DRAFT IRIS SUMMARY

0552
1,4-Dichlorobenzene; CASRN 106-46-7; 00/00/00

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices, Regional Offices, and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR 1,4-DICHLOROBENZENE

File First On-Line 01/01/1994

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	00/00/00
Inhalation RfC Assessment (I.B.)	on-line	00/00/00
Carcinogenicity Assessment (II.)	on-line	00/00/00

_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
Last Revised -- 00/00/0000

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 lesions (Hepatocellular hypertrophy, multifocal to diffuse)	NOEL: 10mg/kg-day, adjusted dose: 7mg/kg-day LOAEL: 50mg/kg-day adjusted dose: 36mg/kg-day	100		2.4E-3mg/kg-day
One year dog study Monsanto Company, 1996	BMDL: 0.237mg/kg-day			

*Conversion Factors and Assumptions – Liver lesions in male and female beagle dogs were analyzed by benchmark dose modeling. The lower 95% confidence limit on the benchmark dose (BMDL) associated with a 10% increased incidence of liver lesions was selected as the point of departure for the RfD.

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Monsanto Company. (1996) M.W. Naylor and L.D. Stout. One Year Study of p-Dichlorobenzene Administered Orally Via Capsule to Beagle Dogs. MRID No. 439888-02. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

The subchronic and chronic oral toxicity of 1,4-dichlorobenzene (1,4-DCB) has been evaluated in a number of animal studies. As detailed in Section I.A.4., liver, hematopoietic system and kidney toxicity are the most sensitive systemic effects of chronic oral exposure, occurring at doses as low as 36 mg/kg-day in beagle dogs (Monsanto Company, 1996), with developmental toxicity, from gestational exposure, occurring in rats at higher levels of exposure (Giavini et al., 1986). In addition, a two-generation study in rats (Bornatowicz et al., 1994) found that developmental toxicity associated with exposure during the perinatal and later pre-weaning periods occurred at dose levels of 90, or 270 mg/kg-day. These results indicate that liver is the most sensitive endpoint for oral exposure to 1,4-DCB and the best basis for RfD derivation.

The chronic beagle dog study evaluated the systemic effects of 1,4-DCB in male and female beagle dogs that were administered the chemical (99.9% pure) in gelatin capsules, 5 days/week, at initial dose levels of 0, 10, 50, or 150 mg/kg-day (adjusted doses; 0, 7, 36, 107 mg/kg-day) (Monsanto Company, 1996) for 1 year. Controls received empty gelatin capsules. Since unexpectedly severe toxicity occurred at the highest dose level, the high dose was adjusted to 100 mg/kg-day (71 mg/kg-day) during the third week of exposure for males and further

reduced to 75 mg/kg-day (54 mg/kg-day) for both sexes at the beginning of week 6. Both males and females at the highest dose level were untreated during the fourth and fifth weeks to allow for recovery, while lower dose animals were administered the test compound continuously. The authors stated that one high dose male (day 12) and one high dose female (day 24) dog died due to inflammatory lung lesions and/or pulmonary hemorrhages while the cause of death of another high dose male (day 25) remained undetected. One control male dog died on day 83 and the cause of death may have been due to a physical displacement of the small intestine, with secondary aspiration pneumonia. Blood and urine were collected pretest, at approximately 6 months and at study termination for hematology, urine analysis, and serum chemistry analyses. Ophthalmoscopic examinations were also conducted pretest and at study termination. All surviving dogs were sacrificed at 12 months and selected organs were examined for gross pathology and histopathology. Pathology examinations included terminal body weights and absolute and relative weights of adrenals, brain, heart, kidneys, liver, pituitary, testes, and thyroids/parathyroids. Histopathological examinations were conducted on tissues obtained from the adrenals, aorta, brain, caecum, colon, duodenum, epididymides, esophagus, eyes, gallbladder, heart, ileum, jejunum, kidneys, liver, lung, lymph nodes, muscle, nerve (sciatic), ovaries, pancreas, parathyroids, pituitary, prostate, rectum, salivary gland, skin, spinal cord, spleen, sternum, stomach, testes, thymus, thyroids, trachea, urinary bladder and uterus.

Absolute and relative liver weights (Table I.A.2.1) were statistically significantly increased in both sexes at the two highest doses (36 and 54 mg/kg-day). Increases in absolute and/or relative adrenal (absolute weight; 125 and 130% control in males; 135 and 141% controls in females; relative weight; 143 and 158% control in males; 138 and 153% control in females) and thyroid (absolute weight; 118 and 123% control in males; 139 and 132% control in females; relative weights; 133 and 149% control in males; 143 and 141% control in females) weights were observed in both sexes at the two highest doses and were considered possible treatment related effects, although no histopathological lesions were found to explain the increase in the adrenals and thyroid (Monsanto Company, 1996).

Histopathological examination revealed several liver lesions only in the dosed groups and were considered either direct or indirect/adaptive effects to 1,4-DCB and were consistent with gross necropsy findings, organ weight data and clinical results. Liver lesions of mild to moderately severe nature were observed in all mid and high dose male and female dogs. Hepatocellular hypertrophy, multifocal to diffuse with increasing dose level were statistically significant ($p \leq 0.01$, Fisher's exact test, one-tailed) in all male and female dogs at mid and high doses and in a single female at the lowest dose level. Hepatocellular pigment deposition was observed in two males and one female from each of the mid and high dose groups. Bile duct/ductile hyperplasia was observed at the highest dose level in one male and female dog. Hepatic portal inflammation was noticed only in the mid and high dose groups in males, while no clear dose-response pattern was observed in the females. Additional hepatic effects included, nodular hyperplasia, bile stasis, chronic active inflammation and hepatic portal inflamation (Monsanto Company, 1996) (Table I.A.2.2).

Table I.A.2.1. Absolute and Relative Liver Weights of Female and Male Beagle Dogs Exposed to 1,4-Dichlrobenzene in Gelatin Capsules (Monsanto Company, 1996)

Effect	Dose (mg/kg-day)						
	0	7	% Control	36	% Control	54	% Control
Absolute Liver Weight (gm) Male	379.8	318.64	84	473.22	125	531.9[a]	140
Absolute Liver Weight (gm) Female	261.8	291.42	111	388.68	148	407.4[b]	156
Relative Liver Weight (%) Male	2.7738	2.8821	104	3.9663[b]	143	4.726[b]	170
Relative Liver Weight (%) Female	2.7078	3.0504	113	4.2028[b]	155	4.6040[b]	170

[a]Significantly different from control ($p \leq 0.05$; Dunnett's)
[b]Significantly different from control ($p \leq 0.01$; Dunnett's)

Table I.A.2.2. Summary of Liver Histopathology Incidence in Female and Male Beagle Dogs Exposed to 1,4-Dichlorobenzene in Gelatin Capsules (Monsanto Company, 1996)

Liver Histopathology	Dose Group (mg/kg-day)							
	M[a]0	F[b]0	M[a]7	F[b]7	M[a]36	F[b]36	M[a]54	F[b]54
Number of Animals Examined	5	5	5	5	5	5	5	5
Multifocal Bile Stasis	0	0	0	0	0	0	0	1
Diffuse Congestion	0	0	0	0	0	0	1	0
Bile Duct/Ductile, Miltifocal Hyperplasia	0	0	0	0	0	0	1	1
Diffuse Hepatocellular Hypertrophy	0	0	0	0	3[c]	2[c]	5[c]	4[c]
Multifocal Hepatocellular Hypertrophy	0	0	0	1	2	3	0	1
Focal Periportal Mononuclear Infiltrate	1	0	1	0	1	2	1	0
Multifocal Periportal Mononuclear Infiltrate	0	1	0	0	1	0	1	0
Multifocal Chronic Active Inflamation	0	0	0	0	0	0	0	1
Focal Chronic Inflamation	0	0	1	0	0	1	0	0
Multifocal Chronic Inflamation	2	5	3	4	5	3	4	3
Focal Portal Inflamation	0	0	0	1	0	1	0	0
Mulitfocal Portal Inflamation	0	0	0	0	0	0	2	1
Nodular Multifocal Hyperplasia	0	0	0	0	0	0	0	1
Multifocal Hepatocytes Pigment Deposition	0	0	0	0	2	1	2	1
Multifocal Kupffer Cells Pigment Deposition	1	1	0	1	1	0	1	1

[a] Male Dogs
[b] Female Dogs
[c]statistically significant at $p \leq 0.01$, Fisher's exact test, one-tailed

In addition to liver lesions, chronic active interstitial inflammation, pleural fibrosis and/or pleural mesothelial proliferation was also observed in the lungs of males at all test levels and females at the mid and high dose (36 and 54 mg/kg-day) level. Although these changes were not observed in the control groups, the lung lesions were not considered to be treatment related since their occurrence was rare and there was not much difference in severity among the treated groups. Kidney collecting duct epithelial vacuolation was reported in a high dose male and at all levels in the females. The authors concluded that the lesion could be associated to the test chemical at the mid and high dose in the females where it was accompanied by increased kidney weights and grossly observed renal discoloration (Monsanto Company, 1996).

