Hexachlorobenzene; CASRN 118-74-1

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 Hexachlorobenzene

File First On-Line 09/26/1988

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	09/26/1988
Inhalation RfC (I.B.)	message	03/01/1991
Carcinogenicity Assessment (II.)	yes	03/01/1991

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Hexachlorobenzene
CASRN — 118-74-1
Last Revised — 09/26/1988

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 effects **Rat Chronic Feeding Study** **Arnold et al., 1985**	NOAEL: 1.6 ppm (diet) (0.08 mg/kg/day) LOAEL: 8.0 ppm (diet) (0.29 mg/kg/day)	100	1	8E-4 mg/kg/day

*Conversion Factors: doses were based on actual food consumption and body weights provided by Arnold at 30 weeks of exposure (U.S. EPA, 1985, 1988).

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

Arnold, D.L., C.A. Moodie, S.M. Charbonneau, et al. 1985. Long-term toxicity of hexachlorobenzene in the rat and the effect of dietary Vitamin A. Fd. Chem. Toxic. 23(9): 779-793.

The derivation of the oral RfD is based on a 130-week study of Arnold et al. (1985). This study involved feeding male and female Sprague-Dawley rats, the F0 generation, diets containing 0, 0.32, 1.6, 8.0, or 40 ppm of hexachlorobenzene (analytical grade) for 90 days prior to mating and until 21 days after parturition (at weaning). The number of offspring (F1 generation) from these matings was reduced to 50 males and 50 females per dose group at 28 days of age and fed their respective parents' diets. Thus, the F1 animals were exposed to hexachlorobenzene and metabolites in utero, from maternal nursing and from their diets for the remainder of their lifetime (130 weeks). No hexachlorobenzene-induced adverse effects were reported in the 0.32 and 1.6 ppm hexachlorobenzene F1 groups, indicating that these levels are NOAELs. Although significant ($p<0.05$) increases were observed in the incidences of periportal glycogen depletion at 1.6 ppm, peribiliary lymphocytosis at 0.32, 1.6 and 40 ppm, and peribiliary fibrosis at 0.32 and 40 ppm in the F1 male rat groups, these effects are not being considered hexachlorobenzene-induced adverse effects because they were observed in a large number of F1 control males as well. The 8.0-ppm F1 groups were reported to have an increase ($p<0.05$) in hepatic centrilobular

basophilic chromogenesis. The 40-ppm F1 groups showed increases ($p<0.05$) in pup mortality, hepatic centrilobular basophilic chromogenesis, and severe chronic nephrosis (males only).

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

UF — An uncertainty factor of 100 was applied; 10 for interspecies and 10 for intraspecies variability.

MF — None

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

The toxicity of long-term dietary exposure of humans to hexachlorobenzene was demonstrated by the epidemic of porphyria cutanea tarda (PCT) in Turkish citizens who accidentally consumed bread made from grain treated with hexachlorobenzene (Cam, 1963; Peters et al., 1966, 1982). In children less than 1 year of age, pink sore disease was observed along with 95% mortality. In addition to the PCT-associated symptoms of skin lesions, hypertrichosis, and hyperpigmentation, the exposure caused neurotoxicity and liver damage. Follow-up studies reported PCT symptoms, reduced growth and arthritic changes in the appendages of children who were directly or indirectly (i.e., through breast milk) exposed. These human data cannot be used for quantitative risk assessment purposes because accurate exposure data (dose and duration) are lacking.

An extensive number of animal research studies have been conducted on hexachlorobenzene including reproductive, teratology and carcinogenicity studies. These studies have been critiqued by U.S. EPA (1985, 1988). Kuiper- Goodman et al. (1977) conducted another study that could be used to derive an oral RfD or the current RfD.

