DRAFT IRIS SUMMARY

0408
1,2-Dichlorobenzene; CASRN 95-50-1; 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 1,2-DICHLOROBENZENE

File First On-Line 08/01/1989

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	00/00/0000
Inhalation RfC Assessment (I.B.)	inadequate data	00/00/0000
Carcinogenicity Assessment (II.)	on-line	00/00/0000

_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- 1,2-Dichlorobenzene
CASRN -- 95-50-1
Last Revised -- 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.

This RfD replaces the previous RfD of 0.09 mg/kg-day entered on IRIS on 3/01/1991. The new RfD is based on the same principal study and NOAEL but uses a lower uncertainty factor.

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
No adverse effects 2-year rat gavage study NTP, 1985	NOAEL: 60 mg/kg-day (Adjusted to 42.9 mg/kg-day)	300	1	1.4E-1
Liver necrosis 13-week rat gavage study NTP, 1985	LOAEL: 125 mg/kg-day (Adjusted to 89.3 mg/kg-day)			

*Conversion Factors and Assumptions – Doses duration-adjusted for exposure on 5 days/week.

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

NTP (National Toxicology Program) (1985). Toxicology and carcinogenesis studies of 1,2-dichlorobenzene (o-dichlorobenzene) (CAS No. 95-50-1) in F344/N rats and B6C3F$_1$ mice (gavage studies). NTP TR 255. NIH Publ. No. 86-2511.

1,2-Dichlorobenzene (>99% pure) in corn oil was administered to groups of 50 male and 50 female F344/N rats by gavage in doses of 0, 60, or 120 mg/kg, 5 days/week for 103 weeks (0, 42.9, or 85.7 mg/kg-day) (NTP, 1985). Evaluations included clinical signs, body weight, and necropsy and histology on all animals. At 1 year, survival in males was 98-100% in the control and low-dose groups, and 88% in the high-dose group, while in females, it was 95-100% in all groups. At termination, survival in the 0, 42.9, and 85.7 mg/kg-day groups was 84, 72, and 38% in males and 62, 66, and 64% in females. Survival to termination in the high-dose male rats was significantly reduced compared with controls (19/50 vs. 42/50, $p<0.001$), but the difference appears to be mainly from causes incidental to treatment. There were 20 incidental deaths in the high-dose group compared to 4 in controls; according to NTP, of the 20 deaths, 3 were accidental, 5 were probably due to gavage error, and 12 may have been caused by aspiration. Mean body weight was slightly reduced (≈5% less than controls) in males throughout the study at

85.7 mg/kg-day; the only effect in females was a small increase compared to controls after week 32 in both dose groups (final body weights were 11-12% increased at 42.9 and 85.7 mg/kg-day). There were no increased incidences of compound-related nonneoplastic lesions in the liver, kidneys, or any other tissues at the two tested doses, indicating that 42.9 mg/kg-day and 85.7 mg/kg-day were the chronic NOAELs in rats. Though no compound-related incidences of nonneoplastic lesions in the liver, kidneys or any other tissues were observed at the two tested doses, these incidences were observed in the liver at the 89.3 mg/kg-day dose in a 1985 NTP subchronic study (NTP, 1985; detailed below) indicating that 42.9 mg/kg-day in the chronic study is a better selection for a NOAEL.

Groups of 50 male and 50 female $B6C3F_1$ mice were similarly administered 1,2-dichlorobenzene in doses of 0, 60, or 120 mg/kg, 5 days/week for 103 weeks (0, 42.9, or 85.7 mg/kg-day) (NTP, 1985). Evaluations included clinical signs, body weight, and necropsy and histology on all animals. No clinical signs were reported, and mean body weight and survival were comparable in control and dosed mice throughout the study, indicating that it is unclear whether an MTD was achieved. The only exposure-related nonneoplastic lesion was a significantly increased [$p<0.05$, Fisher Exact test, conducted as part of the study evaluation in the Source Document (U.S. EPA, 2002)] incidence of renal tubular regeneration in male mice at 85.7 mg/kg-day; incidences in the control, low- and high-dose male groups were 8/48, 12/50, and 17/49, respectively. The tubular regeneration is judged to be non-adverse because no degenerative or necrotic lesions were observed in the kidneys of the male mice, no regeneration or other renal lesions were found in female mice, and the kidney was not identified as a target at higher doses in subchronic mouse studies. Therefore, 85.7 mg/kg-day is considered a chronic NOAEL in mice.