Clinical pathology results revealed a few statistically significant differences in hematology and clinical chemistry parameters and were considered to be related to 1,4-DCB exposure (Monsanto Company, 1996). At the 6 month sampling period, hematological parameters included a reduction in basophils at the high dose level and an increase in platelet counts at the mid and high doses in female dogs. Number of RBCs were significantly reduced in both sexes at the high dose level, while HCT was lowered in the high dose males. At the terminal sampling period, numbers of large unstained cells were reduced in both sexes, platelet count was increased in high dose females and MCV was elevated in mid dose males. Statistically significant differences were observed in various clinical chemistry parameters at the mid and/or high dose levels. Alkaline phosphatase, ALT, AST, and GGT were elevated in both sexes. Direct and total bilirubin, glucose and potassium were elevated, while, creatinine, albumin, and cholesterol were decreased in the high dose female dogs. Albumin levels were reduced in males at the mid and high dose levels. No compound related changes were observed in serum chemistry parameters at the lowest dose. No adverse effects were observed in the urine of males or females at any dose level.

In summary, exposure to 1,4-DCB caused a significant increase in the absolute and relative liver weight in both male and female beagle dogs. This increase was accompanied by several liver lesions in the dosed groups and were considered either direct or indirect/adaptive effects to 1,4-DCB. In addition to liver effects, compound related effects were also observed in kidneys of high dose males and in females at all dose levels. In addition to the pathological and histopathological results, clinical pathology results revealed statistically significant differences in hematological and clinical chemistry parameters. Based on the histopathological and clinical results, the authors concluded that the liver was the most sensitive endpoint in both female and male beagle dogs and identified a no-observed-effect level (NOEL) of 10 mg/kg-day (adjusted dose; 7 mg/kg-day). The 50 mg/kg-day (adjusted dose; 36 mg/kg-day) is suggested as the LOAEL for liver effects.

Compound related liver lesions (diffuse hepatocellular hypertrophy, multifocal chronic inflammation, and multifocal hepatocyte pigment deposition in males and diffuse hepatocellular hypertrophy in females) in both male and female beagle dogs were analyzed by benchmark dose modeling because there was a statistically significant increase in liver lesions in the mid and high dose groups. All dichotomous models in the EPA Benchmark Dose Software (version 1.3.2)

were fit to the incidence data for liver lesions in male and female beagle dogs (Table I.A.2.2). All models, except the Probit, Quantal-linear and Quantal-quadratic models (male beagle dogs) (Table I.A.2.3) adequately (p>0.1) fit the liver lesions as indicated by the chi-square goodness-of-fit statistic (U.S. EPA, 2003). Based on the Log-logistic BMDL of 0.237 mg/kg-day, liver lesions (multifocal chronic inflammation) in male beagle dogs were more sensitive compared to the lesions in the female dogs (Table I.A.2.4).

Table I.A.2.3. BMD modeling of incidence data for liver lesions in male beagle dogs exposed to 1,4-dichlorobenzene (Monsanto Company, 1996). BMDs and BMDLs were calculated based on a BMR of 10% extra risk for the lesion.

Model	AIC	Chi-square p-value	BMD (mg/kg-day)	BMDL (mg/kg-day)
Diffuse Hepatocellular Hypertrophy				
Gamma	8.88452	0.08	24.234	6.09995
Log-Logistic	8.73462	0.00	31.1502	7.7263
Multistage-3 degrees	9.15306	0.25	16.6264	3.78861
Probit	10.7301	0.00	32.0714	7.47999
Quantal Quadratic	10.0978	0.81	10.766	7.68502
Weibull	10.7301	0.00	28.2718	6.05214
Multifocal Chronic Inflammation				
Gamma	24.8958	1.91	2.9798	1.29394
Log-Logistic	26.4232	1.43	1.16546	0.237025
Multistage-3 degrees	24.8958	1.91	2.97979	1.29394
Quantal Linear	24.8958	1.91	2.97971	1.29394
Weibull	24.8958	1.91	2.97971	1.29394
Multifocal Hepatocyte Pigment Deposition				
Gamma	18.045	0.51	18.0286	5.1137
Log-Logistic	18.0067	0.46	17.4673	3.64104
Multistage-3 degrees	16.2062	0.72	20.9665	5.00917
Probit	17.879	0.37	17.542	8.77067
Quantal Linear	16.3776	0.58	10.2144	4.90518
Quantal Quadratic	16.2062	0.72	20.9665	14.5079
Weibull	18.1169	0.55	17.0605	5.06598

Table I.A.2.4. BMD modeling of incidence date for liver lesions in female beagle dogs exposed to 1,4-dichlorobenzene (Monsanto Company, 1996). BMDs and BMDLs were calculated based on a BMR of 10% extra risk for the lesion.

Model	AIC	Chi-square p-value	BMD (mg/kg-day)	BMDL (mg/kg-day)
Diffuse Hepatocellular Hypertrophy				
Gamma	15.7361	0.00	23.4038	4.10099
Log-Logistic	15.7387	0.00	24.1591	4.26188
Multistage-3 degrees	13.7758	0.02	21.6045	4.06118
Probit	15.7342	0.00	24.6023	6.4818
Quantal Linear	15.8457	1.44	5.60153	2.97246
Quantal Quadratic	14.1096	0.26	14.9645	10.8004
Weibull	15.7758	0.02	21.6108	4.06118

For the male liver lesion analysis, the Gamma, Multistage, and Linear models were a better fit to the data than the Log-logistic on the basis of the Akaike's Information Criterion (AIC), but the Log-logistic model was characterized by the closest match between predicted and observed response, as evidenced by the lowest chi-square value. In addition, in this instance, the Gamma and Multistage models were equivalent to the Linear models, as all but one of the model parameters for each of the Gamma and Multistage were constrained by their predefined lower bounds. The end result was that only one parameter needed to be estimated for the Gamma, Multistage, and Linear models, while two parameters were estimated for the Log-logistic model. Presumably, the Gamma and Multistage models would have yielded lower BMDLs had the parameter lower-bound constraints been removed. In general, a 2-parameter model would be superior to a 1-parameter model for fitting dose-response data. In this case, although the 1-parameter linear model appeared to fit the data slightly better than the 2-parameter Log-logistic model, the difference in goodness-of-fit was inconsequential. Therefore, the Log-logistic BMDL of 0.237 mg/kg-day for 10% extra risk of liver lesions in the male beagle dogs was chosen as the point-of-departure for the RfD because it was the most sensitive measure of toxicity and it arose from an unconstrained 2-parameter model.

For comparison purposes, the mean relative organ weights for liver, kidneys, adrenals and thyroid were also analyzed using the benchmark dose approach. Liner models with a constant variance or a non-homogenous variance in the EPA Benchmark Dose Software (version 1.3.2) were fit to the mean relative liver weight data in Table I.A.2.1 and relative weights of the kidneys, adrenals and thyroid (relative weights of kidneys, adrenals and thryoid in Appendix B3 of the Toxicological Review of dichlorobenzenes). Log-likelihood ratio tests for mean relative liver weights in male and female beagle dogs showed that the data were appropriate for modeling. Using the relative deviation at a BMR of 10%, the BMDs and BMDLs for liver weights from the various continuous models were somewhat similar for both male and female

dogs (Table I.A.2.5; kidney, adrenal and thryoid BMD shown in Appendix B3 of the Toxicological Review of dichlorobenzenes). The BMDs and BMDLs for relative liver weights in male and female dogs ranged from 10.1584 to 15.6199 mg/kg-day and 7.65337 to 7.89713mg/kg-day respectively (Table I..A.2.5).

Table I.A.2.5 BMD modeling of relative liver weights in male and female beagle dogs exposed to1,4-dichlorobenzene in gelatin capsules (Monsanto Company, 1996). BMDs and BMDLs were calculated based on a BMR of 10% relative deviation for the relative liver weights.

Model	AIC	BMD (mg/kg-day)	BMDL (mg/kg-day)
Male Dogs			
Polynomial Linear	-9.585979	10.1584	7.65337
Polynomial-2 Degrees	-7.886115	13.4342	7.78095
Power	-3.991585	15.6199	7.80525
Female Dogs			
Polynomial-Linear	-5.550795	10.6472	7.89713
Polynomial-2 Degrees	-5.550795	10.6472	7.89713
Power	-1.550795	10.6472	7.89713

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 100. A total uncertainty factor of 100 was applied to the BMDL of 0.237 mg/kg-day: 10 for interspecies variability, and 10 for interindividual variability.

A 10-fold uncertainty factor was used to account for uncertainty in extrapolating from rats to humans (i.e., interspecies variability). Limited information is available on the toxicity of ingested 1,4-dichlorobenzene in humans, or on differences that may exist between animals and humans in the disposition of, or response to, ingested 1,4-dichlorobenzene. In the absence of data to the contrary, the liver lesions in the mid and high dose male and females beagle dogs and significant increases in relative organ weights in male and female dogs is assumed to be relevant to humans chronically exposed to ingested 1,4-dichlorobenzene.

A 10-fold uncertainty factor was used to account for variation in sensitivity to 1,4-dichlorobenzene within human populations. However, the degree to which humans of varying gender, health status, or genetic makeup may vary in disposing of, or responding to, ingested 1,4-dichlorobenzene has not been unstudied.

The animal oral toxicity database is substantial and generally adequate, including chronic toxicity studies in beagle dogs (Monsanto Company, 1996), chronic toxicity/cancer studies in rats

and mice (NTP, 1987), several subchronic toxicity studies, a developmental toxicity study in rats (Giavini et al., 1986), and a two-generation reproductive and developmental toxicity study in rats (Bornatowicz et al., 1994). Effects of oral exposure to 1,4-dichlorobenzene on various organs was evaluated along with effects in the hematopoietic system. Based on these results, an uncertainty factor of 1 was applied for data base adequacy.

MF = 1. None.

___I.A.4. ADDITIONAL STUDIES/COMMENTS (ORAL RfD)

Information on the toxic effects of 1,4-dichlorobenzene in orally exposed humans is limited to two case reports describing hematological changes, particularly anemia, following known or presumed repeated ingestion of unknown doses of the compound in commercial products (Campbell and Davidson, 1970; Hallowell, 1959).

