1,4-Dichlorobenzene; CASRN 106-46-7

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 1,4-Dichlorobenzene

File First On-Line 01/01/1994

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	yes	01/01/1994
Carcinogenicity Assessment (II.)	not evaluated	

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — 1,4-Dichlorobenzene
CASRN — 106-46-7

Not available at this time.

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

Substance Name — 1,4-Dichlorobenzene
CASRN — 106-46-7
Last Revised — 01/01/1994

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are 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.B.1. Inhalation RfC Summary

Critical Effect	Exposures*	UF	MF	RfC
Increased liver weights in P1 males **Rat Multigeneration Reproductive Study** **Chlorobenzene Producers Assn., 1986**	NOAEL: 301 mg/cu.m (50 ppm) NOAEL(ADJ): 75 mg/cu.m NOAEL(HEC): 75 mg/cu.m LOAEL: 902 mg/cu.m (150 ppm) LOAEL(ADJ): 225 mg/cu.m LOAEL(HEC): 225 mg/cu.m	100	1	8 E-1 mg/cu.m

*Conversion Factors: MW=147.01. Assuming 25 degrees C and 760 mm Hg, NOAEL(mg/cu.m) = 50 ppm x 147.01/24.45= 301 mg/cu.m. NOAEL(ADJ) = NOAEL mg/cu. m. x 6h/day = 75 mg/cu.m. The NOAEL(HEC) was calculated for a gas:extra respiratory effect assuming periodicity was attained. Since the b:a lambda values are unknown for the experimental animal

species (a) and humans (h), a default value of 1.0 is used for this ratio. NOAEL(HEC) = NOAEL(ADJ) x (b:a lambda (a)/b:a lambda (h)) = 301 mg/cu.m.

I.B.2. Principal and Supporting Studies (Inhalation RfC)

Chlorobenzene Producers Association. 1986. Parachlorobenzene: Two-generation Reproduction Study in Sprague-Dawley Rats. Study 86-81-90605. MRID No. 411088-1. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

In a two-generation reproductive study Sprague-Dawley rats (P1) {28/sex/group} were exposed to 1,4-dichlorobenzene (1,4-DCB) vapor at concentrations of 0, 50, 150, or 450 ppm (0, 301, 902, 2705 mg/cu.m) for 10 weeks, 6 hours/day, 7 days/week, then the rats were mated for 3 weeks. For exposure of the next generation, selected F1 weanlings were exposed to 1,4-DCB for 11 weeks then mated. Adult males in the 150 ppm group exhibited reduced body weights and weight gain, reduced food consumption, increased incidence of tremors, unkempt appearance and nasal and ocular discharges. A statistically significant (p=0.01) increase in liver weights was noted at necropsy in the 150 and 450 ppm groups (16 and 38%, respectively). In addition, there was a statistically significant (p-0.01) increase in kidney weight for both parental males and females. At 450 ppm there was a statistically significant (p=0.01) decrease in live births, a decrease in pup weights, and decreased pup survival at day 4 of lactation for both the F1 and F2 generations. In addition, histological observations showed significant increases in incidence of hepatocellular hypertrophy in F0 and F1 males and females. No developmental abnormalities were observed in the pups examined. All dose levels caused hyaline droplet nephrosis in post-puberal males; this change was associated with the formation of alpha-2u-globulin but is recognized as an abnormality specific for male rats and does not have significance relative to human health (U.S. EPA, 1991). The lesions observed in the male rats treated with 1,4-DCB met the criteria for alpha-2u-globulin nephropathy, that is, excessive accumulation of hyaline droplets in the P2 segment of the proximal tubule, single cell necrosis, accumulation of granular casts, increased cellular proliferation in the P2 segment and linear mineralization of tubules. Charbonneau et al. (1989) has demonstrated that 1,4-DCB induces a nephrotoxicity in male rats that is associated with reversible binding to alpha-2u-globulin. The degree of binding follows a dose-response pattern; 2,5-dichlorophenol, the major metabolite of 1,4-DCB, also binds to alpha-2u- globulin, and 1,4-DCB shows much greater binding than 1,2-DCB. These authors postulated that the alpha-2u-globulin accumulation was due to decreased lysosomal catabolism.

