1,4-Dichlorobenzene

0552
1,4-Dichlorobenzene; CASRN 106-46-7; 00/00/0000

Human health assessment information on a chemical substance is included in IRIS only after a comprehensive review of toxicity data by U.S. EPA health scientists from several program offices, regional offices, and the Office of Research and Development. Sections I (Chronic Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the positions that were reached during the review process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website at http://www.epa.gov/iris/backgr-d.htm.

STATUS OF DATA FOR 1,4-DICHLOROBENZENE

File First On-Line 01/01/1994

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

_I. HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

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

1,4-Dichlorobenzene
CASRN – 106-46-7
Section I.A. Last Revised -- 00/00/0000

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (possibly threshold) mode of action. It is expressed in units of mg/kg-day. Please refer to the guidance documents at http://www.epa.gov/iris/backgr-d.htm for an elaboration of these concepts. Because RfDs can be derived for the noncarcinogenic health effects of substances that are also carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical 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. CHRONIC ORAL RfD SUMMARY

Critical Effect	Point of Departure*	UF	RfD
Liver lesions (diffuse hepatocellular hypertrophy)	BMD_{10}: 24 mg/kg-day $BMDL_{10}$: 9.1 mg/kg-day	300	0.03 mg/kg-day

1-year dog study

Monsanto Company, 1996

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*Conversion Factors and Assumptions – Doses were duration-adjusted for exposure on 5 days/week. The incidence of diffuse hepatocellular hypertrophy in male and female beagle dogs was analyzed by benchmark dose modeling. The BMDL associated with a 10% increased incidence ($BMDL_{10}$) of diffuse hepatocellular hypertrophy was selected as the point of departure for the RfD.

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES

Monsanto Company. (1996) One year study of p-dichlorobenzene administered orally via capsule to beagle dogs. In: Naylor, MW; Stout, LD; eds. Monsanto Company, Environmental Health Laboratory, St. Louis, MO; Study No. ML-94-210; MRID No. 439888-02. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

A study of chronic effects on dogs (beagles) evaluated the systemic effects of 1,4-dichlorobenzene in five male and five female beagle dogs per dose group 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 for 1 year (Monsanto Company, 1996). Controls received empty gelatin capsules. Because unexpectedly severe toxicity occurred at the highest dose level, the high dose was adjusted to 100 mg/kg-day during the third week of exposure for males and further reduced to 75 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 time-weighted average dose over the 1-year study in the high-dose group was 75 mg/kg-day, the same as that administered from week 6 to study termination.) The resulting final, time-adjusted doses were 0, 7, 36, and 54 mg/kg-day (adjusted for 5 day/week dosing schedule). One control male, two high-dose males, and one high-dose female dog died before study termination for causes considered unrelated to treatment. 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.

Absolute and relative liver weights were statistically significantly increased in both sexes at the two highest doses (36 and 54 mg/kg-day). Relative liver weights in these dose groups were approximately 150–170% of controls. Increases in absolute and/or relative adrenal (relative weight: 138–158% of controls) and thyroid (relative weights: 133 and 149% of controls) 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 weights of 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 of 1,4-dichlorobenzene 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, was 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/ductule hyperplasia was observed at the highest dose level in one male and one female dog. Additional hepatic effects included nodular hyperplasia, bile stasis, chronic active inflammation and hepatic portal inflammation (Monsanto Company, 1996).

Chronic active interstitial inflammation, pleural fibrosis and/or pleural mesothelial proliferation were also observed in the lungs of males at all test levels and females at the mid- and high-dose levels, but were not considered to be treatment-related because the occurrence was rare and severity differed little among the treated groups. Epithelial vacuolation in kidney collecting ducts was reported in a high-dose male and four females (one low-dose, one mid-dose, and two high-dose). The authors concluded that the lesion could be associated with exposure to the test chemical at the mid- and high-dose levels in the females where it was accompanied by increased kidney weights and, upon gross observation, renal discoloration (Monsanto Company, 1996).