In a subchronic study, groups of 70 male and 70 female Charles River (COBS) rats were fed diets providing 0, 0.5, 2.0, 8.0, or 32.0 mg/kg/day of hexachlorobenzene, dissolved in corn oil, for up to 15 weeks (Kuiper-Goodman et al., 1977). Females were found to be more susceptible to hexachlorobenzene, as indicated by all parameters studied, and an "apparent" NOEL of 0.5 mg/kg/day was concluded by the authors. Increased liver porphyrin levels in females and increases in the size of centrilobular hepatocytes, along with the depletion of hepatocellular marker enzymes were noted with higher doses. In the two highest dose groups, there were increased liver-to- body weight ratios, as well as increased porphyrin levels in the kidney and spleen in both males and females. Exposure to the highest dose resulted in decreased survival, splenomegaly, and ataxia in females; increases in spleen- to-body weight and kidney-to-body weight ratios and intension tremors in males and females; and decreased body weight in males.

I.A.5. Confidence in the Oral RfD

Study — Medium
Database — High
RfD — Medium

The principal chronic study provided an unusual dosing scheme making it difficult to determine the true doses received by each experimental group. The study included extensive evaluation of systemic and neoplastic pathological endpoints and was critically reviewed before release and publication. The sensitive endpoint of porphyria was not evaluated in this study, otherwise a high confidence in the RfD could be assigned. The data base is rated high confidence due to the extensive number of quality research studies available.

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

Source Document — U.S. EPA, 1985, 1988

Other EPA Documentation — None

Agency Work Group Review — 05/26/1988

Verification Date — 05/26/1988

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 Hexachlorobenzene 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 — Hexachlorobenzene
CASRN — 118-74-1

The health effects data for hexachlorobenzene were reviewed by the U.S. EPA RfD/RfC Work Group and determined to be inadequate for derivation of an inhalation RfC. For additional

information on health effects of this chemical, interested parties are referred to the EPA documentation listed below.

U.S. EPA. 1986. Drinking Water Criteria Document for Hexachlorobenzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. EPA-600/X-84-179-1. NTIS PB 86-117777.

U.S. EPA. 1985. Health Assessment Document for Hexachlorobenzene. 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, Research Triangle Park, NC. EPA/600/8-84/015F. NTIS PB 85-150332.

Agency Work Group Review — 11/15/1990

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for Hexachlorobenzene 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.

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 (internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Hexachlorobenzene
CASRN — 118-74-1
Last Revised — 03/01/1991

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 — Hexachlorobenzene, when administered orally, has been shown to induce tumors in the liver, thyroid and kidney in three rodent species.

II.A.2. Human Carcinogenicity Data

Inadequate. The reported epidemiological studies of hexachlorobenzene have not been designed to measure increases in cancer incidence as an endpoint and are inadequate in this context.

Between 1954 and 1959 a large number of individuals in southeastern Turkey were exposed to hexachlorobenzene from the ingestion of seed grain treated with hexachlorobenzene as a fungicide. Approximately 5000 individuals developed adverse effects from this exposure with deaths of children under the age of 2 and about 4000 individuals developing porphyria. A follow-up of 204 patients 25-30 years after the onset of hexachlorobenzene-induced porphyria showed that a majority of the patients still showed symptoms of adverse effects (Cripps et al., 1984). One of these adverse effects was a 37% incidence of enlarged thyroids (thyromegaly), which is well above the average 5% incidence observed in southeastern Turkey. Two of the porphyria patients who underwent thyroidectomy showed no malignant changes. Clinical follow-up of these patients is continuing with emphasis in further evaluating the histopathology of thyromegaly patients.

II.A.3. Animal Carcinogenicity Data

Sufficient. The liver appears to be the primary target organ for hexachlorobenzene-induced cancer, although neoplasms of the thyroid and kidney have been observed as well.

Groups of 94 Sprague-Dawley rats/sex/dose were fed 0, 75, or 150 ppm hexachlorobenzene (purity >99.5%) in the diet for up to 2 years (Erturk et al., 1986). Interim kills of four rats/group were performed at weeks 0, 1, 2, 3, 4, 8, 16, 32, 48, 64, and 80. The remaining 50 animals/group were observed until natural death or until sacrifice at 2 years. Treated animals of both sexes surviving past 12 months showed significant increases in liver and renal tumors. Hemangiohepatomas, hepatocellular carcinomas and bile duct tumors were significantly increased in treated females; males and females in both dose groups had increased incidences of renal cell adenomas and hemangiohepatomas. Females were far more susceptible to hepatocarcinogenicity while males were generally more sensitive to renal carcinogenicity. The time- to-tumor onset in each dose group was generally longer than 1 year. The increase in hepatocellular carcinomas and bile duct tumors in males was not statistically significant. In this same study hepatomas were reported in Syrian golden hamsters that had been exposed for at least 90 days to 200 or 400 ppm hexachlorobenzene in the diet and killed after varying observation periods.

