

Chlorobenzene; CASRN 108-90-7

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 Chlorobenzene

File First On-Line 08/01/1989

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	08/01/1989
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	11/01/1990

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Chlorobenzene
CASRN — 108-90-7
Primary Synonym — Monochlorobenzene
Last Revised — 08/01/1989

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
Histopathologic changes in liver	NOAEL: 27.25 mg/kg/day (adjusted dose: 19 mg/kg/day)	1000	1	2E-2 mg/kg/day
13-Week Dog Study, Oral Exposure (capsule)	LOAEL: 54.5 mg/kg/day			
Monsanto Co., 1967a; Knapp et al., 1971				

*Conversion Factors: Doses adjusted for dosing schedule of 5 days/7 days.

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

Monsanto Company. 1967a. 13-week oral administration - dogs. Monochlorobenzene. Final report. Prepared by Hazelton Laboratories, Project No. 241-105, February 24.

Knapp, W.K., W.M. Busey and W. Kundzins. 1971. Subacute oral toxicity of monochlorobenzene in dogs and rats. Toxicol. Appl. Pharmacol. 19: 393 (Abstract).

Male and female beagle dogs given chlorobenzene orally by capsule at doses of 27.25, 54.5, or 272.5 mg/kg/day, 5 days/week, for 13 weeks. NOAEL = 27.25 mg/kg/day; LOAEL = 54.5 mg/kg/day (slight bile duct proliferation, cytologic alternations, and leukocytic infiltration of the stroma, all in liver). Death; body weight loss; changes in hematology, clinical chemistry, and urine analysis; and pathologic changes in liver (bile duct hyperplasia, cytologic changes, leukocytic infiltration, centrilobular degeneration), kidney, gastrointestinal mucosa, and hematopoietic tissue were observed at 272.5 mg/kg/day.

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

UF — The UF of 1000 allows for uncertainty in the extrapolation of dose levels from laboratory animals to humans (10A), uncertainty in the threshold for sensitive humans (10H), and uncertainty in the effect of duration when extrapolating from subchronic to chronic exposure (10S).

MF — None

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

Other Data Reviewed:

- 1) 90-Day Feeding - rat: NOAEL=50 mg/kg/day; LOAEL=100 mg/kg/day; (increased liver and kidney weights) (Monsanto Co., 1967b; Knapp et al., 1971)
- 2) 6-Month Gavage - rat: NOAEL=14.4 mg/kg/day; LOAEL=144 mg/kg/day; (liver histopathology) (Irish, 1963)
- 3) 90-Day Gavage - rat: NOAEL=60 mg/kg/day; LOAEL=125 mg/kg/day; (increased liver weights) (NTP, 1985)
- 4) 90-Day Gavage - mouse: NOAEL=60 mg/kg/day; LOAEL=125 mg/kg/day; (increased liver weights) (NTP, 1985)
- 5) 2-Year Gavage - rat: NOAEL=60 mg/kg/day; LOAEL=120 mg/kg/day; (liver histopathology in rats) (NTP, 1985)
- 6) 2-Year Gavage - mouse: NOAEL=60 mg/kg/day; LOAEL=120 mg/kg/day; (liver histopathology in rats) (NTP, 1985)
- 7) Developmental - rat: Developmental NOAEL=590 ppm (6 hour/day, equivalent to 216 mg/kg/day) (exposed by inhalation during periods of major organogenesis); Maternal NOAEL=210 ppm (77 mg/kg/day) (John et al., 1984)
- 8) Developmental - rabbit: Developmental NOAEL=590 ppm (6 hour/day, equivalent to 125 mg/kg/day; (exposed by inhalation during periods of major organogenesis); Maternal NOAEL=75 ppm (16 mg/kg/day) (John et al., 1984)

9) 2-Generation Reproduction (inhalation) - rat: Reproductive NOAEL=450 ppm (165 mg/kg/day); Systemic NOAEL=50 ppm (18 mg/kg/day) (Nair et al., 1987)

I.A.5. Confidence in the Oral RfD

Study — Medium

Database — Medium

RfD — Medium

The referenced subchronic study was given medium confidence since it provided both a NOAEL and a LOAEL and incorporated several biochemical and biological endpoints. Several subchronic, chronic, developmental, and reproductive toxicity studies provide supportive data, but they did not give a complete assessment of toxicity. Thus, the database was given medium confidence. A medium level of confidence in the RfD follows.