The subchronic and chronic oral toxicity of 1,4-dichlorobenzene has been investigated in a number of animal studies conducted predominantly in rats and mice. As detailed in the Source Document (U.S. EPA, 2002) and discussed below, liver, and kidney effects are the best studied and most consistently observed findings. A relatively small amount of information is available indicating that 1,4-dichlorobenzene can affect the hematological system and adrenal and thyroid glands at exposure levels equal to or higher than those causing liver and kidney effects.

Hepatic effects induced by subchronic and chronic oral exposures to 1,4-dichlorobenzene ranged from increased liver weight and hepatocyte enlargement to hepatocellular degeneration, necrosis, and tumors in rats, mice, and rabbits (U.S. EPA, 2002). Increases in serum levels of enzymes (e.g., AP and AST) and alterations in other endpoints (e.g., serum cholesterol and triglycerides) indicative of hepatocellular damage or liver dysfunction have also been induced. Increased liver weight is the most sensitive hepatic endpoint in subchronic studies in rats, observed at duration-adjusted doses as low as 107 mg/kg-day for 4-13 weeks and 135 mg/kg-day for 192 days (Hollingsworth et al., 1956; Lake et al., 1997; Umemura et al., 1998), but is not considered adverse without concomitant enzymatic or histopathological changes. There was no indication of subtle liver damage in rats exposed to 107 mg/kg-day for 4 weeks using an immunohistochemical marker of centrilobular hepatocyte injury (size of zone of glutamine synthetase-expressing hepatocytes) (Umemura et al., 1998), and increases in liver porphyrins in rats exposed to $\geq$50 mg/kg-day for 120 days were not considered to be toxicologically significant (Carlson, 1977). Hepatocellular hypertrophy and decreased serum triglycerides occurred in rats exposed to $\geq$214 mg/kg-day for 13 weeks (NTP, 1987; Lake et al., 1997). Degenerative lesions were found in livers of rats exposed to higher doses of 270 mg/kg-day for 192 days (slight cirrhosis and focal necrosis) (Hollingsworth et al., 1956) or 857 mg/kg-day for 13 weeks (hepatocyte degeneration and necrosis) (NTP, 1987), although the findings at 270 mg/kg-day (Hollingsworth et al., 1956) are inconsistent with chronic data showing that exposure to doses as high as 429 mg/kg-day for 103 weeks did not induce liver lesions in rats (NTP, 1987). Mice are

more sensitive than rats to the hepatotoxic effects of 1,4-dichlorobenzene, based on induction of hepatocellular degeneration at doses as low as 429 mg/kg-day for 13 weeks and 214 mg/kg-day for 103 weeks in mice (NTP, 1987). A study in rabbits found cloudy swelling and minimal focal necrosis following exposure to 358 mg/kg-day for 367 days (Hollingsworth et al., 1956), the lowest tested level in this species, but higher than the chronic LOAEL in mice.

The information summarized above indicates that 214 mg/kg-day is the lowest chronic LOAEL for liver effects in mice based on hepatocellular degeneration (NTP, 1987). There is no chronic NOAEL in mice because 214 mg/kg-day is the lowest tested chronic dose in this species. The only data on liver effects in mice at doses below this chronic LOAEL are the subchronic immunohistochemical findings (increased GS expression) suggestive of early hepatocyte injury following exposure to doses as low as 107 mg/kg-day for 4 weeks (Umemura et al., 1998), but the toxicological significance of this marker is unclear because it can reflect neoplastic transformation and progression as well as cell damage (Osada et al., 2000). Histology was not evaluated, and liver weight was only increased at higher doses (429 mg/kg-day) in the same study. The subchronic studies in rats found mild histological alterations (e.g., hepatocellular hypertrophy) at ≥214 mg/kg-day, and necrotic and degenerative effects at ≥270 mg/kg-day (Eldridge et al., 1992; Hollingsworth et al., 1956; Lake et al., 1997; NTP, 1987; Umemura et al., 1998), but no hepatic histopathology occurred at doses ranging from 107 to 429 mg/kg-day in chronic rat studies (NTP, 1987).

Renal changes, including hyaline droplet accumulation, increased kidney weights, and tubular lesions, are characteristically observed effects of subchronic and chronic oral exposure to 1,4-dichlorobenzene in male rats at doses ≥75 mg/kg-day (Bomhard et al., 1988; Lake et al., 1997; NTP, 1987). These findings are detailed in the Source Document (U.S. EPA, 2002) and are not discussed here because there is a scientific consensus that they are related to the $\alpha_{2\mu}$-globulin nephropathy syndrome, which is specific to male rats and not relevant to humans (U.S. EPA, 1991). Kidney nephropathy was also increased in female rats that were exposed to ≥214 mg/kg-day for 103 weeks (NTP, 1987). There was a high incidence of nephropathy in the unexposed control females, indicating that the effect in the treated animals may represent an increase in normal age-related nephropathy. Subchronic studies found increased kidney weight, but no indications of nephrotoxic action (i.e., no histopathology or effects on urinary indices of renal function), in female rats exposed to ≥135 mg/kg-day for 192 days or 600 mg/kg-day for 13 weeks (Bomhard et al., 1988; Hollingsworth et al., 1956). Kidney lesions, mainly tubular degeneration, were also increased in mice that were chronically exposed to ≥214 mg/kg-day for 103 weeks (NTP, 1987). The results of the NTP (1987) study, therefore, indicate that chronic exposure to 1,4-dichlorobenzene has a nephrotoxic potential in female rats and mice of both sexes, and that the LOAEL for renal effects is 214 mg/kg-day, the lowest tested chronic dose in these species and sexes.

The studies evaluated in the Source Document (U.S. EPA, 2002) also showed that subchronic or chronic exposure to 1,4-dichlorobenzene caused other effects in rats and mice at doses equal to or higher than the LOAELs for liver and kidney toxicity; these included

hematological changes (decreased erythrocyte counts, hematocrit, and hemoglobin) in rats at ≥214 mg/kg-day for 13 weeks, increased hyperplasia in the adrenal capsule and mandibular lymph node in mice at ≥214 mg/kg-day for 103 weeks, and increased thyroid follicular gland hyperplasia in mice at 429 mg/kg-day for 103 weeks (NTP, 1987). Developmental toxicity studies provide no indications that 1,4-dichlorobenzene is teratogenic in rats exposed to doses as high as 1000 mg/kg-day during gestation, although fetotoxicity occurred at maternally toxic levels ≥ 500 mg/kg-day (Giavini et al., 1986; Ruddick et al., 1983). Decreased maternal weight gain and increased incidences of extra ribs, a skeletal variation attributable to the maternal toxicity rather than a teratogenic effect of the chemical, occurred in rats at gestational dose levels ≥500 mg/kg-day, but not at 250 mg/kg-day (Giavini et al., 1986).

A two-generation study by Bornatowicz et al.(1994) evaluated reproductive and developmental toxicity in male and female Sprague Dawley rats that were administered 1,4-dichlorobenzene (99% pure) in olive oil by daily gavage at dose levels of 0, 30, 90, or 270 mg/kg-day (Bornatowicz et al., 1994). Study endpoints included clinical observations in adults and pups, body weight and food consumption in maternal animals (during gestation and lactation) and pups (from birth to day 21), reproductive indices (including duration between mating and successful copulation, number of pregnancies, gestation length, and litter size), numbers of live and dead pups, postnatal survival, postnatal developmental milestones (times to erect ears and eyelid separation), and neurobehavioral effects in pups at weaning (auricle reflex, orientation reaction, grasping, and draw-up reflexes). No reproductive or other exposure-related changes were found at 30 mg/kg-day in adult rats or pups (Bornatowicz et al., 1994). Effects occurred at ≥90 mg/kg that included statistically significant (method of analysis and p values not reported) reduced average birth weight in F_1 pups (4.4, 5.7, and 22.6% lower than control group at 30, 90, and 270 mg/kg-day). Significant reductions in body weight were also observed at 270 mg/kg-day in F_1 pups at postnatal days 7, 14, and 21, as well as at 270 mg/kg-day in F_2 pups at birth and postnatal days 4, 7, 14, and 21. The total number of deaths from birth to postnatal day 4 was significantly increased in F_1 pups at 270 mg/kg-day, and in F_2 pups at ≥90 mg/kg-day (33, 467, and 1033% higher than controls at 30, 90, and 270 mg/kg-day).

None of the data in this study were reported on a per-litter basis or analyzed for dose-related trends. Other significant effects on offspring survival indices occurred at 270 mg/kg-day, including reduced total number of live F_1 and F_2 pups at birth, increased total dead F_1 and F_2 pups at birth, and increased total dead F_1 and F_2 pups during postnatal days 5-21. Clinical manifestations were evident in pups of both generations at ≥90 mg/kg-day, including dry and scaly skin until approximately postnatal day 7 (0, 0, ≈70 and 100% of the litters at 0, 30, 90, and 270 mg/kg-day), and tail constriction that appeared between days 4 and 21 in all or nearly all litters (percentages not reported) and occasionally led to loss of parts of the tail (Bornatowicz et al., 1994). The only histopathological finding attributed to exposure was unspecified kidney damage in both generations (effect levels, possible male specificity, and other information not reported).

This study identifies a NOAEL and LOAEL of 30 and 90 mg/kg-day for developmental toxicity based on increased mortality and other effects in F_1 and F_2 pups during the preweaning period. These doses are also a NOAEL and LOAEL for maternal toxicity based on decreased body weight gain. There were no effects on mating and fertility indices in any group.