Clinical pathology results revealed a few statistically significant differences in hematology and clinical chemistry parameters that were considered to be related to 1,4-dichlorobenzene exposure (Monsanto Company, 1996). At the 6-month sampling time point, hematologic parameters included a reduction in basophils at the high-dose level and an increase in platelet counts in the mid- and high-dose female dogs. The numbers of red blood cells (RBCs) were significantly reduced in both sexes at the high-dose level, while the hematocrit (HCT) was lowered in the high-dose males. At the terminal sampling time point, numbers of large unstained cells were reduced in both sexes, platelet count was increased in high-dose females, and mean corpuscular volume (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 (AP), alanine aminotransferase, aspartate aminotransferase (AST), and γ-glutamyl transpeptidase 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-dichlorobenzene caused a significant increase in absolute and relative liver weights in both male and female beagle dogs. This increase was accompanied by several liver lesions in the dosed groups that were considered either direct or indirect/adaptive effects of 1,4-dichlorobenzene. In addition to liver effects, effects were also observed in kidneys of high-dose males and in females at all dose levels. Clinical pathology results revealed statistically significant differences in hematologic and clinical chemistry parameters. Based on the histopathologic and clinical results, the authors concluded that the liver effects were the most sensitive endpoints in both female and male beagle dogs and identified a NOAEL of 10 mg/kg-day (adjusted dose: 7 mg/kg-day). The 50 mg/kg-day dose (adjusted dose: 36 mg/kg-day) was suggested as the LOAEL for liver effects (significantly increased absolute and relative liver weights accompanied by liver histopathologic findings). The liver effects observed in dogs in the Monsanto Company (1996) study were identified as the critical effect for derivation of the 1,4-dichlorobenzene RfD. Liver toxicity has been observed consistently in experimental animals. The dog appears to be more sensitive than rodents to the hepatotoxic effects of 1,4-dichlorobenzene.

The incidence of compound-related diffuse hepatocellular hypertrophy in male and female beagle dogs was analyzed by benchmark dose (BMD) modeling (U.S. EPA, 2000). Because a similar response was observed in the livers of male and female dogs in this study and because there was no clear evidence of a gender-specific response to 1,4-dichlorobenzene, male and female data were combined for purposes of BMD analysis.

All dichotomous models in the EPA Benchmark Dose Software (BMDS, version 1.3.2) (U.S. EPA, 2001) were fit to the incidence data for diffuse hepatocellular hypertrophy in male and female beagle dogs (combined). A 10% extra risk of diffuse hepatocellular hypertrophy was selected as the benchmark response (BMR). This BMR fell near the low end of the range of experimental dose levels (i.e., the observable range) and its selection is consistent with benchmark dose guidance (U.S. EPA, 2000). The log probit model provided the best fit to the data (as indicated by the lowest Akaike Information Criterion [AIC] with a goodness-of-fit *p*-value >0.1) and was used to derive the BMD_{10} and $BMDL_{10}$ of 24.0 and 9.06 mg/kg-day, respectively. Detailed BMD model results are provided in the *Toxicological Review of Dichlorobenzenes* (U.S. EPA, 2006).

The $BMDL_{10}$ of 9.06 mg/kg-day for 10% extra risk of diffuse hepatocellular hypertrophy in the beagle dogs was chosen as the point-of-departure for the RfD.

___I.A.3. UNCERTAINTY FACTORS

UF = 300

A default ten-fold uncertainty factor (UF) was used to account for uncertainty in extrapolating from dogs to humans (i.e., interspecies variability). Glucuronidation and sulfation are substantial detoxification pathways for 1,4-dichlorobenzene. Animal studies demonstrated that 22–36% of the administered dose of 1,4-dichlorobenzene was eliminated as glucuronic acid conjugate, and 27–65% of the administered dose was eliminated as sulfate conjugate (Hissink et al., 1997, 1996; Hawkins et al., 1980; Azouz et al., 1954). Hissink et al. (1997) studied the biotransformation and kinetics of 1,4-dichlorobenzene in male Wistar rats at three oral dose levels (10, 50, and 250 mg/kg). The study authors concluded that 1,4-dichlorobenzene was mainly metabolized to 2,5-dichlorophenol (~90%), which was detected in the urine as its sulfate (50–60%), glucuronide (20–30%), and the free form (5–10%). Minor metabolites were N-acetyl-cysteine-S-dihydro-hydroxy-1,4-dichlorobenzene and the corresponding dehydrated N-acetyl-cysteine-S-1,4-dichloro-benzene, which comprised ~10% of total metabolites. No hydroquinones were observed for the male Wistar rat, not even under conditions of induced oxidative metabolism; therefore, the potential for redox cycling is limited.

