

1,2-Dichlorobenzene; CASRN 95-50-1

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 1,2-Dichlorobenzene

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 — 1,2-Dichlorobenzene

CASRN — 95-50-1

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
No adverse effects observed	NOAEL: 120 mg/kg/day (adjusted to 85.7 mg/kg/day)	1000	1	9E-2 mg/kg/day
2-Year Rat Study, Oral Exposure (gavage)	LOAEL: None			
NTP, 1985				

*Conversion Factors: Doses adjusted for gavage schedule of 5 days/week.

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

NTP (National Toxicology Program). 1985. Toxicology and carcinogenesis studies of 1,2-dichlorobenzene (o-dichlorobenzene) (CAS No. 95-50-1) in F344/N rats and B6C3F1 mice (gavage studies). NTP TR 255. NIH Publ. No. 86-2511.

1,2-Dichlorobenzene in corn oil was given by gavage to F344/N rats and B6C3F1 mice (50 males and 50 females/group) at doses of 0, 60, or 120 mg/kg/day, 5 days/week for 103 weeks (NTP, 1985). Survival of high-dose male rats was decreased compared with controls (19/50 vs. 42/50, $P > 0.001$), but the difference appears largely because of deaths from gavage error (4 controls vs. 20 high-dose). Although an increase ($P > 0.05$) in renal tubular regeneration in high-dose male mice was observed (17/49 compared with 12/50 in the low-dose group and 8/48 in the control group), there was no other evidence of treatment-related renal lesions in either species. Further, the incidence of this lesion in male control mice was below those of three similar control groups that were studied during approximately the same period at the testing facility (31/50, 15/50, 24/50). There was no other evidence of treatment-related effects in this study. Because the decrease in survival and the increase in renal tubular regeneration in the high-dose animals were of questionable significance, a NOAEL of 120 mg/kg/day is established.

1,2-Dichlorobenzene in corn oil was given orally by gavage to F344/N rats and B6C3F1 mice (10 males and 10 females/group) at doses of 0, 30, 60, 125, 250, or 500 mg/kg/day, 5 days/week for 13 weeks (NTP, 1985). Liver necrosis was found in mice and rats given 250 mg/kg/day. Deaths, degeneration and necrosis in the liver, lymphocyte depletion in the spleen and thymus, renal tubular degeneration (male rats only), and slight decreases in hemoglobin, hematocrit and red blood cell counts (rats only) were induced at 500 mg/kg/day.

Hepatocellular necrosis (focal or individual hepatocyte) was observed in 1 male and 3 female rats given 125 mg/kg/day (NTP, 1985). Increases ($P \geq 0.05$) in serum cholesterol at all doses except 60 mg/kg/day in male rats and at doses of 125 to 500 mg/kg/day for female rats; liver weight/body weight ratios in male and female rats at 125 to 500 mg/kg/day; and serum protein at all doses in female rats and at 250 to 500 mg/kg/day in male rats indicate treatment-related liver effects at doses >125 mg/kg/day. However, no evidence of treatment-related liver pathology in rats and mice given 60 or 120 mg/kg/day, 5 days/week in the 2-year NTP (1985) carcinogenicity bioassay and no increase ($P \geq 0.05$) in serum enzymes (SGPT, GGPT, alkaline phosphatase) for either rats or mice in the 13-week study are grounds for considering 125 mg/kg/day as a NOAEL in the 13-week study.

In rats dosed by gavage with 1,2-dichlorobenzene at 18.8, 188, or 376 mg/kg/day, 5 days/week for 192 days, liver and kidney weights were increased at 188 mg/kg/day, and liver pathology and increased spleen weight were observed at 376 mg/kg/day (Hollingsworth et al., 1958). No effects were observed at 18.8 mg/kg/day. Thus, the NOAEL was 18.8 mg/kg/day.

Rats, guinea pigs, mice, rats, and monkeys were exposed by inhalation to 1,2-dichlorobenzene at levels of 49 or 93 ppm, 7 hours/day, 5 days/week for 6 to 7 months. At 93 ppm, body weight gain in rats and spleen weight in guinea pigs were reduced ($P \geq 0.05$) (Hollingsworth et al., 1958). Estimated daily doses with 49 ppm exposure are 387 mg/kg (mouse), 19.3 mg/kg (rat), 14.4 mg/kg (guinea pig), 15.9 mg/kg (rabbit), and 20.3 mg/kg (monkey).