In summary, liver and kidney toxicity are the main systemic effects of subchronic and chronic oral exposure to 1,4-dichlorobenzene in animals (U.S. EPA, 2002). Mice are more sensitive to liver toxicity than the rats, and the 214 mg/kg-day LOAEL for liver effects in mice (NTP, 1987) is the same as the LOAEL for nephropathy in mice and female rats (NTP, 1987). These systemic LOAELs are higher than the LOAEL of 50 mg/kg-day (adjusted dose; 36 mg/kg-day) (Monsanto Company, 1996) used as the basis for the RfD derived in Section I.A.2.

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study -- Medium
Data Base -- Medium
RfD -- Medium

The overall confidence in this RfD assessment is medium. The principal study is a well conducted 1-year dog study that investigated a variety of systemic endpoints including absolute and relative organ weights, histopathological examination and clinical endpoints. The rest of the animal oral toxicity database is large and includes subchronic and chronic toxicity studies in rats and mice, a two-generation rat study that investigated a variety of reproductive and postnatal developmental effects and a prenatal developmental toxicity study in rats. Developmental toxicity has not been evaluated in a second species, and effects on the thyroid and pituitary, neurobehavioral endpoints, the immune system, and male reproduction have not been adequately studied.

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Source Document -- U.S. EPA (2002).

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS summary. A record of these comments is included as an appendix to U.S. EPA (2002).

Agency Consensus Date -- __/__/__ *[note: leave this BLANK until consensus is reached*]

___I.A.7. EPA CONTACTS (ORAL RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (301)345-2870 (phone), (301)345-2876 (FAX), or hotline.iris @epamail.epa.gov (email address).

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- 1,4-Dichlorobenzene
CASRN -- 106-46-7
Last Revised -- 00/00/0000

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 generally 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.

This RfC replaces the previous RfC of 0.8 mg/m^3 entered on IRIS on 11/01/1996. The new RfC is based on a different endpoint from the same principal study and application of a newer methodology.

__I.B.1. INHALATION RfC SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfC
Postnatal developmental toxicity (reduced 4-day survival in F_1 offspring)	NOAEL: 1268 mg/m^3 LOAEL: 3233 mg/m^3	100	1	1.0 mg/m^3
Rat two-generation study Tyl and Neeper-Bradley, 1989	BMCL: 559 mg/m^3 $BMCL_{ADJ}$: 99.8 mg/m^3 $BMCL_{HEC}$: 99.8 mg/m^3			

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*Conversion Factors and Assumptions -- MW=147.01. Assuming 25° C and 760 mm Hg, 1 ppm = 1 ppm x 147.01/24.45 = 6.01 mg/m^3. Benchmark dose modeling was conducted on the mean 4-day survival index (no. pups surviving 4 days ÷ total no. live pups at birth) in F_1 offspring. The lower 95% confidence interval on the benchmark concentration (BMCL) associated with a 5% decrease in pup survival index was selected as the point of departure for the RfC. The BMCL was duration adjusted for intermittent exposure (6 hours/day, 5 days/week): $BMCL_{ADJ}$ = (559 mg/m^3) (6/24) (5/7) = 99.8 mg/m^3. The $BMCL_{HEC}$ was calculated for a gas:extra respiratory effect assuming periodicity was attained. The ratio of blood:gas partition coefficients (b:a lambda values) is not available for 1,4-dichlorobenzene in rats and humans. Using a default value of 1.0 for the ratio of partition coefficients, the $BMCL_{HEC}$ is 99.8 mg/m^3.

___I.B.2. PRINCIPAL AND SUPPORTING STUDIES (INHALATION RfC)

Tyl, R.W. and T.L. Neeper-Bradley (1989). Two-generation reproduction study of inhaled paradichlorobenzene in Sprague-Dawley (CD) rats. Bushy Run Research Center Project Report 51-593. January 16, 1989. Sponsored by The Chemical Manufacturers Association, Chlorobenzenes Program, Washington, DC.

A two-generation inhalation reproduction study of 1,4-dichlorobenzene was conducted in which groups of 28 Sprague-Dawley rats of each sex were exposed to vapor concentrations of 0, 50, 150, or 450 ppm for 6 hours/day, 5 days/week for 10 weeks (Tyl and Neeper-Bradley, 1989). Mean analytical concentrations (±SD) in the three exposure groups were 66.3±8.47, 211±8.0, and 538±50.5 ppm (398, 1268, or 3233 mg/m^3) (see discussion in the following paragraph). Additional groups of 10 females were similarly exposed for 10 weeks in a satellite study. The animals in the main study were paired within groups for a 3-week mating period to produce the F_1 generation. Main study males that did not successfully mate in the first 10 days of the mating period were paired with the satellite females for 10 days. Main study females that did not successfully mate during the first 10 days of the mating period were paired with proven males for the remaining 11 days of the mating period. Exposures of the main study F_0 females were continued throughout the mating period and the first 19 days of gestation, discontinued from gestation day 20 through postnatal day 4, and then resumed until sacrifice at weaning on postnatal day 28. Exposures of the satellite F_0 females were continued through mating until sacrifice on gestation day 15. Exposures of the F_0 males continued until sacrificed at the end of the study and satellite mating periods. Groups of 28 F_1 weanlings/sex and satellite groups of 10 F_1 female weanlings were exposed for 11 weeks and mated as described above to produce the F_2 generation. Additionally, 20 F_1 weanlings/sex from the control and high exposure groups served as recovery animals that were observed without exposure for 5 weeks prior to sacrifice. Complete necropsies were performed on all F_0 and F_1 adult (parental) animals, F_1 recovery animals, F_1 weanlings not used in the rest of the study, and F_2 weanlings, and histology was evaluated in the F_0 and F_1 parental animals. Histological examinations were conducted on the liver and kidneys in all groups and on selected other tissues (pituitary, vagina, uterus, ovaries, testes, epididymides, seminal vesicles, prostate, and tissues with gross lesions) in the control and

high exposure groups. The kidney evaluation included examination for the presence of α2μ droplets. Additional endpoints evaluated in the parental generations included clinical observations, mortality, body weight, and food consumption. Mating and fertility indices were determined for F_0 and F_1 males and females, and gestational, live birth, postnatal survival (4-, 7-, 14-, 21-, and 28-day), and lactation indices were determined for the F_1 and F_2 litters.

The initial analytical method was determined to be inadequate by the investigators due to problems associated with sampling (syringe from stainless steel tubes extending into the breathing zone), such that there was an underestimation of the vapor concentrations during the first 80 days of the study. Analyses obtained by charcoal absorption methods during the last third of the study indicated chamber concentrations that were in good agreement with nominal concentrations. Mean charcoal tube analytical/nominal ratios and the original nominal data were used to recalculate actual chamber atmosphere concentrations for exposure days 1-171. The mean chamber concentrations (±SD) for the 284 days of exposure were determined to be 66.3±8.47, 211±8.0 and 538±50.5 ppm (398, 1268 and 3233 mg/m^3) in the three exposure groups.

There were no effects on reproductive parameters in either generation, although systemic toxicity occurred at all dose levels in F_0 and F_1 adult rats (Tyl and Neeper-Bradley, 1989). Hyaline droplet nephropathy was found in F_0 and F_1 adult males at ≥66 ppm. Manifestations of this male rat-specific renal syndrome included α2μ globulin accumulation and increased kidney weights at ≥66 ppm and other characteristic histological changes (e.g., tubular cell hyperplasia) at 538 ppm. Body weights and weight gain were significantly reduced in F_0 and F_1 adult males and F_1 adult females during the pre-breeding exposure periods at 538 ppm. Relative liver weights were significantly ($p<0.05$ or $p<0.01$) increased in F_0 adult males at ≥66 ppm, F_0 adult females and F_1 adult males at ≥211 ppm, and F_1 adult females at 538 ppm. Absolute liver weights were significantly increased in F_0 adult males at ≥211 ppm, and in F_0 adult females and F_1 adult males and females at 538 ppm. The liver weight effects were more pronounced in males than females. Mean relative liver weights in the 66, 211, and 538 ppm adult male groups were 4.8, 13.9, and 52.1% higher than controls in the F_0 generation (sacrificed at week 15) and 0, 6.7, and 43.7% higher than controls in the F_1 generation (sacrificed at week 17). Hepatocellular hypertrophy was observed in the livers of F_0 and F_1 males and females at 538 ppm; no hepatic histological changes were induced at the lower exposure concentrations. The increases in liver weight and hepatocellular hypertrophy are considered to be adaptive and not adverse liver effects because there were no accompanying degenerative lesions. Other effects also occurred in the F_0 and F_1 males and females at 538 ppm, indicating that there was a consistent pattern of adult toxicity at the high exposure level, including reduced food consumption and increased incidences of clinical signs (e.g., tremors, unkempt appearance, urine stains, salivation, and nasal and ocular discharges); these effects only sporadically occurred at 211 ppm. Additional effects at 538 ppm included reduced gestational and lactational body weights in F_0 and/or F_1 parental females, and effects in F_1 and/or F_2 offspring on a total pup basis that included reduced numbers of live pups at birth and postnatal day 4, and decreased body weight gain in pups throughout the lactation period.

In summary, the LOAEL is 538 ppm (3233 mg/m^3) based on toxicity in adult animals, including signs of neurotoxicity and eye and nasal irritation, as well as postnatal developmental toxicity in their pups. The most serious effect at the LOAEL is reduced postnatal survival in the pups. The only effect that was clearly and consistently exposure-related at lower concentrations was increased liver weight at 211 ppm, but this is not considered to be adverse due to lack of any accompanying histological changes, indicating that 211 ppm (1268 mg/m^3) is the NOAEL.