The results of the NTP (1985) 103-week studies in rats and mice indicate that the chronic NOAELs are 42.9 mg/kg-day and 85.7 mg/kg-day and that insufficient data are available to identify a critical effect for chronic exposure. Subchronic studies in these species identified the liver as the most sensitive target for repeated oral exposures to 1,2-dichlorobenzene (Hollingsworth et al., 1958; NTP, 1985; Robinson et al., 1991). These studies found liver lesions in rats exposed to duration-adjusted dose levels of 270 mg/kg-day for 192 days, rats exposed to 400 mg/kg-day for 90 days, and rats and mice exposed to $\geq$179 mg/kg-day for 13 weeks, as well as non-adverse increases in liver weight and serum ALT in rats at $\geq$100 mg/kg-day, as detailed below and in Section I.A.4.

The lowest subchronic effect level is 89.3 mg/kg-day, based on degenerative liver lesions and increased relative liver weight in rats (NTP, 1985). In this study, groups of 10 male and 10 female F344/N rats were administered 1,2-dichlorobenzene (>99% pure) in corn oil by gavage in doses of 0, 30, 60, 125, 250 or 500 mg/kg, 5 days/week for 13 weeks (0, 21.4, 42.9, 89.3, 179, or 357 mg/kg-day). Evaluations included clinical signs, body weight and food consumption, hematology, clinical chemistry, urine volume, urine uroporphyrins and coproporphyrins, liver porphyrins, organ weights, and necropsies in all groups of animals. Complete histological examinations were performed on all control and high-dose animals; histology exams in lower

dose groups were limited to liver, kidneys and thymus at 89.3 and 179 mg/kg-day. Final body weights were within 7% of control values in all groups of both sexes except for the 357 mg/kg-day male rats, which were 19% less than controls. Early deaths that were presumed by the researchers to be due to gavage error occurred in two females at 357 mg/kg-day and in one male each from the 0, 21.4, and 89.3 mg/kg-day groups.

Effects mainly occurred in the liver, as shown by histopathological changes, including centrilobular degeneration or necrosis of individual hepatocytes in most of the rats (8/10 males and 7/8 surviving females, as well as the two females that died early) at 357 mg/kg-day (NTP, 1985). Liver pathology (necrosis of individual hepatocytes) was also significantly increased [$p<0.05$, Fisher Exact test, conducted as part of the evaluation of the study in the Source Document (U.S. EPA, 2002)] at 179 mg/kg-day (4/9 males and 5/10 females) relative to controls. Although milder degenerative liver lesions were noted in a few animals (1/10 males and 3/10 females) at 89.3 mg/kg-day, the incidence of these lesions were not significantly increased at this dose compared with controls. No liver lesions were reported in male or female controls. Relative liver weight was significantly increased at $\geq$89.3 mg/kg-day in both sexes, but there were no increases in serum levels of liver enzymes [ALT, AP, or γ-glutamyltranspeptidase (GGPT)] at any dose. Changes in other serum chemistry indices included increases in cholesterol and total protein that were generally slight, particularly at lower dose levels. Serum cholesterol was significantly ($p<0.05$) increased in males at $\geq$21.4 mg/kg-day (50.0, 17.6, 26.5, 70.6 and 109% higher than controls in the low to high dose groups, not significant at 42.9 mg/kg-day) and females at $\geq$89.3 mg/kg-day (12.2, 12.2, 32.6, 26.5, and 51.0%). Serum total protein was significantly increased in females at $\geq$21.4 mg/kg-day (7.8, 4.7, 6.3, 6.3 and 17.2%) and males at $\geq$179 mg/kg-day (-1.4%, 1.4%, 0, 7.1 and 7.1%). Blood urea nitrogen was not increased in any dose group of either sex, although 24-hour urine volume was 57% higher than controls in 357 mg/kg-day males. Additional effects observed at 357 mg/kg-day included renal tubular degeneration (6/10 males), lymphoid depletion in the thymus (4/10 males), and some slight hematologic changes (e.g., minimal decreases in hemoglobin, hematocrit, erythrocyte counts, and mean corpuscular volume in both sexes). Urinary concentrations of uroporphyrin and coproporphyrin were 3-5 times higher than controls in the 357 mg/kg-day males and females, but this increase was not considered indicative of porphyria because total porphyrin concentration in the liver was not altered at any dose level and no pigmentation indicative of porphyria was observed by ultraviolet light at necropsy. At 89.3 mg/kg-day, there was a significant increase in relative liver weight and slight changes in serum cholesterol. Slight decreases in serum triglycerides (500 mg/kg-day, males; 250 mg/kg-day, females) and serum protein (250-500 mg/kg-day, males; 30-500 mg/kg-day, females) were observed which may reflect hepatic effects of the chemical at these doses. The 89.3 mg/kg-day is a LOAEL on the basis of significant increase in relative liver weight and the appearance of degenerative liver lesions (1/10 males and 3/10 females). A NOAEL was not identified in this study due to the lack of histopathology data at the two lower doses (21.4 mg/kg-day and 42.9 mg/kg-day).