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

Source Document — U.S. EPA, 1986

U.S. EPA, 1986 received EPA Science Advisory Board Review 7/86.

Other EPA Documentation — None

Agency Work Group Review — 06/24/1985, 07/08/1985, 07/22/1985, 04/16/1987, 01/19/1989.

Verification Date — 01/19/1989

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 Chlorobenzene 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 — Chlorobenzene
CASRN — 108-90-7
Primary Synonym — Monochlorobenzene

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Chlorobenzene
CASRN — 108-90-7
Primary Synonym — Monochlorobenzene
Last Revised — 11/01/1990

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 — D; not classifiable as to human carcinogenicity

Basis — No human data, inadequate animal data and predominantly negative genetic toxicity data in bacterial, yeast, and mouse lymphoma cells.

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

Inadequate. Only one study, an NTP (1985a) gavage study in rats and mice has been performed. Groups of F344/N rats and B6C3F1 mice (50/sex/dose) were administered chlorobenzene (>99% pure) by gavage in corn oil 5 days/week for 103 weeks. Fifty animals/sex/species served as untreated and vehicle controls. The rats received 60 or 120 mg/kg/day; the female mice groups received 60 or 120 mg/kg/day and the male mice groups 30 or 60 mg/kg/day. Body weights in all groups of both species were comparable.

At the end of the study survival in the male rats was 68, 78, 64, and 52% for the untreated-control, vehicle-control, low-, and high-dose groups, respectively; survival in the female rat groups was 74, 58, 60, and 62% for the untreated-control, vehicle-control, low-, and high-dose groups, respectively. Using the pairwise comparison test, only the high-dose male rats had a statistically significant elevation in mortality relative to their vehicle controls. No chlorobenzene-related signs of clinical toxicity were observed in the rats during the experiment; histological examination of the liver showed hepatocellular necrosis (graded as minimal to mild in all groups) caused by chlorobenzene. A statistically significant positive trend in the incidence of hepatocellular neoplastic nodules was observed in male rats; the incidence was 4/50, 2/50, 4/49 and 8/49 for the untreated-control, vehicle-control, low-, and high-dose groups, respectively. No hepatocellular tumors were observed in dosed male rats and none of the high-dose males with neoplastic nodules showed signs of hepatocellular necrosis. There was no increase in neoplastic nodules, hepatocellular carcinomas or combined neoplastic nodules and hepatocellular carcinomas in females. In the high-dose females, there was a single incidence of hepatocellular carcinoma. The incidence of neoplastic liver nodules in female rats was 1/49, 0/50, 1/50, and 1/50 in the untreated-control, vehicle-control, low-, and high-dose groups, respectively. No other significant increase in site-specific tumors or neoplastic pathology was observed in rats; however, a transitional cell bladder papilloma was observed in one low-dose and in one high-dose male rat and a kidney tubular cell carcinoma was observed in a high-dose female. These rare tumor types were not observed in the untreated or vehicle control groups.

In the female mice, survival was approximately 78% in all groups. In male mice, however, survival was reduced in both dosed groups; it was 70, 78, 56, and 58 in the untreated-control, vehicle-control, low-, and high-dose groups, respectively. The mortality in the dosed males was statistically significantly increased. No chlorobenzene-related clinical toxicity and no significant increase in site-specific tumors or neoplastic pathology were observed in any mouse group.