The F_1 and F_2 pup postnatal survival data in Table I.B.2.1 were analyzed by benchmark dose modeling to determine potential points of departure for the RfC. None of the continuous variable models in the EPA Benchmark Dose Software (version 1.3.1) adequately ($p<0.1$) fit the F_1 or F_2 survival data as assessed by the chi-square goodness-of-fit statistic. Linear models with either an assumed constant variance or with variance modeled as a power function of the mean were fit to the F_1 pup survival data using EPA Benchmark Dose Software (version 1.3.1). Log-likelihood ratio tests indicated that both models described the data, and that a non-homogeneous variance model was more consistent with the data than a constant variance model (U.S. EPA, 2002). Akaike's Information Criteria (AIC) for the non-homogeneous variance model was slightly lower than the AIC for the constant variance model, indicating a better fit of the data. The non-homogeneous variance model therefore was selected to calculate the BMC and BMCL for reduced 4-day survival in F_1 rat pups, using a 5% decrease in pup survival index (compared with the control) as the BMR. A 5% decrease was selected (instead of 10% or one standard deviation change from the control), because the effect (decreased postnatal survival) is severe and one that would be of high concern if it occurred in human populations. The BMC and BMCL are 146 and 93 ppm, respectively. The BMCL of 93 ppm (559 mg/m^3) was selected as the point of departure for the RfC.

Table I.B.2.1. Selected Developmental Effects in Rats Exposed to 1,4-Dichlorobenzene for Two Generations (Tyl and Neeper-Bradley, 1989)

Developmental Effect	Exposure Concentration (ppm)			
	0	66	211	538
4-day survival index[a] in F_1 pups [mean ± SD (no. litters)]	93.8 ± 20.33 (n=24)	97.5 ± 3.57 (n=20)	92.7 ± 21.07 (n=27	82.0[b] ± 29.25 (n=22)
4-day survival index[a] in F_2 pups [mean ± SD (no. litters)]	99.1 ± 2.25 (n=22)	99.4 ± 2.80 (n=20)	99.3 ± 1.99 (n=24)	71.3[b] ± 41.96 (n=21)

[a]4-Day survival index = no. pups surviving 4 days per litter ÷ total no. live pups at birth per litter x 100 (average of all litters)
[b]Significantly different ($p<0.05$) from control group as reported by study investigators

___I.B.3. UNCERTAINTY AND MODIFYING FACTORS (INHALATION RfC)

UF = 100. A total uncertainty factor (UF) of 100 was applied to the BMCL: 3 for interspecies variability, 10 for interindividual variability, and 3 for database deficiencies.

A 3-fold uncertainty factor is used to account for the interspecies variability in extrapolating from rats to humans. The interspecies extrapolation factor encompasses two areas of uncertainty: pharmacokinetics and pharmacodynamics. In this assessment, the pharmacokinetic component is addressed by the dosimetry adjustment [i.e., calculation of the human equivalent exposure for time and concentration ($BMCL_{HEC}$)]. Accordingly, only the pharmacodynamic area of uncertainty remains as a partial factor for interspecies uncertainty ($10^{0.5}$ or approximately 3).

A 10-fold uncertainty factor is used to account for variation in sensitivity within human populations. Results of studies in rats and rabbits (Hayes et al., 1985; Hodge et al., 1977) indicate that teratogenic and fetotoxic effects from gestational exposure to 1,4-dichlorobenzene, if they occur, would only occur at exposure levels that are maternally toxic and similar to or higher than cross-generational doses inducing developmentally toxic effects during early postnatal periods. The two-generation study in rats (Tyl and Neeper-Bradley, 1989) indicates that the early postnatal period is a susceptible age/developmental period for toxicity to 1,4-dichlorobenzene, but the degree to which humans of varying gender, health status, or genetic makeup may vary in disposition of or response to the chemical is unstudied.

A 3-fold uncertainty factor is used to account for deficiencies in the database. Available information on health effects in people is insufficient for identifying sensitive systemic endpoints in humans. The chronic inhalation toxicity of 1,4-dichlorobenzene was investigated in two species (rats and mice), but both studies have limitations. The chronic study in rats (Imperial Chemical Industries Limited, 1980) is limited by failure to achieve a clear effect level and a less-than-lifetime exposure duration (76 weeks). The chronic mouse study also lacks an effect level and lifetime exposure duration (57 weeks), and is further limited by unavailability of an adequate report. Information on the systemic toxicity of subchronic inhalation exposure is available from a multiple species study, but some of the data are compromised by reporting insufficiencies (Hollingsworth et al., 1956). The prenatal developmental toxicity of inhaled 1,4-dichlorobenzene has been sufficiently studied (Hayes et al., 1985; Hodge et al., 1977). The two-generation reproductive study (Tyl and Neeper-Bradley, 1989) was generally well conducted but the spacing of the exposure levels limits characterization of exposure-response relationships (essentially all effects occurred at the highest of three tested concentrations). The chronic inhalation study in rats showed no exposure-related changes in the nasal passages or other parts of the respiratory tract in rats exposed to 500 ppm of 1,4-dichlorobenzene (Imperial Chemical Industries Limited, 1980), but additional studies are needed to fully characterize respiratory system effects of the chemical.

MF =1

___I.B.4. ADDITIONAL STUDIES/COMMENTS (INHALATION RfC)

Information on the toxicity of inhaled 1,4-dichlorobenzene in humans is available from limited observations in exposed workers and a few case reports. The only effect described in workers exposed to 1,4-dichlorobenzene was painful irritation of the eyes and nose that was usually experienced at 50-80 ppm, although the irritation threshold was higher (80-160 ppm) in workers acclimated to exposure (Hollingsworth et al., 1956). Case reports of people who inhaled 1,4-dichlorobenzene suggest that the liver and nervous system are systemic targets of toxicity in humans, but are limited by lack of adequate quantitative exposure information and/or verification that 1,4-dichlorobenzene was the sole causal factor (Cotter, 1953; Miyai et al., 1988; Reygagne et al., 1992). The hepatic, neurologic and eye/nose irritation observations in humans are consistent with effects observed in animals exposed to high concentrations of the chemical.

Adequate information on the systemic toxicity of inhaled 1,4-dichlorobenzene in animals is available from a multispecies subchronic toxicity study (Hollingsworth et al., 1956), a subchronic immunotoxicity study in guinea pigs (Suzuki et al., 1991), and a chronic toxicity study in rats (Imperial Chemical Industries Limited, 1980), as detailed in the Source Document (U.S. EPA, 2002). The immunotoxicity study found no effects in guinea pigs exposed to $\leq$50 ppm for 12 weeks (highest tested concentration) (Suzuki et al., 1991), although the exposure schedule was not specified. The other studies had exposure schedules that were similar (5-7 hours/day and 5 days/week), and showed a general pattern in which increased liver weight was the predominant effect at concentrations below those inducing overt toxicity, consistent with observations in adult animals in the two-generation study (Tyl and Neeper-Bradley, 1989) used to derive the RfC (see Section I.B.2). Liver weight was increased in guinea pigs exposed to $\geq$96 ppm and rats exposed to $\geq$158 ppm for 5-7 months (Hollingsworth et al., 1956), rats exposed to 500 ppm for 76 weeks (Imperial Chemical Industries Limited, 1980), and rats exposed to $\geq$66 ppm for 15-17 weeks in the two-generation reproduction study (Tyl and Neeper-Bradley, 1989), but increases in liver weight in the absence of concomitant enzymatic and histopathological changes are not considered to be adverse. Hepatic histological changes were observed in rats at 158 ppm (cloudy swelling, congestion or granular degeneration), but considered of questionable significance by the investigators, and were not reported at 358 ppm in the same study (Hollingsworth et al., 1956), indicating that neither 158 or 358 ppm is a reliable LOAEL for liver pathology in rats. Hepatic histological effects were also observed in guinea pigs at 341 ppm and seem to have been more severe (cloudy swelling with fatty degeneration, focal necrosis and slight cirrhosis) than in rats, but only occurred in some (number not reported) of the animals (Hollingsworth et al., 1956). These findings suggest that 341 ppm is a LOAEL for liver histopathology in guinea pigs, but confidence is low due to imprecise and brief qualitative reporting of the results, a general limitation of the Hollingsworth et al. (1956) study.

Liver histopathology was described as slight to moderate (cloudy swelling and central necrosis) in guinea pigs, rats and rabbits exposed to 798 ppm, and overt signs of toxicity (e.g., marked tremors, weight loss, eye irritation and unconsciousness) were found in all of these species at the same level (Hollingworth et al., 1956), showing that this concentration is a LOAEL

for 1,4-dichlorobenzene. Similar clinical signs, including tremors, salivation, and ocular and nasal discharges, as well as non-adverse hepatic histological alterations (hepatocellular hypertrophy without degenerative changes) consistent with the increased liver weight, occurred in adult F_0 and F_1 rats exposed to 538 ppm for 15-17 weeks in the two-generation reproduction study (Tyl and Neeper-Bradley, 1989). Other effects at 538 ppm included reduced gestational and lactational body weights in F_0 and/or F_1 parental females, and toxic effects in the F_1 and F_2 offspring as detailed in the summary of the principal study in Section I.B.2. Considering the available data, the lowest subchronic LOAEL for systemic toxicity is 538 ppm based on effects in adult rats in the two-generation study, including signs of neurotoxicity and eye and nasal irritation (Tyl and Neeper-Bradley, 1989). This concentration is also the LOAEL for postnatal developmental toxicity in their pups as detailed in Section I.B.2. The only effect that was clearly and consistently exposure-related at 1,4-dichlorobenzene concentrations lower than 538 ppm was increased liver weight in adult rats at 211 ppm in the two-generation study, but this is not considered to be adverse due to lack of any accompanying histological changes.