The NOAEL/LOAEL approach is the most appropriate method for deriving an RfD for 1,2-dichlorobenzene. Using this approach, the chronic NOAEL of 42.9 mg/kg-day is the basis

for the RfD. The lack of a LOAEL in the 103-week study (NTP, 1985) precludes analyzing the chronic data using benchmark dose (BMD) modeling. BMD analysis was performed on the 13-week liver histopathology data (Table I.A.2.1) to compare points of departure (the lower 95% confidence limit on the BMD [BMDL]) for subchronic effects with the chronic NOAEL. All dichotomous models in the EPA Benchmark Dose Software (version 1.3.1) were fit to the incidence data for liver lesions in the most sensitive animals (male and female rats and male mice). Akaike's Information Criteria (AIC) was used to assess the model with the best fit in each data set, and the best-fitting model was used to calculate a BMD associated with 10% extra risk for liver toxicity and its BMDL. The Quantal-quadratic, Quantal-linear and Probit models provided the best fits of the male rat, female rat, and male mouse incidence data, respectively. The BMDs and BMDLs (rounded values) are, respectively, 86.1 and 68.1 mg/kg-day for the male rats, 22.0 and 14.7 mg/kg-day for the female rats, and 126.1 and 82.1 mg/kg-day for the male mice.

Table I.A.2.1. Liver Lesions in Rats and Mice Exposed to 1,2-Dichlorobenzene for 13 Weeks (NTP, 1985).

(Individual cell or focal necrosis; centrilobular degeneration also occurred in the high-dose group)	Duration-adjusted Oral Dose (mg/kg-day)					
	0	21.4	42.9	89.3	179	357
male rats	0/10	ND	ND	1/10	4/9[a]	8/10[a]
female rats	0/10	ND	ND	3/10	5/10[a]	9/10[a]
male mice	0/10	ND	ND	0/10	4/10[a]	9/10[a]
female mice	0/10	ND	ND	0/10	0/10	9/10[a]

[a]Significantly higher ($p<0.05$) than controls; Fisher Exact Test performed as part of study evaluation (U.S. EPA, 2002).
ND - no histological examinations conducted in this group.

The lower of the two chronic NOAELs among 42.9 and 82.7 mg/kg-day was selected as the basis for the RfD derivation for three reasons. First, BMDL ranges between 14.7 mg/kg-day and 82.1 mg/kg-day were calculated using the NTP subchronic study with 14.7 mg/kg-day in female rats being the lowest BMDL. However, the subchronic study size was too small to adequately differentiate the liver effects between the treated and control groups. Second, the subchronic LOAEL would appear to have minimal severe effect. Finally, there was a lack of liver effects at a slightly lower dose (120 mg/kg-day) in the chronic study compared to liver effects at a dose of 125 mg/kg-day in the subchronic study. Since there is a higher confidence in a chronic study when compared to a subchronic study, the chronic NOAEL of 42.9 mg/kg-day (NTP, 1985) was judged to be the most appropriate value on which to base the oral RfD.

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

UF = 300. A total uncertainty factor of 300 was applied to the chronic NOAEL of 42.9 mg/kg-day: 10 for interspecies variability, 10 for interindividual variability, and 3 for database deficiencies.

A 10-fold uncertainty factor is used to account for the interspecies variability in extrapolating from laboratory animals (rats) to humans. No information is available on the toxicity of 1,2-dichlorobenzene in orally-exposed humans. PBPK models for oral exposure to 1,2-dichlorobenzene are under development (Hissink et al., 1997). As discussed in the Source Document (U.S. EPA, 2002), the models suggest that humans may be more or less susceptible to the acute hepatoxicity of the chemical than rats, depending on mechanism of toxicity.