Groups of 30-60 Syrian golden hamsters/sex/dose were fed 0, 50, 100, or 200 ppm hexachlorobenzene (>99.5% pure) in the diet over lifetime (Cabral et al., 1977). After 50 weeks, survival in treated groups was comparable to controls; however, there was reduced lifespan among high-dose male and female animals after 70 weeks exposure. A significant dose-related increase in the incidence of hepatomas and liver hemangioendotheliomas was observed in males and in females. The incidence of hepatomas was statistically significantly increased in each treated group compared to controls while liver hemangioendothelioma incidence was statistically significantly elevated in the high-dose groups of both sexes and in middle-dose males. While thyroid alveolar adenomas were observed in all treated groups except low-dose males (none were observed in control groups), a significantly increased incidence was found only in high-dose males. There was a significant dose-related increase in the incidence of thyroid alveolar adenomas in males.

Smith and Cabral (1980) reported 100% incidence of liver tumors in small groups of female Agus (14) and Wistar (6) rats receiving 100 ppm hexachlorobenzene in arachis oil in the diet for 90 weeks compared to 0% in small groups of controls (12 Agus and 4 Wistar rats). In a 2-generation feeding study parental Sprague-Dawley rats were fed 0.32-40 ppm hexachlorobenzene in the diet for 3 months. Following mating, females were maintained on the diet through pregnancy and lactation. Pups received 0.32-40 ppm dietary hexachlorobenzene for 130 weeks. F1 females in the high-dose group had significant elevation in the incidence of

neoplastic liver nodules (10/49 vs. 0/49 for controls) and adrenal pheochromocytomas (17/49 vs. 0/49 for controls), and F1 males showed increased parathyroid tumors (12/49 vs. 2/48 for controls) (Arnold et al., 1985).

Hepatomas were produced in a dose-related fashion in both male and female Swiss mice exposed through the diet to 50, 100, or 200 ppm hexachlorobenzene for up to 120 weeks (Cabral et al., 1979). The females in the high-dose group were observed to have a liver tumor incidence (14/41) significantly elevated over controls (0/49).

Short-term exposure to hexachlorobenzene did not significantly increase tumor incidence. Shorter exposures of Swiss mice (15 weeks) to 300 ppm hexachlorobenzene in the diet produced negligible incidences of liver tumors (1/26 female, 1/16 male) (Cabral et al., 1979). Lower doses of hexachlorobenzene (10 or 50 ppm) administered in the diet for 24 weeks did not result in increased liver tumor formation in ICR mice. There was hypertrophy of the centrilobular region, however, and 50 ppm hexachlorobenzene was found to enhance tumor induction and nodular hyperplasia in combination with 250 ppm polychlorinated terphenyl (Shirai et al., 1978).

II.A.4. Supporting Data for Carcinogenicity

Hexachlorobenzene is mutagenic for Saccharomyces cerevisiae (Guerzoni et al., 1976), but did not induce dominant lethal mutations in rats exposed by gavage (Simon et al., 1979); nor did it revert histidine auxotrophs of Salmonella typhimurium (Lawlor et al., 1979).

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

II.B.1. Summary of Risk Estimates

Oral Slope Factor — 1.6 per (mg/kg)/day

Drinking Water Unit Risk — 4.6E-5 per (ug/L)

Extrapolation Method — Linearized multistage, extra risk

Drinking Water Concentrations at Specified Risk Levels:

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

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

Tumor Type — hepatocellular carcinoma
Test Animals — rat/Sprague-Dawley, female
Route — diet
Reference — Erturk et al., 1986

Administered Dose (ppm)	Human Equivalent Dose(mg/kg)/day	Tumor Incidence
0	0	0/52
75	0.73	36/56
150	1.46	48/55

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

Doses above are based on average food consumption and body weight data calculated by the study authors. Animals at risk (denominator) were those surviving until 12 months, the time of appearance of the first tumors. Note that this slope factor differs slightly from that reported in the Health Assessment Document (Lewis, 1989). This difference may result from rounding dose or body weight numbers differently and/or using a default rat body weight in the calculation of the human equivalent dose. A slope factor based on data from male hamsters was 1.7 per mg/kg/day (Cabral et al., 1977).