There is no evidence that reproductive toxicity or prenatal developmental toxicity are critical effects of inhaled 1,4-dichlorobenzene, as detailed in the Source Document (U.S. EPA, 2002) and summarized below. No effects on reproduction were found in the two-generation study (Tyl and Neeper-Bradley, 1989), indicating that 538 ppm is a NOAEL for reproductive toxicity in rats. The 538 ppm reproductive NOAEL in rats is supported by a NOAEL of 450 ppm for reproductive performance in male mice that were exposed for 6 hours/day for 5 days prior to weekly mating with unexposed females for 8 weeks (Anderson and Hodge, 1976). No maternal toxicity or prenatal developmental toxicity occurred in rats that were exposed to 75-500 ppm for 6 hours/day on days 6-15 of gestation (Hodge et al., 1977), indicating that the highest NOAEL for these effects in rats is 500 ppm. A developmental study in which rabbits were exposed to 100-800 ppm for 6 hours/day on gestation days 6-18 found evidence of fetotoxicity (a minor variation of the circulatory system) only at 800 ppm (Hayes et al., 1985), indicating that 800 ppm is a LOAEL for developmental effects in rabbits. This concentration was also maternally toxic to the rabbits, as shown by body weight loss early in gestation, and higher than the LOAELs for hepatotoxicity and postnatal developmental toxicity in the other studies.

The chronic inhalation study showed no exposure-related histological changes in the nasal passages or other parts of the respiratory tract in rats exposed to 500 ppm of 1,4-dichlorobenzene for 5 hours/day, 5 days/week for up to 76 weeks (Imperial Chemical Industries Limited, 1980), but additional studies are needed to fully characterize respiratory system effects of the chemical. The lack of additional information on respiratory tract effects of 1,4-dichlorobenzene is an important limitation of the inhalation database, because both 1,4- and 1,2-dichlorobenzene are a known nose and eye irritant in humans (Hollingsworth et al., 1956, 1958), and the olfactory epithelium is a sensitive target of inhaled 1,2-dichlorobenzene in mice (Zissu, 1995), as detailed in the Source Document (U.S. EPA, 2002).

___I.B.5. CONFIDENCE IN THE INHALATION RfC

Study -- Medium
Data Base -- Medium
RfC -- Medium

The overall confidence in this RfC assessment is medium, reflecting the adequacy of the principal study and inhalation data base. The principal study is a generally well conducted two-generation study that examined an array of endpoints including a various reproductive and postnatal developmental indices, as well as histology in adults and offspring. An insufficiency of the principal study is the spacing of the test concentrations which limits characterization of exposure-response relationships, because essentially all of the observed effects occurred at the highest of three levels. The prenatal developmental toxicity of inhaled 1,4-dichlorobenzene has been sufficiently studied in two species. The database also includes chronic inhalation studies in two species (rats and mice), but both studies are limited by failure to achieve a clear effect level and less-than-lifetime exposure durations. The chronic mouse study is further limited by unavailability of an adequate report. Information on the systemic toxicity of subchronic inhalation exposure is available from a multiple species study, but the data are generally compromised by reporting insufficiencies. The chronic inhalation study in rats showed no effects in the nasal passages or other parts of the respiratory tract, but additional studies are needed to fully characterize respiratory system effects of the chemical.

___I.B.6. EPA DOCUMENTATION AND REVIEW OF THE INHALATION RfC

Source Document -- U.S. EPA, 2002

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS summary. A record of these comments is included as an appendix to U.S. EPA (2002).

Agency Consensus Date -- __/__/__ *[Leave this BLANK until consensus is reached]*

___I.B.7. EPA CONTACTS (INHALATION RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (301)345-2870 (phone), (301)345-2876 (FAX), or hotline.iris @epamail.epa.gov (email address).

__II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- 1,4-Dichlorobenzene
CASRN -- 106-46-7
Last Revised -- 00/00/0000

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 µg/L drinking water or risk per µg/cu.m air breathed. The third form in which risk is presented is a concentration of the chemical in drinking water or air associated with 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 Draft Revised Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999) and in the IRIS Background Document. 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

Evidence of animal carcinogenicity is based on findings of increased tumor incidences in male rat kidneys and in the livers of male and female mice following oral exposure. The kidney tumors in rats are not relevant to humans because the mechanism is specific to male rats. The mechanistic basis of the mouse liver tumors has not been adequately defined and are assessed to be relevant to humans. Therefore, under the proposed cancer guidelines (U.S. EPA, 1999), 1,4-dichlorobenzene is considered *likely to be carcinogenic* in humans.

___II.A.2. HUMAN CARCINOGENICITY DATA

None.

___II.A.3. ANIMAL CARCINOGENICITY DATA

Information on carcinogenicity of 1,4-dichlorobenzene in animals is available from chronic oral and inhalation studies in rats and mice (NTP, 1987; Chlorobenzene Producers

Association, 1997; Imperial Chemical Industries Limited, 1980; Riley et al., 1980), as detailed below.

In the chronic oral study in rats (NTP, 1987), groups of 50 male and 50 female F344/N rats were treated with 1,4-dichlorobenzene (>99% pure) in corn oil by gavage on 5 days/week for 103 weeks. The dosages in this study were 0, 150, or 300 mg/kg (0, 107, or 214 mg/kg-day) in males and 0, 300, or 600 mg/kg (0, 214, or 429 mg/kg-day) in females. Evaluations consisted of body weight, clinical signs, necropsy, and histology in all animals. Mean body weights of the high-dose males and females were generally slightly lower than those of the controls (5-8% after week 38 and 5-7% after week 55, respectively). Survival of the high dose males was similar to controls for most of the study, but decreased towards the end of the study (30% lower than controls after week 97). No significant effects on survival were observed for low-dose males or any of the female treatment groups. Nonneoplastic lesions and tumors were induced in the kidneys of the male rats. Incidences of nonneoplastic renal lesions in male rats were increased at $\geq$107 mg/kg-day and included epithelial hyperplasia of the renal pelvis, mineralization of the collecting tubules in the renal medulla, and focal hyperplasia of renal tubular epithelium. Kidney tumors that were induced in the male rats included dose-related increased incidences of tubular cell adenocarcinoma (1/50, 3/50, 7/50) and combined tubular cell adenoma or adenocarcinoma (1/50, 3/50, 8/50) that were statistically significant in the high dose group relative to controls (NTP, 1987). The male rat-specific hyaline droplet ($\alpha_{2\mu}$-globulin) nephropathy syndrome likely contributed to the nonneoplastic kidney lesions as well as the renal tumors. A dose-related increase in the incidence of mononuclear cell leukemia was also observed in male rats (5/50, 7/50, 11/50) that was significant in the high-dose group. However, even in the high-dose group, the incidence of the leukemia (22%) was comparable to historical vehicle control incidences (14% ± 8%) in previous NTP studies. No evidence of carcinogenesis was seen in female F344 rats at either dose level. Based on these data, NTP concluded that there was clear evidence of carcinogenicity in male F344 rats, as shown by an increased incidence of renal tubular cell adenocarcinomas, and no evidence of carcinogenicity in female F344 rats.

In the chronic oral study in mice (NTP, 1985), groups of 50 male and 50 female $B6C3F_1$ mice were administered 0, 300, or 600 mg/kg (0, 214, or 429 mg/kg-day) doses of 1,4-dichlorobenzene (>99% pure) in corn oil by gavage on 5 days/week for 103 weeks. Evaluations consisted of body weight, clinical signs, necropsy, and histology in all animals. Body weight and survival were comparable in the control and treated mice. Nonneoplastic lesions and tumors in the liver were prominent effects of exposure in both sexes, as summarized in Table II.A.3.1. The nonneoplastic liver lesions were increased at both dose levels and included hepatocellular degeneration with cell size alteration (cytomegaly and karyomegaly) and individual cell necrosis. No increases in hepatic or bile duct hyperplasia were found in either sex. Hepatocellular adenoma, hepatocellular carcinoma, and combined hepatocellular adenoma or carcinoma occurred with positive dose-related trends in both male and female mice, with the incidences in the low-dose males and high-dose groups of both sexes being significantly greater

than those in the control groups. Additionally observed in the high-dose male mice were four cases of hepatoblastoma, an extremely rare type of hepatocellular carcinoma. No hepatoblastomas were found in the control or low-dose male mice or in any of the female groups. The increased incidence rate for hepatoblastoma was not quite statistically significant (p=0.074), but comparison to historical incidence rates in previous NTP studies (0/1091 in vehicle controls and 0/1784 in untreated controls) suggested that the lesion was probably related to treatment. The combined incidence of adrenal gland pheochromocytomas or malignant pheochromocytomas occurred with a significant positive trend (0/47, 2/48, 4/49) in male mice, but the incidence rates were lower than the historical control values for this tumor. The incidence of alveolar/bronchiolar carcinomas was slightly increased in low-dose male mice (0/50, 5/50, 0/50), but these tumors were not observed in the high-dose male mice, and the incidence of combined alveolar/bronchiolar adenomas or carcinomas was not significantly increased in either the low- or high-dose male mice (6/50, 13/50, 2/50). Based on the increased incidences of hepatocellular neoplasms, NTP concluded that there was clear evidence of carcinogenicity in male and female $B6C3F_1$ mice.