A 10-fold uncertainty factor is used to account for variation in sensitivity within human populations. No effects on developing fetuses were reported in a poorly reported study in which rats were gestationally exposed to oral doses of 200 mg/kg-day (Ruddick et al., 1983), indicating that developmental toxicity of 1,2-dichlorobenzene, if it does occur, would only occur at levels higher than the critical LOAEL for systemic toxicity (liver effects). However, there is no information on the degree to which humans of varying gender, age, health status, or genetic makeup might vary in the disposition of, or response to, ingested 1,2-dichlorobenzene.

A 3-fold uncertainty factor is used to account for deficiencies in the database. There is no information on the toxicity of 1,2-dichlorobenzene in orally-exposed humans. A limited amount of information is available on health effects in people who were occupationally exposed to 1,2-dichlorobenzene, but the data are insufficient for identifying sensitive systemic endpoints in humans (see U.S. EPA, 2002). Regarding chronic oral toxicity of 1,2-dichlorobenzene in animals, the only available study (NTP, 1985) was conducted in two species and was generally well-designed. The chronic NTP (1985) studies in rats and mice were limited by the use of only two dose levels and the lack of chemical induced effects. The subchronic NTP studies in rats and mice are sufficient to identify the liver as a critical target, as well as a critical LOAEL for hepatotoxicity. The oral database for 1,2-dichlorobenzene lacks adequate assessments of neurotoxicity and immunotoxicity, as well as endpoints known to be sensitive to other isomers of dichlorobenzene (e.g., thyroid and pituitary, as shown by oral testing with 1,3-dichlorobenzene). The only information on developmental toxicity is from a poorly reported study (Ruddick et al., 1983) that found no evidence of maternal or fetal effects in rats at dose levels higher than the critical LOAEL for systemic effects; data on developmental toxicity in a second species are lacking. The primary limitations of the oral data base are the lack of an adequate developmental toxicity study and reproductive toxicity study in either sex, although an inhalation two-generation study of 1,2-dichlorobenzene in rats has been conducted (Bio/dynamics, 1989). Because the inhalation study found no effects on reproduction in either generation at exposure levels higher than those causing liver effects in the parental animals, it can be used to partially address the datagap for oral exposure. Therefore, an uncertainty factor of 3 is used for database deficiencies.

MF = 1. None.

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

No information is available on the toxicity of 1,2-dichlorobenzene in humans following oral exposure. Support for the liver as the critical target of 1,2-dichlorobenzene toxicity in animals is provided by subchronic oral studies in rats (Hollingsworth et al., 1958; Robinson et al., 1991) and mice (NTP, 1985) that found hepatic histopathology at adjusted doses $\geq$89.3 mg/kg-day, as detailed below.

Groups of 10 young adult white female rats (strain not specified) were administered 1,2-dichlorobenzene in olive oil-gum arabic emulsion by gavage in doses of 18.8, 188 or 376 mg/kg, 5 days/week for 138 doses in 192 days (13.5, 135 or 270 mg/kg-day) (Hollingsworth et al., 1958). A group of 20 vehicle-exposed females was used as controls. Body weight, absolute organ weights (liver, kidneys, spleen, and heart), hematology, bone marrow values and histology were evaluated. Unspecified numbers of deaths from respiratory infection occurred that were reported to be well-distributed among the groups. No exposure-related effects were observed at 13.5 mg/kg-day, and there were no body weight, hematological, or bone marrow changes at higher doses. Statistically significant ($p \leq 0.02$) increases in absolute liver and kidney weights (37-47% and 22-30% higher than control values, respectively) occurred at $\geq$135 mg/kg-day. Additional effects were found at 270 mg/kg-day that included slight to moderate cloudy swelling in the liver and significantly decreased spleen weight. No additional relevant information (e.g., incidences of liver lesions) was reported. The increases in liver and kidney weight in the absence of histopathological or other corroborating evidence of tissue damage are considered to be adaptive, rather than adverse, changes. Therefore, a NOAEL of 135 and LOAEL of 270 mg/kg-day are identified in rats on the basis of liver pathology.