Krishnaswamy et al. (2003) studied the glucuronidation of serotonin in vitro and showed that dogs were among the poorest glucuronidaters based on the order of uridine diphosphoglucuronosyl transferase activities in animal liver microsomes where: rat > mouse > human > dog > rabbit. Although glucuronidation of serotonin measured in the above study may not be the same as hydroxylated metabolites of 1,4-dichlorobenzene, this study demonstrates significant differences in rates of glucuronidation between species. Species differences were also found for sulfation. Andersen (1985) studied the degree of tyrosine sulfation in 10 mammalian species. The percentage of sulfation varied from 24.4 ± 4.2 (mean ± SEM) in dogs to 46.8 ± 3.3 in humans, 55.9 ± 2.3 in rats, 64.8 ± 2.1 in mice, and 68.2 ± 2.8 in rabbits. Note that dogs were the poorest sulfaters while humans showed a percentage of sulfation that was twice that seen in dogs. Sulfation rates of rats and mice were closer to those in humans than to those in dogs. Furthermore, Fischer et al. (1995) demonstrated that after 2 and 6 hours of incubation the metabolism of 1,4-dichlorobenzene in human liver slices resulted in similar levels of glucuronide and sulfate conjugates as seen in Sprague-Dawley and F344 rats.

Since sulfation and glucuronidation are major detoxification pathways of 1,4-dichlorobenzene, mice and rats should be the least sensitive species as they have higher rates of sulfation and glucuronidation than dogs. This observation is consistent with the findings from in vivo toxicity studies in rodents and mice. The LOAEL in the National Toxicology Program (NTP, 1987) 13-week rat study (based on limited associated serum enzymes) was 214 mg/kg-day. The mouse LOAEL in the Eldridge et al. (1992) study was 429 mg/kg-day (and the NOAEL was 214 mg/kg-day). In the Monsanto Company (1996) 1-year dog study, the NOAEL was 7 mg/kg-day and the LOAEL was 36 mg/kg-day.

Human metabolism of 1,4-dichlorobenzene is similar to the metabolism in rats and mice, with activities of glucuronide and sulfate conjugation in humans similar to the rat. Like rats and mice, humans are expected to be less sensitive to 1,4-dichlorobenzene toxicity than dogs.

Nevertheless the information on species differences in rates of glucuronidation and sulfation is insufficient to warrant a less than 10 default uncertainty factor, particularly without knowledge of the mode of action. This is based on the fact that there appear to be no data for the direct comparison of the toxicokinetics of 1,4-dichlorobenzene in dogs and humans. Sulfation and glucuronidation are important in only one portion of the 1,4-dichlorobenzene metabolic pathway (CYP2E1 appears to be the first step, at least in rats) and no comparative data are available to address the potential interspecies differences with respect to other toxicokinetic parameters. Support for the dog as a species more sensitive to 1,4-dichlorobenzene than humans (and thus an UF for interspecies variability smaller than the default of 10) comes from information on the glucuronide and sulfation phase II pathways. However, baseline studies with human liver slices identify glutathione as the predominant phase II metabolite. It is not known to what extent the phase II biotransformation reactions influence the overall metabolism (detoxification) of 1,4-dichlorobenzene. Because the importance of the phase II biotransformation reaction on toxicity is not known, interspecies differences in the toxicity of 1,4-dichlorobenzene cannot be predicted. Therefore, the default ten-fold UF was used to account for uncertainty in extrapolating from dogs to humans (i.e., interspecies variability).

A default 10-fold UF was used to account for interindividual variation in sensitivity to 1,4-dichlorobenzene in human populations. The degree to which humans of varying gender, age, health status, or genetic makeup may vary in disposing of, or responding to ingested 1,4-dichlorobenzene has not been studied. Accordingly, a 10-fold UF for variation in the general population was used.

A subchronic to chronic UF was not necessary because the point of departure was derived from a chronic study.

A UF to account for the extrapolation from a LOAEL to a NOAEL was not applied because BMD modeling was used to determine the point of departure for derivation of the 1,4-dichlorobenzene RfD.