Table II.A.3.1. Liver Lesions in the NTP (1987) Two-year Gavage Study of 1,4-Dichlorobenzene in $B6C3F_1$ Mice

Lesion	Male Mice			Female Mice		
	Vehicle Control	214 mg/kg-day[a]	429 mg/kg-day[a]	Vehicle Control	214 mg/kg-day[a]	429 mg/kg-day[a]
Number of mice examined	50	49	50	50	48	50
Hepatocellular adenoma	5	13	16	10	6	21
Hepatocellular carcinoma	14	11	32	5	5	19
Hepatocellular adenoma or carcinoma	17	22	40	15	10	36
Hepatoblastoma[b]	0	0	4	0	0	0
Hepatocellular degeneration	0	36	39	0	8	36
Cell size alteration	0	38	40	0	4	27
Focal necrosis	1	35	37	1	4	30

[a]Duration-adjusted dose
[b]All hepatoblastomas were observed in mice that had hepatocellular carcinomas.

In the chronic inhalation study in rats (Imperial Chemical Industries Limited, 1980), groups of 76-79 Wistar rats of each sex were chamber exposed to 0, 75, or 500 ppm of 1,4-dichlorobenzene for 5 hours/day, 5 days/week for up to 76 weeks (Imperial Chemical Industries Limited, 1980). Five rats/sex/group were sacrificed at 26-27, 52-53, and 76-77 weeks, and the remaining animals were sacrificed after a 32-week recovery period (at week 112). There were no exposure-related effects on clinical signs, survival, food or water consumption, blood chemistry, or hematology in either sex (Imperial Chemical Industries Limited, 1980; Riley et al., 1980). Body weight gain was slightly reduced (≈3-5% less than controls) in both groups of male rats during the first few weeks of the study, but was comparable to controls by week 10 and throughout the rest of the study. Comprehensive histological examinations (including nasal sinuses, trachea and lung) were performed on all rats found moribund or dead, or killed at the interim or terminal sacrifices. There was no clear histological evidence of any treatment-related toxic or carcinogenic effects in any tissues. The adequacy of this study for carcinogenicity evaluation is limited by a failure to reach a maximum tolerated dose, as well as the less-than-lifetime exposure duration and short observation period.

In the chronic inhalation study in mice, groups of 75 female SPF Swiss mice were exposed to 1,4-dichlorobenzene at vapor concentrations of 0, 75, or 500 ppm for 5 hours/day, 5 days/week, for 57 weeks, followed by observation for 18-19 weeks (Riley et al., 1980). The study originally included similar groups of male mice, but was terminated because of high mortality attributed to fighting and probable respiratory infection. A high background incidence of respiratory disease was observed in all groups of males as well as females. Study endpoints appear to be the same as in the Imperial Chemical Industries Limited (1980) rat inhalation study summarized above. There was no histological evidence of compound-related toxic or carcinogenic effects, but the exposure and observation durations were insufficient for adequate assessment of carcinogenic potential. Evaluation of this study is further complicated by the lack of a primary report; unlike the rat study summarized above, the mouse study was reviewed from a secondary source (Loeser and Litchfield, 1983) because the complete report was not available.

The translation of an incomplete summary of a Japanese inhalation carcinogenicity study of 1,4-dichlorobenzene in rats and mice is available (Chlorobenzene Producers Association, 1997). Groups of 50 male and 50 female F344/DuCrj rats and 50 male and 50 female Crj:BDF_1 mice were exposed to 0, 20, 75, or 300 ppm of 1,4-dichlorobenzene on 5 days/week for 104 weeks. Incidences of liver tumors in male and female mice and lung tumors in female mice were increased as summarized in Table II.A.3.2. The available summary of this study provides no additional information on the experimental design or results.

Table II.A.3.2. Liver and Lung Tumors in Two-year Mouse Inhalation Study of 1,4-Dichlorobenzene (Chlorobenzene Producers Association, 1997)

Lesion	0 ppm	20 ppm	75 ppm	300 ppm
Number of male mice examined	49	49	50	50
Hepatoma	12	17	16	38
Hepatic histiocytoma carcinoma	0	3	1	6
Number of female mice examined	50	50	49	50
Hepatoma	2	4	2	41
Hepatocellular adenoma	2	10	6	20
Lung bronchiole/alveolar epithelial carcinoma	1	1	1	4

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

The potential for 1,4-dichlorobenzene to promote liver tumors in rats was evaluated in a subchronic initiation-promotion bioassay (Gustafson et al., 1998). Male F344 rats were given a single intraperitoneal injection of 0.9% saline (12 animals) or 200 mg/kg of *N*–nitroso-diethylamine (NDEA) in saline (18 animals), followed by oral administration of 1,4-dichlorobenzene beginning two weeks later. Rats promoted with 1,4-dichlorobenzene were treated with doses of 0.1 or 0.4 mmol/kg-day (14.7 or 58.8 mg/kg-day) in corn oil by gavage for 6 weeks. Control rats were similarly treated with corn oil alone or NDEA in corn oil. All animals were partially hepatectomized 1 week after the start of 1,4-dichlorobenzene exposure. The study was ended at the end of week 8, and immunohistochemical analysis was performed to identify preneoplastic glutathione *S*-transferase-expressing foci in the liver. No 1,4-dichlorobenzene-related increased incidences of hepatic foci were found, suggesting that the compound is not a liver tumor promoter in rats.

No studies are available that investigated genotoxic effects of 1,4-dichlorobenzene in humans, although genotoxicity has been extensively studied in animal systems, as detailed in the Source Document (U.S. EPA, 2002). Negative results were reported in the vast majority of a variety of assays, including gene mutation in *S. typhimurium* and mouse lymphoma cells *in vitro*; DNA damage in rat and human hepatocytes *in vitro*; unscheduled DNA synthesis in mouse hepatocytes and rat kidney cells *in vivo*, sister chromatid exchange in Chinese hamster ovary cells *in vitro*; mouse bone marrow cells and erythrocytes *in vivo*; chromosomal aberrations in rat bone marrow cells *in vivo*; and dominant lethal mutations in mice. Some studies, including

mammalian cell evaluations for chromosomal aberrations, sister-chromatid exchanges, and micronucleus formation, were equivocal and inconsistent, with findings that included both positive and negative effects (Carbonell et al., 1991; Canonero et al., 1997; NTP, 1987; Mohtashamipur et al., 1987; Miyagawa et al., 1995; Morita et al., 1997; Robbiano et al., 1999; Tegethoff et al., 2000). In animals, the preponderance of studies and overall weight of evidence indicate that 1,4-dichlorobenzene is non-genotoxic. The minimal evidence for genotoxicity of 1,4-dichlorobenzene is consistent with the IARC (1999) conclusion that there is weak evidence for the genotoxicity of 1,4-dichlorobenzene in mammalian cells *in vitro*, and that no conclusion can be drawn from the *in vivo* data.

The human relevance of the 1,4-dichlorobenzene-induced kidney tumors in rats and liver tumors in mice in the NTP (1987) bioassay has been extensively studied and debated. Regarding effects in the kidney, there is a widespread scientific consensus that 1,4-dichlorobenzene causes both renal toxicity and tumors through a non-DNA-reactive mechanism that is specific to male rats and is not present in female rats or other species, including humans (Barter and Sherman, 1999; IARC, 1999; U.S. EPA, 1991). Substantial evidence indicates that the renal effects are produced by a sequence of events initiated by binding of 1,4-dichlorobenzene with the male rat-specific protein $\alpha_{2\mu}$-globulin. $\alpha_{2\mu}$-Globulin nephropathy is characterized by a series of histopathological changes, including hyaline droplet accumulation in the proximal convoluted tubules and consequent cellular damage and regenerative cell proliferation, which are mechanistically linked to the formation of kidney tumors (Bomhard et al., 1988; Charbonneau et al., 1989; Lake et al., 1997; NTP, 1987). Based on widely recognized criteria for establishing the role of $\alpha_{2\mu}$-globulin nephropathy in male rat renal carcinogenesis, it is generally accepted that $\alpha_{2\mu}$-globulin-associated kidney tumors are not relevant to humans (Barter and Sherman, 1999; IARC, 1999; U.S. EPA, 1991).

In contrast to the kidney tumors in male rats, the mechanism by which 1,4-dichlorobenzene induces liver tumors in mice is not well defined. As discussed in the Source Document (U.S. EPA, 2002) and other evaluations (Barter and Sherman, 1999; IARC, 1999), available evidence indicates that the mechanism leading to the formation of the mouse liver tumors is non-genotoxic and is based on sustained mitogenic stimulation and proliferation of the hepatocytes. Some of the data indicate that the cell proliferation may be a threshold response to cytotoxicity, which would be consistent with the results of the NTP (1987) bioassay. NTP found that liver tumor incidences were only increased in mice that also showed hepatotoxic effects, but not in low-dose female mice, which had little or no hepatotoxicity. The proliferation is believed to result from an increase in the rate of cell division, a decrease in the rate of apoptosis, or a combination of the two, based on evidence for decreases in apoptosis and increases in BrdU labeling index, DNA synthesis, or cumulative replicating fraction in livers of exposed mice (Eldridge et al., 1992; James et al., 1998; Lake et al., 1997; Sherman et al., 1998; Umemura et al., 1992, 1996, 1998). However, similar effects were found in the livers of exposed rats, even though 1,4-dichlorobenzene did not induce liver tumors in rats (Eldridge et al., 1992; James et al., 1998; Hasmall et al., 1997; Lake et al., 1997; Sherman et al., 1998; Umemura et al., 1992, 1996, 1998). Additionally, the mitogenic effects of 1,4-dichlorobenzene may not be sustained

throughout long-term exposure (Eldridge et al., 1992; Lake et al., 1997), and NTP (1987) did not report hepatic hyperplasia among responses significantly elevated following chronic exposure to 1,4-dichlorobenzene, although other hepatotoxic effects were noted. Thus, the evidence supporting a sustained proliferative response following 1,4-dichlorobenzene exposure as the mode of action for 1,4-dichlorobenzene-induced tumor formation is incomplete.