The NOAEL established from this study was 50 ppm (301 mg/cu m) and the LOAEL is 150 ppm (902 mg/cu.m); the critical effect was the significant increase in liver weights of P1, parental males.

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF — An uncertainty factor of 10 was used to account for sensitive subpopulations among humans. An uncertainty factor of 3 rather than 10 was used to account for interspecies differences since dosimetry adjustments were applied. An additional factor of 3 was used since the NOAEL was based on a subchronic rather than chronic study. A full factor of 10 was not used because the LOAEL estimated by a route-to-route extrapolation from the chronic NTP (1987) oral study suggested limited progression of the hepatic lesions when terminal results were compared with interim kills. In addition, comparison of histopathologic results from the interim and final kills of the Riley et al. (1980) study also indicated that there was no progression in severity of liver lesions.

MF — None

I.B.4. Additional Studies/Comments (Inhalation RfC)

An NTP (1987) chronic bioassay study was performed for 1,4-DCB in which 50 male and female F344 rats and 50 male and female B6C3F1 mice were assigned to each dose group. Female rats and both sexes of mice received 0, 300 and 600 mg/kg and male rats received 0, 150 and 300 mg/kg-day of 1,4-DCB in corn oil gavage for 2 years. An increased incidence of nephropathy was noted in low-dose and high-dose female rats when compared with vehicle controls (43, 64 and 84% incidence in control, low and high-dose groups, respectively). There were no other significant dose-related lesions noted in female rats. From the results noted in female rats a LOAEL of 300 mg/kg-day was determined. The renal lesions noted in male rats can be attributed to excess production of alpha-2u-globulin; these lesions will not be discussed since they have been determined to be inappropriate for human health considerations (U.S. EPA, 1991). The non-neoplastic lesions noted in male mice included thymic lymphoid depletion, hepatic cellular degeneration and focal necrosis, and focal hyperplasia of adrenal cortex. The non-cancer lesions noted in female mice included lymphoid hyperplasia, and hepatocellular degeneration. Comparison of the results of interim kills and terminal sacrifices indicated that hepatic lesions did not progress with time, either for incidence or severity. This finding supports the choice of the Chlorobenzene Producers Assn. (1986) study as critical. The LOAEL established in male and female mice is 300 mg/kg-day.

Since the critical adverse effect occurred in the adult animals in a reproductive study of short duration and because the Riley et al. (1980) 2- year inhalation study was of limited value for risk assessment, an objective was to identify chronic data that supported the choice of hepatic lesions and showed that the severity of liver effects did not progress. (The Riley et al., 1980 study showed similar incidence and severity of hepatic and renal lesions in the control and exposed groups and the rats did not receive 1,4-DCB exposure for extended times during the study.)

The 1987 NTP study was a chronic bioassay done via oral administration (corn oil gavage). Although the only pharmacokinetic data available (Hawkins, et al., 1980; Umemura et al., 1989) were limited for a number of reasons (differences in vehicle to that of the Riley study, limited number of doses and test animals), a route-to-route extrapolation using the NTP data was attempted to gauge where the chronic hepatic toxicity would fall relative to that of the principal study (CPA, 1986). The data conversions, rationale and calculations for this extrapolation are provided elsewhere (Cicmanec, 1993).

The route-to-route extrapolation involves considerable uncertainty and is not used as a quantitative basis for RfC derivation. Nevertheless, the equivalent inhalation exposure concentration calculated from the NTP study is within the same order of magnitude as both the Riley et al. (1980) data and the principal study, so that these chronic systemic toxicity data were considered supportive of the Chlorobenzene Producers Assn. (1986) as the principal study.