In 1986, the Environmental Health Committee of the Science Advisory Board reviewed this study; overall, the Committee considered the study to be of good quality, but the Committee questioned the biological significance of the increased incidence of neoplastic liver nodules (Doull and Abrahamson, 1986). The NTP report does not specify the number of liver sections pathologically examined or which sections of the liver were examined; the location of the liver sections could cause the difference in the number and the diagnosis of lesions formed. Liver nodules are currently not considered necessarily to be progressive, and consequently lethal to the host. In this study, there was no incidence of hepatocellular carcinoma in male rats after 2 years of the study. The incidence of liver nodules in the untreated control male rats, however, was significantly higher than the recent historical NTP controls (67/3618, 1.9%).

II.A.4. Supporting Data for Carcinogenicity

Chlorobenzene was not mutagenic for *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 or TA1538, with or without addition of rat liver or hamster liver homogenate (duPont, 1977; Lawlor et al., 1979; Merck, 1978; Monsanto, 1976a; NTP, 1982; Simmon et al., 1979). Chlorobenzene did not induce DNA damage in *Escherichia coli* strains WP2 uvr A+ rec A+ or WP100 uvr A- rec A- or *S. typhimurium* strains TA1978 uvr B+ or TA1538 uvr B- (Lawlor et al., 1979; Simmon et al., 1979). Chlorobenzene caused increases in the number of revertants in *Actinomyces antibioticus*-400 (Keskinova, 1968) and *Aspergillus nidulans* (Prasad, 1970; Prasad and Pramer, 1968) and mitotic disturbances in *Allium cepa* (Ostergen and Levan, 1943). Chlorobenzene did not induce specific locus forward mutations in mouse lymphoma L5178Y cells, either with or without metabolic activation (Monsanto, 1976b). Chlorobenzene induced reciprocal recombination in *Saccharomyces cerevisiae* strain D3 with metabolic activation (Simmon et al., 1979), but was ineffective in *S. cerevisiae* strain D4 with or without metabolic activation (Monsanto, 1976a).

In carcinogenesis studies with 1,2-dichlorobenzene and 1,3-dichlorobenzene in rats and mice (NTP, 1985b, 1987), 1,3-dichlorobenzene induced kidney tumors in male rats and liver tumors in both sexes of mice. Neither compound induced liver tumors in rats.

The NTP (1985a) study speculated that chlorobenzene was related to the carcinogen, benzene, because of similarities in structure, metabolism and hematological effects in rodents; and therefore, a toxic human response could be predicted based upon a rodent model.

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

None.

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

None.

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

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1986, 1989

The Health Effects Criteria Document on Chlorobenzene by the Office of Drinking Water has undergone public review and Science Advisory Board review (1986).

The proposed drinking water standard for chlorobenzene has been reviewed by EPA and the public (1989 Federal Register notice).

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

Agency Work Group Review — 04/04/1990

Verification Date — 04/04/1990

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 Chlorobenzene 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 — Chlorobenzene
CASRN — 108-90-7
Primary Synonym — Monochlorobenzene

VI.A. Oral RfD References

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John, J.A., W.C. Hayes, T.R. Hanley, Jr., K.A. Johnson, T.S. Gushow and K.S. Rao. 1984. Inhalation teratology study on monochlorobenzene in rats and rabbits. Toxicol. Appl. Pharmacol. 76: 365-373.

Knapp, W.K., W.M. Busey and W. Kundzins. 1971. Subacute oral toxicity of monochlorobenzene in dogs and rats. Toxicol. Appl. Pharmacol. 19: 393. (Abstract).

Monsanto Chemical Company. 1967a. 13-week oral administration -- dogs. Monochlorobenzene. Final report. Prepared by Hazelton Laboratories, Project No. 241-105, February 24.

Monsanto Chemical Company. 1967b. Three-month subacute oral study -- rats. Monochlorobenzene. Final report. Prepared by Hazelton Laboratories, Project No. 241-104, March 9.

Nair, R.S., J.A. Barter, R.E. Schroeder, A. Knezevich and C.R. Stack. 1987. A two-generation reproduction study with monochlorobenzene vapor in rats. Fund. Appl. Toxicol. 9: 678-686.