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

___II.B.1. SUMMARY OF RISK ESTIMATES

____II.B.1.1. Oral Slope Factor: 1.3 x 10^{-2} $(mg/kg\text{-}day)^{-1}$ (human equivalent dose)

____II.B.1.2. Drinking Water Unit Risk: 3.7 x 10^{-4} $(mg/L)^{-1}$

____II.B.1.3. Extrapolation Method: Linearized multistage extrapolation using incidence data for hepatocellular adenomas or carcinomas in male mice.

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	0.27 mg/L
E-5 (1 in 100,000)	0.027 mg/L
E-6 (1 in 1,000,000)	0.0027 mg/L

___II.B.2. DOSE-RESPONSE DATA (CARCINOGENICITY, ORAL EXPOSURE)

Oral cancer bioassays for 1,4-dichlorobenzene were performed in male and female rats and mice by NTP (1987), as summarized in Section II.A.3. The rat study found no tumor increases in females and, in males, a significant increase in the incidence of renal tubular adenomas or adenocarcinomas associated with male rat-specific hyaline droplet ($\alpha_{2\mu}$-globulin) nephropathy and considered not to be relevant to carcinogenicity in humans (U.S. EPA, 1991). The mouse study found that hepatocellular adenoma, hepatocellular carcinoma, and combined hepatocellular adenoma or carcinoma occurred with positive dose-related trends in both male and female mice, with the incidences in the low-dose males and high-dose groups of both sexes being significantly greater than those in the control groups. Additionally observed in the high-dose male mice were four cases of hepatoblastoma, an extremely rare type of hepatocellular carcinoma. Based on the increased incidences of hepatocellular neoplasms, NTP concluded that there was clear evidence of carcinogenicity in male and female $B6C3F_1$ mice. This study was used for dose-response analysis for oral exposure.

Data on the combined incidence of hepatocellular adenoma or carcinoma in male and female mice from the NTP (1987) study were used for dose-response assessment. These data are shown in Table II.B.1. The doses shown are average daily doses in the gavage study. Animals dying before the first appearance of liver tumors in any group of that sex were censored from the group totals when figuring the denominators. This adjustment was made so that the denominators included only those animals at risk for developing tumors.

Table II.B.1. Tumor Incidence Data Used for Dose-Response Assessment for 1,4-Dichlorobenzene

Species/ Strain/Sex	Tumor Type and Location	0 (mg/kg-day)	214 (mg/kg-day)	429 (mg/kg-day)
Male $B6C3F_1$ Mouse	Hepatocellular adenoma or carcinoma	17/44	22/40	40/42
Female $B6C3F_1$ Mouse	Hepatocellular adenoma or carcinoma	15/44	10/44	36/44

Data taken from NTP (1987). Denominators were adjusted for early mortality, as per U.S. EPA (2002)

In accordance with the proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999), a $BW^{3/4}$ scaling factor was used to convert the doses in the animal study to human equivalent doses (HED) to be used for modeling. This is accomplished as follows:

$$HED = Dose \times \sqrt[4]{W / 70kg} * (Le / L)^3$$

where:

HED = human equivalent dose
Dose = average daily dose in animal study
W = animal body weight (kg)
70 = kg reference human body weight
Le = duration of experiment
L = lifespan of the animal

For the NTP (1987) study, the duration of the study was equal to the lifespan of the mice (103 weeks). Growth in treated male and female mice was similar to the respective controls. Therefore, time-weighted average body weights in the controls were used to represent animal body weights in the above equation (0.040 kg for males and 0.032 kg for females). The animal doses and corresponding HEDs are shown in Table II.B.2.

Table II.B.2. HEDs Corresponding to Average Daily Animal Doses in NTP (1987) Using a $BW^{3/4}$ Scaling Factor and Time-weighted Average Body Weights for Male and Female Mice from the Study

Animal Dose (mg/kg-day)	0	214	429
HED for use with male incidence data (mg/kg-day)	0	33	66
HED for use with female incidence data (mg/kg-day)	0	31	63

U.S. EPA (1999) *Draft Revised Guidelines for Carcinogen Risk Assessment*, allows the derivation of a quantitative estimate for carcinogenicity using both linear and non-linear approaches. However, the evidence supporting a non-genotoxic mode of action is insufficient which precludes the application of a non-linear approach to quantify the carcinogenic risk from exposure to1,4-dichlorobenzene. Thus a linear approach for the derivation of a quantitative estimate of cancer risk for ingested 1,4-dichlorobenzene was taken.

A linear approach results in calculation of an oral slope factor that describes the cancer risk per unit dose of the chemical at low doses. In accordance with the 1999 *Draft Revised Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1999), a linearized multistage model (Global86) was fit to the data, and cancer slope factors (95% upper confidence limits on the low dose slope q_1*) were calculated by the model.

The results of the linear analyses are shown in Tables II.B.3 (male data) and II.B.4 (female data). The q_1* values were calculated by Global86. Background tumor incidence was estimated in the model, and calculations were based on extra risk. The q_1* based on the male data ($1.3x10^{-2}$ per mg/kg-day) is an order of magnitude greater than that based on the female data ($3.3x10^{-3}$ per mg/kg-day). The largest of the calculated slope factors, which is most protective of human health, is chosen as the slope factor for the chemical ($1.3x10^{-2}$ per mg/kg-day), based upon the combined incidence of hepatocellular adenomas or carcinomas in male $B6C3F_1$ mice.

Table II.B.3. q_1* Values Based on Combined Hepatocellular Adenoma or Carcinoma Incidence Data in Male $B6C3F_1$ Mice

0 (mg/kg-day)	33[a] (mg/kg-day)	66[a] (mg/kg-day)	q_1^{*} [b] $(mg/kg\text{-}day)^{-1}$
17/44	22/40	40/42	$1.3x10^{-2}$

[a] HED calculated as described above.
[b] q1* calculated by GLOBAL86 (background estimated in model, based on extra risk, 2° polynomial chosen by GLOBAL86)

Table II.B.4. q_1* Values Based on Combined Hepatocellular Adenoma or Carcinoma Incidence Data in Female $B6C3F_1$ Mice

0 (mg/kg-day)	31[a] (mg/kg-day)	63[a] (mg/kg-day)	q_1^{*} [b] $(mg/kg\text{-}day)^{-1}$
15/44	10/44	36/44	3.3×10^{-3}

[a] HED calculated as described above.
[b] q1* calculated by GLOBAL86 (background estimated in model, based on extra risk, 3° polynomial chosen by GLOBAL86)

___II.B.3. ADDITIONAL COMMENTS (CARCINOGENICITY, ORAL EXPOSURE)

None.

___II.B.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, ORAL EXPOSURE)

There is clear evidence that ingested 1,4-dichlorobenzene was carcinogenic in male and female mice. The NTP (1987) bioassay found increased incidences of liver tumors in mice, and incidence data on hepatocellular adenomas and carcinomas in this study were used for cancer dose-response assessment for oral exposure. Linear analysis presented in section II.B.2 showed that the largest slope factor, which is most protective of human health, is 1.3×10^{-2} per mg/kg-day, based upon the combined incidence of hepatocellular adenomas or carcinomas in male mice.

II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not applicable. Available inhalation carcinogenicity data for 1,4-dichlorobenzene are inadequate, precluding quantitative assessment of inhalation cancer risk.

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

Source Document -- U.S. EPA, 2002

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS summary. A record of these comments is included as an appendix to U.S. EPA, 2002.

___II.D.2. EPA REVIEW (CARCINOGENICITY ASSESSMENT)

Agency Consensus Date -- __/__/__ *[Leave BLANK until consensus is reached]*

___II.D.3. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (301)345-2870 (phone), (301)345-2876 (FAX), or hotline.iris @epamail.epa.gov (email address).

_III. [reserved]
_IV. [reserved]
_V. [reserved]

_VI. BIBLIOGRAPHY

Substance Name -- 1,4-Dichlorobenzene
CASRN -- 106-46-7
Last Revised -- 00/00/0000

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_VII. REVISION HISTORY

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

Date	Section	Description
08/01/1991	I.B.	Inhalation RfC under review
08/01/1992	I.B.6.	Work group review date added
01/01/1994	I.B.	Inhalation RfC on-line
01/01/1994	VI.B.	Inhalation RfC references on-line
02/01/1995	IV.	Regulatory actions on-line
03/01/1995	IV.C.	Clean Water Act section added
11/01/1996	I.B.7.	Primary contact's office changed
04/01/1997	III., IV., V.	Drinking Water Health Advisories, EPA Regulatory Actions, and Supplementary Data were removed from IRIS on or before April 1997. IRIS users were directed to the appropriate EPA Program Offices for this information.
01/12/2000	I., II.	This chemical is being reassessed under the IRIS Program.
00/00/00	I., II., III., IV., V., VI., VII., VIII.	Reassessment of 1,4-Dichlorobenzene.

_VIII. SYNONYMS

Substance Name -- 1,4-Dichlorobenzene
CASRN -- 106-46-7
Last Revised -- 00/00/0000

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