A UF of 3 was used to account for database deficiencies. Although the animal oral toxicity database is substantial and includes a chronic toxicity study 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 2-generation reproductive and developmental toxicity study in rats (Bornatowicz et al., 1994), developmental toxicity has been evaluated in only one species, the rat. In the two generation rat study (Bornatowicz, 1994) increased pup mortality was reported at maternal exposures of greater than or equal to 90 mg/kg-day. This frank effect occurred at a dose that was within an order of magnitude of the point of departure. Therefore, a UF factor of 3 was used to account for the uncertainty associated with the database with respect to both the developmental and reproductive data.

___I.A.4. ADDITIONAL STUDIES/COMMENTS

Information on the toxic effects of 1,4-dichlorobenzene in orally exposed humans is limited to two case reports describing hematologic changes, particularly anemia, following known or presumed repeated ingestion of unknown doses of the compound in commercial products (Campbell and Davidson, 1970; Hallowell, 1959). Decreases in RBC count, HCT, and hemoglobin were observed in a subchronic oral study in rats (NTP, 1987), although the 1,4-dichlorobenzene dose level causing these hematologic changes also induced liver and kidney toxicity in chronically exposed rats and mice, as discussed below.

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. Liver and kidney effects are the most extensively studied and most consistently observed findings. A relatively small amount of information is available indicating that 1,4-dichlorobenzene can affect the hematologic system and adrenal and thyroid glands at exposure levels equal to or higher than those causing liver and kidney effects. Reproductive and developmental studies have been performed in rats indicating that offspring are particularly sensitive to 1,4-dichlorobenzene toxicity during the postnatal preweaning period.

Hepatic effects induced by subchronic and chronic oral exposures to 1,4-dichlorobenzene ranged from increased liver weight and hepatocyte enlargement to hepatocellular degeneration, lesions, necrosis, and tumors in dogs, rats, mice, and rabbits. 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 also were induced. Increased liver weight was the most sensitive hepatic endpoint in subchronic studies in rats, observed at doses as low as 107 mg/kg-day for 4–13 weeks and 135 mg/kg-day for 192 days (Umemura et al., 1998; Lake et al., 1997; Hollingsworth et al., 1956), but was not accompanied by concomitant enzymatic or histopathologic changes, and was therefore not considered adverse. Hepatocellular hypertrophy and decreased serum triglycerides occurred in rats exposed to ≥214 mg/kg-day for 13 weeks (Lake et al., 1997; NTP, 1987). 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). The findings at 270 mg/kg-day (Hollingsworth et al., 1956) seem inconsistent with NTP (1987) 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).

Hepatocellular degeneration was observed 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.

Renal changes, including hyaline droplet accumulation, increased kidney weights, and tubular lesions were observed in studies of subchronic and chronic oral exposure to 1,4-dichlorobenzene in male rats at doses ≥75 mg/kg-day (Lake et al., 1997; Bomhard et al., 1988; NTP, 1987). These findings are generally recognized as attributable to the α_{2u}-globulin

nephropathy syndrome, which is specific to male rats and not relevant to humans (see further discussion in the *Toxicological Review of Dichlorobenzenes* [U.S. EPA, 2006]). 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, indicated that chronic exposure to 1,4-dichlorobenzene had a nephrotoxic potential in female rats, and in mice of both sexes, and that the LOAEL for renal effects was 214 mg/kg-day, the lowest tested chronic dose in these species and sexes.

Subchronic or chronic exposure to 1,4-dichlorobenzene caused other effects in dogs, rats, and mice at doses equal to or higher than the LOAEL for liver and kidney effects, including hematologic changes (decreased basophils, RBC count, HCT, and hemoglobin, and increased platelet count and MCV), hyperplasia in the adrenal capsule and mandibular lymph node in mice, and thyroid gland follicular hyperplasia in mice. Developmental toxicity studies provided no indication that 1,4-dichlorobenzene was teratogenic in rats exposed to doses as high as 1000 mg/kg-day during gestation, although fetotoxicity occurred at maternally toxic doses of ≥500 mg/kg-day (Giavini et al., 1986; Ruddick et al., 1983). Decreased maternal weight gain and increased incidence of extra ribs, a skeletal variation attributable to the maternal toxicity rather than a teratogenic effect of the chemical, occurred in rats at gestational doses ≥500 mg/kg-day, but not at 250 mg/kg-day (the lowest tested dose) (Giavini et al., 1986).