Groups of 10 male and 10 female Sprague-Dawley rats were treated with 1,2-dichlorobenzene in corn oil by gavage in doses of 0, 25, 100, or 400 mg/kg-day for 90 consecutive days (Robinson et al., 1991). Endpoints evaluated during the study included clinical signs, body weight, and food consumption. Evaluations at the end of the exposure period included hematology (8 indices), serum chemistry [12 indices including alkaline phosphatase (AP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and blood urea nitrogen (BUN)], urinalysis (6 indices), ophthalmic condition, and selected organ weights (brain, liver, spleen, lungs, thymus, kidneys, adrenal glands, heart, and testes or ovaries). Histological examinations were performed on selected tissues (liver, kidneys, spleen, adrenal glands, thymus, brain, heart, lungs, and testes or ovaries) in all high-dose rats and one-half of each control group. No clinical signs or effects on survival were observed. Body weight gain was not affected in female rats, but significantly decreased in the males at 400 mg/kg-day (final body weights were 12.8% lower than controls). The only observed alterations in food consumption were increased total food consumption in the females rats at 400 mg/kg-day group during weeks 11-13. Statistically significant changes in organ weights included dose-

related increases in absolute and relative liver weights in both sexes at ≥100 mg/kg-day, increases in absolute and relative kidney weights in both sexes at 400 mg/kg-day (absolute kidney weight was also increased in females at 100 mg/kg-day), and decreases in absolute (both sexes) and relative (males only) spleen weights at 400 mg/kg-day.

No compound-related alterations in urinalysis or hematological parameters were observed (Robinson et al., 1991). Clinical chemistry changes included increased serum ALT in males at ≥100 mg/kg-day, increased BUN in males at 400 mg/kg-day, and increased total bilirubin in both sexes at 400 mg/kg-day. The increases in serum ALT were statistically significant, but did not increase with dose, and serum levels of other liver-associated enzymes were not increased (AST, LDH and AP). Histopathological alterations were only observed in the liver. Statistically significant increases in the incidences of centrilobular degeneration, centrilobular hypertrophy, and single cell necrosis (males only) were observed in both sexes at 400 mg/kg-day. The degeneration, hypertrophy, and necrosis in the high-dose rats occurred in 10/10, 9/10, and 7/10 males and 8/10, 10/10, and 5/10 females, respectively; none of these lesions were present in control animals of either sex. As indicated above, histological examinations were not performed in the low- and middle-dose groups, and were limited to one half of each control group. Changes in serum ALT and liver weight at 100 mg/kg-day were not considered as evidence of hepatotoxicity because the increase in serum ALT was not supported by changes in other serum enzymes that are also indicators of liver damage . In addition, the serum ALT did not increase with an increase in dose. Due to a lack of clear evidence of tissue damage, the increase in liver weight is considered to be an adaptive response to an exposure of 100 mg/kg-day of 1,2-DCB. A dose of 400 mg/kg-day is a LOAEL based on hepatic degeneration, hypertrophy and necrosis in rats. A NOAEL was not identified because the 100 mg/kg-day rats were not examined for pathology.

Effects of subchronic oral exposure in mice were studied by NTP (1985). Groups of 10 male and 10 female B6C3F$_1$ mice were administered 1,2-dichlorobenzene (>99% pure) in corn oil by gavage in doses of 0, 30, 60, 125, 250 or 500 mg/kg, 5 days/week for 13 weeks (0, 21.4, 42.9, 89.3, 179 or 357 mg/kg-day). Evaluations included clinical signs, body weight and food consumption, hematology, clinical chemistry, urine uroporphyrins and coproporphyrins, liver porphyrins, organ weights, and necropsies in all groups of animals. Complete histological examinations were performed on all control and high-dose animals; histology exams in lower dose groups were limited to the liver, spleen, thymus, heart, and muscle at 179 mg/kg-day, and only the liver at 89.3 mg/kg-day. Mortality occurred in 4/10 males and 3/10 females at 357 mg/kg-day, as well as in one male at 179 mg/kg-day. Final body weights were within 6% of control values in all groups of both sexes except for the 357 mg/kg-day males and females, which were 11 and 19% less than controls, respectively. Effects observed in the liver included histopathological changes at 357 mg/kg-day (centrilobular necrosis, necrosis of individual hepatocytes, and/or hepatocellular degeneration in 9/10 males and 9/10 females) and 179 mg/kg-day (necrosis of individual hepatocytes, hepatocellular degeneration and/or pigment deposition in 4/10 males). No compound-related liver lesions were observed in females at 179 mg/kg-day, mice of either sex at 89.3 mg/kg-day, or controls. Relative liver weights were