NTP (National Toxicology Program). 1985. Toxicology and carcinogenesis studies of chlorobenzene (CAS No. 108-90-7) in F344/N rats and B6C3F1 mice (gavage studies). U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. NTP No. 261. NIH Publ. No. 83-2517.

U.S. EPA. 1986. Drinking Water Criteria Document for Chlorobenzene. Office of Drinking Water, Washington, DC.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

E.I. duPont deNemours and Company. 1977. Mutagenic activity of monochlorobenzene in the Salmonella-microsome assay. Haskell Laboratory for Toxicology and Industrial Medicine. Unpublished report.

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Keskinova, D.V. 1968. The effect of dimethylcyclodiazomethane in chlorobenzene solution on the process of mutagenesis in *Actinomyces antibioticus*-400. *Genetika*. 4(8): 121-125.

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Monsanto Company. 1976b. Mutagenicity evaluation of B10-76-86-CP-5535 (LOX). Final report. LBI Project No. 2547. Litton Bionetics, Kensington, MD. Unpublished.

NTP (National Toxicology Program). 1982. Environmental Mutagen Test Development Program, Research Triangle Park, NC. (Cited in NTP, 1985a)

NTP (National Toxicology Program). 1985a. Toxicology and carcinogenesis studies of chlorobenzene (CAS No. 108-90-7) in F344/N rats and B6C3F1 mice (gavage studies). U.S.

Department of Health and Human Services. Public Health Service. National Institutes of Health. NTP No. 261. NIH Publ. No. 83-2517.

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NTP (National Toxicology Program). 1987. Toxicology and carcinogenesis studies of 1,4-dichlorobenzene (CAS No. 106-46-7) in F344/N rats and B6C3F1 mice (gavage studies). NTP TR 319. NIH Publ. No. 86-2575.

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Prasad, I. 1970. Mutagenic effects of the herbicide 3,4-dichloro-ropionanilide and its degradation products. *Can. J. Biochem*. 16: 369-372.

Prasad, I. and D. Pramer. 1968. Mutagenic activity of some chloroanilines and chlorobenzenes. *Genetics*. 60: 212-213.

Simmon, V.F., E.C. Ricco and M.V. Pierce. 1979. In vitro microbiological genotoxicity tests of chlorobenzene, m-dichlorobenzene, o-dichlorobenzene and p-dichlorobenzene. Final report. SRI International, Menlo Park, CA. Unpublished.

U.S. EPA. 1986. Draft Health Effects Criteria Document for Chlorobenzene. Criteria and Standards Division, Office of Drinking Water, Washington, DC.

U.S. EPA. 1989. National Primary and Secondary Drinking Water Regulations; Proposed Rule. Monochlorobenzene. *Federal Register*. 54(97): 22087-22088.

VII. Revision History

Substance Name — Chlorobenzene

CASRN — 108-90-7

Primary Synonym — Monochlorobenzene

Date	Section	Description
08/01/1989	I.A.	Oral RfD summary on-line
11/01/1990	II.	Carcinogen assessment on-line
10/28/2003	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Chlorobenzene

CASRN — 108-90-7

Primary Synonym — Monochlorobenzene

Last Revised — 08/01/1989

- 108-90-7
- BENZENE CHLORIDE
- BENZENE, CHLORO-
- CHLOORBENZEEN (Dutch)
- CHLORBENZENE
- CHLORBENZOL
- CHLOROBENZEN (Polish)
- CHLOROBENZENE
- CHLOROBENZENU (Czech)
- CHLOROBENZOL
- CLOROBENZENE (Italian)
- MCB
- MONOCHLOORBENZEEN (Dutch)

- MONOCHLORBENZENE
- MONOCHLORBENZOL (German)
- MONOCHLOROBENZENE
- MONOCHLOROBENZENE (Italian)
- NCI-C54886
- PHENYL CHLORIDE
- UN 1134