Reproductive and developmental toxicity were evaluated in a two-generation study in rats (Bornatowicz et al., 1994). No effects on mating and fertility indices were observed at any dose, although toxicity occurred in the offspring at doses ≥90 mg/kg-day, including reduced birth weight (F_1 pups) and increased total number of deaths from birth to postnatal day 4 (F_1 and F_2 pups), clinical manifestations of dry and scaly skin and tail constriction (F_1 and F_2 pups), reduced neurobehavioral performance (F_2 pups), and increased relative liver weight in adult F_1 males. No exposure-related changes were found at 30 mg/kg-day, indicating that this was the NOAEL for reproductive and developmental toxicity in rats.

In summary, liver, kidney, and perinatal developmental toxicity are the main observed effects of subchronic and chronic oral exposure to 1,4-dichlorobenzene in animals. The rat and mouse are less sensitive to liver toxicity than the dog; the hepatic LOAEL in dogs was 36 mg/kg-day, which is the same as the LOAEL for kidney effects in female beagle dogs (Monsanto Company, 1996). There is sufficient evidence from a two-generation study in rats that oral exposure to 1,4-dichlorobenzene can cause developmental toxicity perinatally and during the later pre-weaning period, including decreased birth weight and neonatal pup survival, at doses ≥90 mg/kg-day.

___I.A.5. CONFIDENCE IN THE CHRONIC ORAL RfD

Study -- Medium
Data Base -- Medium-High
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, histopathology, and clinical endpoints. The animal oral toxicity database for 1,4-dichlorobenzene 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.

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

Source Document -- U.S. EPA (2006).

This assessment was peer reviewed by a group of external scientists. Comments from the peer reviewers were evaluated carefully and considered by the Agency during the finalization of this assessment. A record of these comments is included in Appendix A of the *Toxicological Review of Dichlorobenzenes* (U.S. EPA, 2006).

Agency Completion Date -- __/__/__

___I.A.7. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

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

1,4-Dichlorobenzene
CASRN – 106-46-7
Section I.B. Last Revised -- 00/00/0000

The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). The inhalation RfC (generally expressed in units of mg/m^3) is analogous to the oral RfD and is similarly intended for use in risk assessments

for health effects known or assumed to be produced through a nonlinear (possibly threshold) mode of action.

Inhalation RfCs are derived according to *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). Because RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical 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.

The previous RfC for 1,4-dichlorobenzene, posted on the IRIS database in 1992, was 0.8 mg/m^3. This RfC was based on a **NOAEL (HEC) of 75 mg/m^3** from a rat multigeneration reproductive study (Chlorobenzene Producers Association, 1986; also cited as Tyl and Neeper-Bradley, 1989) and application of a UF of 100.

__I.B.1. CHRONIC INHALATION RfC SUMMARY

Critical Effect	Point of Departure*	UF	RfC
Eosinophilic changes to the olfactory epithelium in female rats	$BMC_{10(HEC)}$: 3.97 mg/m^3 $BMCL_{10(HEC)}$: 2.52 mg/m^3	30	0.08 mg/m^3

Chronic study in rats and mice

Aiso et al. (2005b); Japan Bioassay Research Center (1995)

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*Conversion Factors and Assumptions -- 1 ppm = 6.01 mg/m^3 (at 25 °C and 760 mm Hg). The NOAEL and LOAEL were adjusted to continuous exposure. Benchmark dose modeling was conducted on the eosinophilic changes to the olfactory epithelium in female rats. The BMCL associated with a 10% increase in olfactory effects ($BMCL_{10}$) was selected as the point of departure for the RfC. The $BMCL_{HEC}$ was calculated using the rules for a category 1 gas with effects in the extrathoracic region as described by U.S. EPA (1994): HEC = human equivalent concentration = duration-adjusted concentration × $RGDR_{ET}$, where $RGDR_{ET}$ = regional gas dose ratio for the extrathoracic region = 0.16. See the *Toxicological Review of Dichlorobenzenes* (U.S. EPA, 2006) for more details.

___I.B.2. PRINCIPAL AND SUPPORTING STUDIES

Aiso, S; et al. (2005b) Carcinogenicity and chronic toxicity in mice and rats exposed by inhalation to para-dichlorobenzene for two years. J Vet Med Sci 67:1019-1029.