significantly increased at 357 mg/kg-day in both sexes, but there were no exposure-related changes in serum levels of ALT, AP or GGPT in either sex at any dose (no other clinical chemistry indices were examined in the mice). Additional effects, observed only at 357 mg/kg-day, included mineralization of the myocardial fibers of the heart and skeletal muscle (3/10 males and 8/10 females), and lymphoid depletion in the thymus (2/10 males and 2/10 females) and spleen (4/10 males and 2/10 females). There were no hematological changes considered to be biologically significant. The urinary concentration of coproporphyrin was 3-5 times higher than controls in the 357 mg/kg-day females. The increase in urinary coproporphyrin was considered to be moderate, but not indicative of porphyria, because total porphyrin concentration in the liver was only increased 2-fold in 357 mg/kg-day females, not altered in males at any dose level, and not accompanied by pigmentation indicative of porphyria observed by ultraviolet light at necropsy. The hepatic histopathology findings in mice indicate that the NOAEL and LOAEL are 89.3 and 179 mg/kg-day, respectively.

No information is available on reproductive toxicity following oral exposure to 1,2-dichlorobenzene. An oral developmental toxicity study of 1,2-dichlorobenzene is available as an abstract with inadequately reported methods and results. In this study (Ruddick et al., 1983), pregnant female Sprague-Dawley rats were administered 50, 100 or 200 mg/kg-day doses of 1,2-dichlorobenzene by gavage on gestational days 6-15 (use of controls not reported). Maternal body weight gain, 15 unspecified biochemical parameters, and histology were used to evaluate maternal toxicity. The fetuses were evaluated for litter size, fetal weights, deciduoma, skeletal and visceral changes, and histopathology. No teratological effects were reported. No other information regarding developmental or maternal toxicity was noted. Based on the limited available information, 200 mg/kg-day is a NOAEL for maternal and developmental toxicity of 1,2-dichlorobenzene in rats. This NOAEL is higher than the critical LOAEL of 89.3 mg/kg-day based on the subchronic evidence for liver effects in rats (NTP, 1985).

___I.A.5. CONFIDENCE IN THE ORAL RfD

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

The overall confidence in this RfD assessment is medium, reflecting medium confidence in the principal study and database. The principal study was conducted in two species and is chronic in duration, but is limited by the use of only two dose levels and no identifiable LOAEL. The oral database has sufficient subchronic studies to identify the liver as a target of toxicity and a critical LOAEL based on hepatotoxicity, but lacks adequate assessments of neurotoxicity and immunotoxicity, as well as endpoints known to be sensitive to other isomers of dichlorobenzene (e.g., thyroid and pituitary, as shown by oral testing with 1,3-dichlorobenzene). The only information on developmental toxicity is from a poorly reported study in rats; data in a second

species are lacking. Reproductive toxicity has not been evaluated following oral exposure, although relevant information is available from an inhalation two-generation study.

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

An RfC cannot be calculated for 1,2-dichlorobenzene due to inadequate data on effects of long-term exposures. Information on the toxicity of inhaled 1,2-dichlorobenzene in humans is limited to results of two industrial hygiene surveys, a workplace mortality study, and a series of case reports, as detailed in the Source Document (U.S. EPA, 2002). Findings included observations that occupational exposure can cause irritation of the eyes and respiratory passages, but none of the human data are sufficient for risk assessment. A short-term study in mice showed that the upper respiratory tract is a sensitive target for inhalation exposures to 1,2-dichlorobenzene, as serious nasal olfactory lesions occurred at concentrations below the lowest exposure levels that caused systemic effects in subchronic animal studies (U.S. EPA, 2002). The available subchronic inhalation studies did not evaluate the respiratory tract, indicating that a critical effect for long-term exposures to 1,2-dichlorobenzene cannot be identified. In the absence of an identifiable critical effect, derivation of an RfC for 1,2-dichlorobenzene is precluded.

__I.B.1. INHALATION RfC SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfC
	NOAEL:			
	LOAEL:			
	BMCL:			

*Conversion Factors and Assumptions --

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

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

UF = ...
MF =.....

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

___I.B.5. CONFIDENCE IN THE INHALATION RfC

Study -- _____
Data Base -- _____
RfC -- _____

The overall confidence in this RfC assessment is

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

Source Document -- _____

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 _____.