The unit risk should not be used if the water concentration exceeds 2E+2 ug/L, since above this concentration the slope factor may differ from that stated.

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

Significant increases in malignant tumors were observed among an adequate number of animals observed for their lifetime. Slope factors have been calculated from 14 different data sets encompassing 3 species, 4 studies and various endpoints. These fell within a range of approximately 1 order of magnitude (8.3E-2 to 1.7E+0).

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

II.C.1. Summary of Risk Estimates

Inhalation Unit Risk — 4.6E-4 per (ug/cu.m)

Extrapolation Method — Linearized multistage, extra risk

Air Concentrations at Specified Risk Levels:

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

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

Calculated from data in Section II.B.2.

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

The unit risk should not be used if the air concentration exceeds 2E+1 ug/cu.m, since above this concentration the unit risk may not be appropriate.

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

The inhalation risk estimate was based on data from oral exposure.

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

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1985, 1988

The values in the 1985 Health Assessment Document for Chlorinated Benzenes received extensive peer and public review.

The values in the 1988 Drinking Water Criteria Document for Hexachlorobenzene have received external and Agency Review.

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

Agency Work Group Review — 08/13/1986, 02/03/1988, 01/04/1989, 03/01/1989

Verification Date — 03/01/1989

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 Hexachlorobenzene 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 — Hexachlorobenzene
CASRN — 118-74-1

VI.A. Oral RfD References

Arnold, D.L., C.A. Moodie, S.M. Charbonneau, et al. 1985. Long-term toxicity of hexachlorobenzene in the rat and the effect of dietary Vitamin A. Food. Chem. Toxicol. 23(9): 779-793.

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Kuiper-Goodman, T., D.L. Grant, C.A. Moodie, G.O. Korsrud and I.C. Munro. 1977. Subacute toxicity of hexachlorobenzene in the rat. Toxicol. Appl. Pharmacol. 40: 529-549.

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U.S. EPA. 1988. Drinking Water Criteria Document for Hexachlorobenzene. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC.

VI.B. Inhalation RfC References

U.S. EPA. 1986. Drinking Water Criteria Document for Hexachlorobenzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. EPA-600/X-84-179-1. NTIS PB 86-117777.

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VI.C. Carcinogenicity Assessment References

Arnold, D.L., C.A. Moodie, S.M. Charbonneau, et al. 1985. Long-term toxicity of hexachlorobenzene in the rat and the effect of dietary vitamin A. Food Chem. Toxicol. 23(9): 779-793.

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Simon, G.S., R.G. Tardiff and J.F. Borzelleca. 1979. Failure of hexachlorobenzene to induce dominant lethal mutations in the rat. Toxicol. Appl. Pharmacol. 47: 415-419.

Smith, A.G. and J.R. Cabral. 1980. Liver-cell tumours in rats fed hexachlorobenzene. Cancer Lett. 11(2): 169-172.

U.S. EPA. 1985. Health Assessment Document for Chlorinated Benzenes. 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/600/8-84-015F. NTIS PB 85- 150332.

U.S. EPA. 1988. Drinking Water Criteria Document for Hexachlorobenzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. EPA-600/X-84-179-1. NTIS PB 86-117777.

VII. Revision History

Substance Name — Hexachlorobenzene
CASRN — 118-74-1

Date	Section	Description
09/26/1988	I.A.	Oral RfD summary on-line
03/01/1991	I.B.	Inhalation RfC message on-line
03/01/1991	II.	Carcinogenicity assessment on-line
10/28/2003	I.A.6., I.B.,	Screening-Level Literature Review Findings message has been

Date	Section	Description
	II.D.2.	added.

VIII. Synonyms

Substance Name — Hexachlorobenzene
CASRN — 118-74-1
Last Revised — 09/26/1988

- 118-74-1
- granox
- Hexachlorobenzene
- pentachlorophenyl chloride
- perchlorobenzene