Pregnant F344/N rats and New Zealand rabbits were exposed by inhalation to 0, 100, 200, or 400 ppm 1,2-dichlorobenzene 6 hours daily on days 6 through 15 (rats) or 6 through 18 (rabbits) of gestation (Hayes, 1985). Body weight gain was lower ($P \geq 0.05$) in rats at all doses and in rabbits at 400 ppm, during the first 3 days of exposure. Liver weights (absolute and relative to body weight) were increased in rats at 400 ppm. No developmental toxicity was evident at any dose. Estimated daily doses at 100 ppm exposure are 40 mg/kg (rat) and 32 mg/kg (rabbit).

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 because of the lack of studies assessing reproductive effects and adequate chronic toxicity in a second species (10D).

MF — None

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

Taking into consideration the 13-week and 2-year NTP studies together, the NOAEL is supported. The 1000-fold uncertainty factor takes into account data gaps and endpoints assessed in the 13-week NTP study which were not assessed in the 2-year NTP study.

I.A.5. Confidence in the Oral RfD

Study — Medium

Database — Low

RfD — Low

The chronic study, coupled with results of subchronic studies provides a NOAEL and LOAEL for several toxicologic endpoints, but the chronic study did not assess biochemical and clinical endpoints. Therefore, a medium level of confidence is assigned. Lack of reproductive and adequate additional supporting toxicity studies in nonrodent species lead to low confidence in the database. Low confidence in the RfD follows.

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

Source Document — U.S. EPA, 1987.

Drinking Water Criteria Document for ortho-Dichlorobenzene, meta-Dichlorobenzene, para-Dichlorobenzene. Office of Drinking Water, Washington, DC.

Science Advisory Board review of ODW health advisory document in 1986, and ODW criteria document in 1987. Public comments on proposed drinking water regulation in 1985.

Agency Work Group Review — 06/24/1985, 07/08/1985, 04/20/1988, 02/16/1989

Verification Date — 02/16/1989

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 — 1,2-Dichlorobenzene
CASRN — 95-50-1

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — 1,2-Dichlorobenzene
CASRN — 95-50-1
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 — Based on no human data and evidence of both negative and positive trends for carcinogenic responses in rats and mice.

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

Inadequate. Two carcinogenicity studies were conducted by the National Toxicology Program (NTP, 1985) using 1,2-dichlorobenzene. Groups of 50 F344/N rats/sex and 50 B6C3F1 mice/sex were gavaged with 0, 60 or 120 mg/kg of the chemical in corn oil, 5 days/week for 103 weeks. In the rat study, survival in the 0, 60 and 120 mg/kg groups was 84, 72 and 38% in males and 62, 66 and 64% in females; NTP concluded that a maximum-tolerated-dose (MTD) had been achieved. Survival was statistically significantly reduced in the high-dose males due to causes incidental to treatment (3 accidental deaths, 5 deaths due to gavage error, and 12 deaths caused by aspiration). An increased incidence of pheochromocytomas of the adrenal gland was found in low-dose males (significant by life table test) but not the high-dose males (9/50, 16/50, 6/49 in the control, low- and high-dose groups, respectively). The increased incidence of pheochromocytomas in low-dose males was discounted because there was no dose-response trend or high-dose effect, no malignant pheochromocytomas had been observed, and no incidence increase was seen in females; additionally, the biological consequence of this endpoint is often questioned because pheochromocytomas are not considered to be a life-threatening condition. There was a decrease in the incidence of testicular interstitial cell tumors (47/50, 49/50 and 41/50).

In the mouse study, no significant differences in survival were noted in the treatment groups when compared with controls. It is unclear if an MTD had been achieved. A dose-related increase was seen in malignant histiocytic lymphoma in male mice (0/50, 1/50, 4/50 for control, low- and high-dose groups, respectively) and female mice (0/49, 0/50, 3/49 for control, low- and high-dose groups, respectively). An increased incidence of alveolar and bronchiolar carcinomas (combined) in male mice (4/50, 2/50 and 10/50 for the control, low- and high-dose groups, respectively) was significant by a trend test; the combined incidence of alveolar and bronchiolar adenomas and carcinomas (8/50, 8/50 and 13/50, respectively) did not show a significant elevation. One high-dose male had a testicular interstitial cell tumor. In males there was a

decrease in the incidence of hepatocellular adenomas (8/50, 5/49 and 2/46, respectively) and carcinomas (14/50, 10/49 and 9/46, respectively).