In the Hollingsworth et al. (1956) study, rats, guinea pigs and rabbits were exposed to 0, 96, 158, 341 or 798 ppm (0, 577, 950, 2050 or 4800 mg/cu.m) of 1,4-DCB for 7 hours/day, 5 days/week for 6-7 months. Clinically, animals receiving the highest concentration showed marked tremors, weakness, loss of weight, eye irritation and unconsciousness. Microscopic examination of tissues revealed moderate, cloudy swelling of the liver and kidneys and centrilobular hepatic necrosis. The NOAEL determined from this study is 577 mg/cu.m (NOAEL (HEC) = 120 mg/cu.m). The LOAEL established in this study was 950 mg/cu.m (HEC=198 mg/cu.m) on the basis of increases in liver and kidney weights. Microscopically cloudy swelling of the liver and kidney centrilobular cellular degeneration of the liver were observed at this dose. Companion oral dosing studies were reported for ducks, rats and rabbits in this paper at doses of 10, 100 and 500 mg/kg. Clinical, gross, and microscopic changes were seen only at 500 mg/kg. The liver and kidney were also the target organs for the oral studies.

Groups of 76-79/sex of Alderly Park Wistar rats were chamber-exposed to 1,4-DCB vapor at 0, 75 or 500 ppm (0, 451 or 3006 mg/cu.m. for 5 hours/day, 5 days/week for 76 weeks (Riley et al., 1980). At the termination of exposure, a recovery period of 36 weeks for surviving rats was included. Clinical observations, clinical chemistry, and urinalysis were performed at weeks 5, 14, 27, 40 and 50 of the study. Complete histopathology (45 tissues/rat including complete respiratory tract) was performed on all rats that died or were killed except those that were cannibalized or severely autolyzed. Interim kills (5 rats/sex) were performed at 26 and 52 weeks. At 500 ppm there were increases in liver and kidney weights at some time points but not all. Kidney weights for males at 500 ppm were increased 16% above controls at 26 weeks, 33% at 76 weeks and 10% at the end of the recovery week. Kidney weights for females were increased 21% at the end of the recovery period. Focal chronic hepatitis, focal hepatic vacuolation and focal necrosis were observed at 500 ppm but similar lesions were also seen in control rats at the end of

the recovery period. Moderate nephropathy, suppurative nephritis, and papillary mineralization were seen at 500 ppm but similar changes were seen in the control group.

Microscopic examination of the nasal cavity revealed olfactory epithelial degeneration, respiratory epithelial hyperplasia, subacute rhinitis, squamous metaplasia and adenitis of nasal glands in moderate incidence, however, similar changes were noted in the control groups. Changes in the lungs that were noted included the presence of peribronchial lymphoid accumulations, chronic interstitial inflammatory infiltrates, alveolar histiocytosis and the presence of pigmented and foamy histiocytes. The NOAEL(HEC) established was 67 mg/cu.m and the LOAEL(HEC) was 447 mg/cu.m on the basis of increased liver and kidney weights.

Hayes et al. (1985) exposed rabbits to 0, 100, 300 or 800 ppm (0, 601, 1804 or 4810 mg/cu.m) for 6 hours/day on days 6-18 of gestation. Twenty-four to 28 dams and their litters were examined at the various dose levels. The maternal body weight gain during gestation as well as absolute and relative liver and kidney weights were also determined. The number of litters, corpora lutea/dam, implantation sites/dam, fetuses/litter, resorptions/litter, fetal sex ratio, fetal body weights and fetal crown-rump lengths were determined. Only the differences in percentage of implantations resorbed and percentage of litters with resorptions for the 300 ppm group were statistically significant. The occurrence of retroesophageal positioning of the right subclavian artery was increased in the 800 ppm group and was determined to be not indicative of a teratogenic response. The authors concluded that no significant teratogenic or fetotoxic effects were observed at 100, 300 or 800 ppm.

Anderson and Hodge (1976) exposed mice to 0, 75, 225 or 450 ppm (0, 451, 1353 or 2706 mg/cu.m) for 6 hours/day for 5 days. No reduction in reproductive performance was observed at any dose.