Other EPA Documentation -- _____

Agency Consensus Date -- __/__/__ *[note: 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 -- 1,2-Dichlorobenzene
CASRN -- 95-50-1
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

EPA concludes that *the data are inadequate for an evaluation of human carcinogenic potential for 1,2-dichlorobenzene*, under the draft revised guidelines for carcinogen risk assessment (U.S. EPA, 1999). These assessments are based on no human carcinogenicity data and inadequate evidence of carcinogenicity in animals.

___II.A.2. HUMAN CARCINOGENICITY DATA

None.

___II.A.3. ANIMAL CARCINOGENICITY DATA

Inadequate.

Data on cancer in animals are limited to one chronic oral bioassay in which no exposure-related tumors were found in rats and mice (NTP, 1985). The findings are inadequate evidence of carcinogenicity because it is unclear whether an MTD was achieved in either species, as detailed below.

In the NTP (1985) chronic rat study, groups of 50 male and 50 female F344/N rats were gavaged with 1,2-dichlorobenzene (>99% pure) in corn oil in doses of 0, 60, or 120 mg/kg, 5 days/week for 103 weeks (0, 42.9, or 85.7 mg/kg-day). Evaluations included clinical signs, body weight, and necropsy and histology on all animals. At 1 year, survival in males was 98-100% in the control and low-dose groups, and 88% in the high-dose group, while in females, it was 95-100% in all groups. At termination, survival in the 0, 42.9 and 85.7 mg/kg-day groups was 84, 72 and 38% in males and 62, 66 and 64% in females. Survival to termination in the high-dose male rats was significantly reduced compared with controls (19/50 vs. 42/50, $p<0.001$), but the difference appears to be mainly from causes incidental to treatment. There were 20 incidental deaths in the high-dose group compared to 4 in controls; according to NTP, of the 20 deaths, 3 were accidental, 5 were probably due to gavage error, and 12 may have been caused by aspiration. Due to the probable gavage-related deaths in the high-dose male rats, the lower survival of this group does not necessarily mean that the maximum tolerated dose was either reached or exceeded. Mean body weight was slightly reduced ($\approx$5% less than controls) in males throughout the study at 85.7 mg/kg-day; the only effect in females was a small increase compared to controls after week 32 in both dose groups (final body weights were 11-12% increased at 42.9 and 85.7 mg/kg-day). There were no compound-related increased incidences of nonneoplastic lesions in the liver, kidneys, or any other tissues, as discussed in Section I.A.2. of this file.

There were no 1,2-dichlorobenzene-related increases in tumor incidence in the rats (NTP, 1985). The incidence of adrenal gland pheochromocytomas was statistically significantly ($p<0.05$) increased in low-dose males by the life table test. (Mortality adjusted incidences were of 20.9, 40.5, and 21.7% in the control, low-dose and high-dose groups, respectively). However, the increase in low-dose males was not significant by the incidental tumor test (considered by NTP to be the more appropriate mortality-adjusted test for analysis of nonfatal types of tumors, such as adrenal pheochromocytomas) or by the Fisher Exact test (without mortality adjustment), nor was there a significant trend in the Cochran-Armitage test. No increase in pheochromocytomas was seen in high-dose males. The increased incidence of pheochromocytomas in the low-dose male rats was discounted by NTP (1985), because there was no dose-response trend or high-dose effect, no increased incidence in females, no observation of malignant pheochromocytomas, and questionable toxicological significance of the life table test results. In addition, pheochromocytomas were not considered by the NTP researchers to be a life-threatening condition. Incidences of interstitial-cell tumors of the testis were elevated in

control and treated groups (47/50, 49/50, 41/50), and occurred with a significant positive trend when analyzed by the life-table test. However, the increase detected by the life-table test was discounted by NTP because this tumor is not considered to be life threatening, and no significant results were obtained by the incidental tumor test, which is the more appropriate test for non-fatal tumors. The Cochran-Armitage test showed a significant negative trend for the interstitial cell tumors.