II.A.4. Supporting Data for Carcinogenicity

1,2-Dichlorobenzene, at concentrations up to 333 ug/plate, did not produce reverse mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535 or TA1537 with and without liver homogenates from Sprague-Dawley rat or Syrian hamster (NTP, 1985). In an abstract, Lawlor et al. (1979) reported that 1,2-dichlorobenzene (doses not specified) did not produce reverse mutations in TA98, TA100, TA1535, TA1537 or TA1538 with and without rat liver homogenates. An increase in the frequency of mutations by 1,2-dichlorobenzene was reported in auxotrophic strain of *Aspergillus nidulans* (Prasad and Pramer, 1968). Chromosome studies, in workers occupationally exposed for 4 days (8 hours/day) to 1,2-dichlorobenzene vapors (the concentration was thought to have exceeded 100 ppm), showed a statistically significant increase in the incidence of chromosomal alterations (in chromosomes isolated from peripheral blood cells) when compared to chromosomes isolated from the blood cells of a control population (Zapata-Gayon et al., 1982). The number of single and double chromosome breaks was also increased. A followup study 6 months after the initial exposure indicated a significant increase in only double chromosome breaks.

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, 1985

The 1985 Health Assessment Document for Chlorinated Benzenes has received Agency Review.

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

Agency Work Group Review — 12/06/1989

Verification Date — 12/06/1989

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 — 1,2-Dichlorobenzene

CASRN — 95-50-1

VI.A. Oral RfD References

Hayes, W.C., T.R. Hanley, Jr., T.S. Gushow, K.A. Johnson, and J.A. John. 1985. Teratogenic potential of inhaled dichlorobenzene in rats and rabbits. *Fund. Appl. Toxicol.* 5: 190-202.

Hollingsworth, R.L., V.K. Rowe, F. Oyen, T.R. Torkelson, and E.M. Adams. 1958. Toxicity of o-dichlorobenzene. Studies on animals and industrial experience. *A.M.A. Arch. Indust. Health* 17: 180-187.

NTP (National Toxicology Program). 1985. Toxicology and carcinogenesis studies of 1,2-dichlorobenzene (o-dichlorobenzene) (CAS No. 95-50-1) in F344/N rats and B6C3F1 mice (gavage studies). NTP TR 255. NIH Publ. No. 86-2511.

U.S. EPA. 1987. Drinking Water Criteria Document for ortho-Dichlorobenzene, meta-Dichlorobenzene, para-Dichlorobenzene. Office of Drinking Water, Washington, DC.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

Lawlor, T., S.R. Haworth and P. Voytek. 1979. Evaluation of the genetic activity of nine chlorinated phenols, seven chlorinated benzenes, and three chlorinated hexanes. *Environ. Mutagen.* 1(2): 143. (Abstr.)

NTP (National Toxicology Program). 1985. Toxicology and carcinogenesis studies of 1,2-dichlorobenzene (o-dichlorobenzene) (CAS No. 95-50-1) in F344/N rats and B6C3F1 mice (gavage study). NTP, Research Triangle Park, NC. NTP-TR- 255. NIH Publ. No. 86-2511.

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

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 Solide Waste and Emergency Response, Washington, DC.

Zapata-Gayon, C., N. Zapata-Gayon and A. Gonzalez-Angulo. 1982. Clastogenic chromosomal aberrations in 26 individuals accidentally exposed to ortho dichlorobenzene vapors in the National Medical Center in Mexico City. *Arch. Environ. Health.* 37(4): 231-235.

VII. Revision History

Substance Name — 1,2-Dichlorobenzene
CASRN — 95-50-1

Date	Section	Description
08/01/1989	I.A.	Oral RfD summary on-line

Date	Section	Description
11/01/1990	II.	Carcinogen assessment on-line

VIII. Synonyms

Substance Name — 1,2-Dichlorobenzene

CASRN — 95-50-1

Last Revised — 08/01/1989

- 95-50-1
- BENZENE, 1,2-DICHLORO-
- BENZENE, o-DICHLORO-
- CHLOROBEN
- CHLORODEN
- CLOROBEN
- DCB
- o-DICHLORBENZENE
- o-DICHLOR BENZOL
- o-DICHLOROBENZENE
- 1,2-DICHLOROBENZENE
- o-DICHLOROBENZENE
- DICHLOROBENZENE, ORTHO
- DILANTIN DB
- DILATIN DB
- DIZENE
- DOWTHERM E
- NCI-C54944
- ODB
- ODCB
- ORTHODICHLOROBENZENE
- ORTHODICHLOROBENZOL
- SPECIAL TERMITE FLUID
- TERMITKIL
- UN 1591