal Carcinogenicity Data

Osborne-Mendel rats (50/sex/dose) and B6C3F1 mice (50/sex/dose) were gavaged with a mixture of two hexachlorodibenzo-p-dioxin isomers (1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD) in a 1:2 ratio suspended in a 9:1 corn oil:acetone vehicle (NTP, 1980a). Treatment was twice weekly for 104 weeks at doses of 0, 1.25, 2.5 or 5.0 ug/kg/week for rats and male mice and 0, 2.5, 5 or 10 ug/kg/week for female mice. There were 75 each rats and mice of each sex as vehicle controls and 25 each female and male rats and mice in the untreated control group. A dose-related depression in mean body weight gain was noted in male and female rats. In rats and mice there was a dose-related toxic hepatitis consisting of degenerative liver changes and necrosis. A significant dose-related increase in incidence of hepatocellular carcinomas or neoplastic nodules was noted in male rats. NTP concluded that evidence for carcinogenicity in male rats was inconclusive. Incidence of hepatocellular carcinomas, nodules, and adenomas was significantly increased in female rats relative to vehicle controls both medium- and high-dose). Incidence of hepatocellular carcinomas and adenomas was increased in a dose-related manner in male and female mice, reaching statistical significance when the high-dose males were compared with vehicle controls.

Thirty Swiss-Webster mice/sex were skin-painted with a 1:2 mixture of 1,2,3,6,7,8- and 1,2,3,7,8,9-hexachlorodibenzo-p-dioxin in acetone 3 times a week for 104 weeks (NTP, 1980b). Doses of 0.005 ug/application for the initial 16 weeks were followed by a 0.01 ug/application for the remainder of the study. No carcinogenic response related to treatment was observed.

II.A.4. Supporting Data for Carcinogenicity

There are no published reports of genetic toxicology testing of hexachlorodibenzo-p-dioxins.

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

II.B.1. Summary of Risk Estimates

Oral Slope Factor — 6.2E+3 per (mg/kg)/day

Drinking Water Unit Risk — 1.8E-1 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-4 ug/L
E-5 (1 in 100,000)	6E-5 ug/L
E-6 (1 in 1,000,000)	6E-6 ug/L

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

Tumor Type: liver tumors (see table)
Test animals: mouse, rat (see table)
Route: gavage
Reference: NTP, 1980a

Administered Dose (ug/kg/week)	Human Equivalent Dose (ug/kg/week)	Tumor Incidence
mouse/B6C3F1/male (adenomas and carcinomas)		
0	0	27/75
vehicle	0	15/73
1.25	0.014	14/50
2.5	0.027	14/49
5.0	0.054	24/48

Administered Dose (ug/kg/week)	Human Equivalent Dose (ug/kg/week)	Tumor Incidence
rat/Osborne-Mendel/female (neoplastic nodules and hepatocellular carcinomas)		
0	0	1/73
vehicle	0	2/75
1.25	0.03	5/50
2.5	0.06	7/50
5.0	0.12	18/50

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

A geometric mean of the slope factors for male mice and female rats was used. Slope factors for each species and sex were as follows: male rat = 5.9E+2 per (mg/kg)/day, female rat = 3.5E+3 per (mg/kg)/day, male mouse = 1.1E+4 per (mg/kg)/day, female mouse = 2.9E+3 per (mg/kg)/day. Generally, the estimate derived from data for most sensitive species/sex was used. In this case female rat data were also used for the following reasons: 1) the spontaneous tumor incidence was lower in the rats; 2) statistically significant increases in incidence were observed at the mid- and high-dose in rats vs. high-dose only in mice; 3) there was a more distinct dose-response trend in the rats.

The unit risk should not be used if the water concentration exceeds 6E-2 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 their expected lifetime. Risk estimates from data sets from two species (see Section II.B.2.) range within a factor of 20.

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

II.C.1. Summary of Risk Estimates

Inhalation Unit Risk — 1.3E+0 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-5 per ug/cu.m
E-5 (1 in 100,000)	8E-6 per ug/cu.m
E-6 (1 in 1,000,000)	8E-7 per ug/cu.m

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

Calculated from oral data in II.B.2. as follows: Unit risk = 6.2E+3 per (mg/kg)/day x E-3 mg/ug x 0.75 x 20 cu.m/day x 1/70 kg = 1.3/ug/cu.m

where: 6.2E+3 per (mg/kg)/day = oral slope factor

0.75 = assumed percentage of inhaled material absorbed
20 cu.m/day = assumed breathing rate for adult human

70 kg = assumed weight for adult human

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

The unit risk should not be used if the air concentration exceeds 8E-3 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

The 1985 Health Assessment Document received both Agency and external review.

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

Agency Work Group Review — 01/07/1987

Verification Date — 01/07/1987

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 Hexachlorodibenzo-p-dioxin, mixture (HxCDD) conducted in November 2001 identified one or more significant new studies. IRIS users may request the references for those studies from 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 — Hexachlorodibenzo-p-dioxin (HxCDD), mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD
CASRN — 57653-85-7
CASRN — 19408-74-3

VI.A. Oral RfD References

None

VI.B. Inhalation RfD References

None

VI.C. Carcinogenicity Assessment References

NTP (National Toxicology Program). 1980a. Bioassay of 1,2,3,6,7,8- and 1,2,3,7,8,9-hexachlorodibenzo-p-dioxin (gavage) for possible carcinogenicity. DHHS Publ. No. (NIH) 80-1754.

NTP (National Toxicology Program). 1980b. Bioassay of 1,2,3,6,7,8- and 1,2,3,7,8,9-hexachlorodibenzo-p-dioxin (dermal study) for possible carcinogenicity. DHHS Publ. No. (NIH) 80-1758.

U.S. EPA. 1985. Health Assessment Document for Polychlorinated Dibenzo-p- dioxin. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Air Quality Planning and Standards, Washington, DC. EPA 600/8/84-014F.

VII. Revision History

Substance Name — Hexachlorodibenzo-p-dioxin (HxCDD), mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD
CASRN — 57653-85-7
CASRN — 19408-74-3

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

VIII. Synonyms

Substance Name — Hexachlorodibenzo-p-dioxin (HxCDD), mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD
CASRN — 57653-85-7
CASRN — 19408-74-3
Last Revised — 03/31/1987

- 19408-74-3
- 57653-85-7
- DIBENZO-p-DIOXIN, 1,2,3,6,7,8-HEXACHLORO-
- DIBENZO-p-DIOXIN, 1,2,3,7,8,9-HEXACHLORO-
- 1,2,3,6,7,8-HEXACHLORODIBENZO-p-DIOXIN
- 1,2,3,7,8,9-HEXACHLORODIBENZO-p-DIOXIN
- Hexachlorodibenzo-p-dioxin, mixture
- Hexachlorodibenzo-p-dioxin
- HxCDD