In the NTP (1985) chronic mouse study, groups of 50 male and 50 female B6C3F$_1$ mice were gavaged with 1,2-dichlorobenzene (>99% pure) in corn oil at doses of 0, 60 or 120 mg/kg on 5 days/week for 103 weeks (0, 42.9 or 85.7 mg/kg-day). Evaluations included clinical signs, body weight, and necropsy and histology on all animals. No clinical signs were reported, and mean body weight and survival were comparable in control and dosed mice throughout the study, indicating that it is unclear whether an MTD was achieved. The only exposure-related nonneoplastic lesion was renal tubular regeneration in high dose males, as discussed in Section I.A.2. There were no clear compound-related increased incidences of neoplasms in the mice. Incidences of malignant histiocytic lymphomas showed a significant positive dose-related trend in male mice (0/50, 1/50, 4/50) and female mice (0/49, 0/50, 3/49), but NTP considered numbers of animals with all types of lymphomas to be a more appropriate basis for comparison. Because malignant lymphocytic lymphomas occurred in male mice (7/50, 0/50, 0/50) with a significant negative dose-related trend, and the combined incidence of all types of lymphomas was not significantly different than that in controls for the male mice (8/50, 2/50, 4/50) or female mice (11/49, 11/50, 13/49) by any of the statistical tests, the increase in histiocytic lymphomas was discounted by NTP. Alveolar/bronchiolar carcinomas were significantly increased in the high-dose male mice (4/50, 2/50, 10/50). The incidences showed a significant positive increasing trend by the Cochran-Armitage test, but not by the life-table or incidental tumor test. The increase in alveolar/bronchilar carcinomas was discounted by NTP because the more appropriate combined incidence of male mice with alveolar/bronchiolar adenomas or carcinomas (8/50, 8/50, 13/50) was not significantly greater than controls in any of the tests. NTP (1985) concluded that there was no evidence of carcinogenicity in the male or female rats or mice.

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Genotoxic effects of 1,2-dichlorobenzene were investigated in various test systems with generally mixed results. Reverse mutation assays were negative in *S. typhimurium* and *E. coli* and positive in *S. cerevisiae*. Tests for DNA damage in *S. typhimurium*, *E. coli*, and *S. cerevisiae* were all negative, although positive in *B. subtilis* (Connor et al., 1985; Shimizu et al., 1983; NTP, 1987; Paolini et al., 1998; Waters et al., 1982). Results of a forward mutation assay in mouse lymphoma cells were positive (Myhr and Caspary, 1991), but tests for replicative DNA synthesis in cultured human lymphocytes and DNA repair in primary rat hepatocytes were negative (Perocco et al., 1983; Williams et al., 1989). Sister-chromatid exchanges were induced in Chinese hamster ovary (CHO) cells with activation, although chromosomal aberrations were not (Loveday et al., 1990). *In vivo* exposure induced micronucleus formation in mice (Mohtashamipur et al., 1987).

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

Not applicable.

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

Not applicable.

__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 -- __/__/__ *[note: 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 -- 1,2-Dichlorobenzene
CASRN -- 95-50-1
Last Revised -- 00/00/0000

__VI.A. ORAL RfD REFERENCES

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__VI.B. INHALATION RfC REFERENCES

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__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

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_VII. REVISION HISTORY

Substance Name -- 1,2_Dichlorobenzene
CASRN -- 95-50-1

Date	Section	Description
08/01/1989	I.A.	Oral RfD summary on-line
08/01/1989	VI.	Bibliography on-line
01/01/1990	II.	Carcinogen assessment now under review
06/01/1990	I.A.2.	Text edited
11/01/1990	II.	Carcinogen assessment on-line
11/01/1990	VI.C.	Carcinogen references added
01/01/1991	II.D.2.	Agency review and verification dates corrected
03/01/1991	I.A.7.	EPA contacts changed
01/01/1992	IV.	Regulatory Action section on-line
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 1,2-Dichlorobenzene.

_VIII. SYNONYMS

Substance Name -- 1,2-Dichlorobenzene
CASRN -- 95-50-1
Last Revised -- 00/00/0000

95-50-1
Benzene, 1,2-dichloro-
Bbenzene, o-dichloro-
Chloroben
Chloroden
Cloroben
p-Chlorophenyl chloride
DCB
o-Dichlorbenzene
o-Dichlor benzol

o-Dichlorobenzene
1,2-Dichlorobenzene
o-Dichlorobenzene
Dichlorobenzene, ortho
Dilantin db
Dilatin db
Dizene
Dowtherm e
NCI-c54944
ODB
ODCB
Orthodichlorobenzene
Orthodichlorobenzol
Special Termite Fluid
Termitkil
UN 1591