The summary of reports for human exposure to 1,4-DCB presented in the Health Assessment Document for Chlorinated Benzenes (U.S. EPA, 1985) indicates that malaise and nausea are frequently observed as well as hepatic manifestations such as yellow atrophy and cirrhosis of the liver. Proteinuria, bilirubinuria, hematuria and anemia are also observed. A Japanese report describes a young woman who was exposed to unusually high concentrations of 1,4-DCB continuously at home. Her exposure had lasted for 6 years before a clinical examination was performed. She presented with severe cerebellar ataxia, dysarthria, moderate weakness in all limbs and hyporeflexia. Once removed from the contaminated environment, her bedroom, her symptoms disappeared after 8 months. The authors emphasized the similarities of rapid reversibility of CNS symptoms to those reported by Hollingsworth et al., (1956) in rats, rabbits and guinea pigs and attributed it to rapid elimination of 1,4-DCB (Miyai et al., 1988).

I.B.5. Confidence in the Inhalation RfC

Study — Medium
Database — Medium
RfC — Medium

Confidence in the principal study is medium. The critical study employed an extensive reproductive protocol including histopathologic examination of tissues of adults and offspring. Confidence in the database is rated medium. There are a number of supporting studies for the developmental and reproductive toxicology database. Supporting data for chronic exposure was obtained by performing a route-to-route extrapolation from the chronic NTP (1987) study and resonably close correlation for the LOAEL was found. This comparison was done in order to justify using the adult liver data following 10 weeks of exposure from the Chlorobenzene Producers Assn. (1986) study. Essentially the results of the NTP (9187) study and the Riley et al. (1980) study, which were chronic lifetime exposures, indicate a lack of progression of the hepatic lesions. This information, in turn, supports the use of the Chlorobenzene Producers Assn. (1986) study as the critical study and obviates to some extent the concern for the lack of chronic data. Medium confidence in the RfC follows.

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — U.S. EPA, 1985

Agency Work Group Review — 06/23/1988, 10/13/1988, 08/15/1991, 12/12/1991, 06/25/1992

Verification Date — 06/25/1992

I.B.7. EPA Contacts (Inhalation RfC)

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 — 1,4-Dichlorobenzene
CASRN — 106-46-7

This substance/agent has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential.

VI. Bibliography

Substance Name — 1,4-Dichlorobenzene
CASRN — 106-46-7

VI.A. Oral RfD References

None

VI.B. Inhalation RfC References

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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. EPA/600/8-84/015F.

U.S. EPA. 1991. Alpha-2u-Globulin: Association with Chemically Induced Renal Toxicity and Neoplasia in the Male Rat. Prepared for the Risk Assessment Forum, U.S. EPA, Washington, DC 20460. EPA/625/3-91/019F.

VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — 1,4-Dichlorobenzene
CASRN — 106-46-7

Date	Section	Description
01/01/1994	I.B.	Inhalation RfC on-line

VIII. Synonyms

Substance Name — 1,4-Dichlorobenzene
CASRN — 106-46-7

- 106-46-7
- 1,4-DICHLOORBENZEEN [DUTCH]
- 1,4-DICHLOROBENZENE
- 1,4-DICLOROBENZENE [ITALIAN]
- BENZENE, 1,4-DICHLORO-
- BENZENE, P-DICHLORO-
- CASWELL NO. 632
- DI-CHLORICIDE
- DICHLOROBENZENE, PARA
- EPA PESTICIDE CHEMICAL CODE 061501
- EVOLA
- HSDB 523
- NCI-C54955
- NSC 36935
- PARADI
- PARADICHLORBENZOL [GERMAN]
- PARADICHLOROBENZENE
- PARADICHLOROBENZOL
- PARADOW
- PARAMOTH
- PARAZENE
- P-CHLOROPHENYL CHLORIDE
- PDB
- P-DICHLOORBENZEEN [DUTCH]
- P-DICHLORBENZOL [GERMAN]

- P-DICHLOROBENZENE
- P-DICHLOROBENZOL
- P-DICLOROBENCENO [SPANISH]
- P-DICLOROBENZENE [ITALIAN]
- PERSIA-PERAZOL
- RCRA WASTE NUMBER U070
- RCRA WASTE NUMBER U072
- SANTOCHLOR
- UN 1592