Japan Bioassay Research Center. (1995) Toxicology and carcinogenesis studies of p-dichlorobenzene in F344/DuCrj rats and Crj:BDF1 mice (2-year inhalation studies). Submitted to the U.S. Environmental Protection Agency by the Japan Bioassay Research Center.

In a chronic evaluation of the toxicity of inhaled 1,4-dichlorobenzene (Japan Bioassay Research Center [JBRC], 1995), groups of rats and mice of both sexes were exposed to 0, 20, 75, or 300 ppm for 6 hours/day, 5 days/week for 104 weeks. This study was subsequently published by Aiso et al. (2005b). A large number of biochemical changes occurred in high-dose rats and mice, but could not be evaluated because the study did not present data for these endpoints. Exposure to 1,4-dichlorobenzene resulted in increased incidence of moderate or greater severity eosinophilic changes of the olfactory epithelium in both sexes of rats (1/50, 2/50, 2/50, and 7/50 lesions in males and 27/50, 29/50, 39/50, and 47/50 lesions in females in the 0, 20, 75, and 300 ppm groups, respectively); the increases were statistically significant in 300 ppm males and 75 and 300 ppm females. In 300 ppm female rats only, significantly increased incidences of eosinophilic changes and metaplasia of the respiratory epithelium were seen, and an increased incidence of mineralization of the renal papilla and centrilobular hepatocellular hypertrophy was reported in 300 ppm male rats. On histologic examination, male mice showed a significant increase in centrilobular hepatocellular hypertrophy in the 300 ppm group only (0/49, 0/49, 0/50, and 34/49 in the 0, 20, 75, and 300 ppm groups, respectively), and a significant increase in mineralization of the testis in the 75 and 300 ppm groups (27/49, 35/49, 42/50, and 41/49 in the 0, 20, 75, and 300 ppm groups, respectively). No nonneoplastic changes in histologic endpoints were reported in female mice. Thus, the chronic inhalation data identified a NOAEL of 20 ppm and a LOAEL of 75 ppm for eosinophilic changes of the olfactory epithelium in female rats, and mineralization of the testis in male mice.

Benchmark dose analysis was performed on the incidence data for both eosinophilic changes in the olfactory epithelium in female rats, and mineralization of the testis in male mice from the JBRC study (Aiso et al. 2005b; JBRC, 1995). The results for the nasal lesions are presented in the *Toxicological Review of Dichlorobenzenes*, Appendix B.4 (U.S. EPA, 2006), and the results for the testicular lesions are presented in Appendix B.5 (U.S. EPA, 2006).

The exposure concentrations were duration-adjusted for continuous exposure, using the following formula:

$$Conc_{[continuous]} = Conc \times 5 \text{ days}/7 \text{ days} \times 6 \text{ hours}/24 \text{ hours}$$

The resulting duration-adjusted exposure concentrations were 0, 3.5, 13.4, and 53.3 ppm for rats, and 0, 3.6, 13.4, and 53.3 ppm for mice.

For changes in the olfactory epithelium in female rats, the HEC was calculated using the rules for a category 1 gas with effects in the extrathoracic region, as described by and using reference values found in U.S. EPA (1994) and U.S. EPA (1988):

$$HEC = \text{Duration-adjusted concentration} \times RGDR_{ET}$$

where:

$RGDR_{ET} = 0.16$

(see *Toxicological Review of Dichlorobenzenes*, Section 5.2.3.2.1 for calculation

of the $RGDR_{ET}$)

The HECs for the chronic rat study are therefore 0, 0.56, 2.1, and 8.5 ppm. These correspond to HECs of 0, 3.4, 12.6, and 51.1 mg/m^3 for the 0, 20, 75, and 300 ppm exposure groups, respectively (using a ppm to mg/m^3 conversion factor of 6.01). The incidence of olfactory epithelial lesions of moderate or greater severity in female rats, from the JBRC study (Aiso et al., 2005b; JBRC, 1995), was 27/50, 29/50, 39/50, and 47/50 for the 0, 20, 75, and 300 ppm groups, respectively. Dose-response modeling of the incidence data was performed using dichotomous models available in U.S. EPA's Benchmark Dose Software (BMDS, version 1.3.2) (U.S. EPA, 2001). Based on BMD technical guidance (U.S. EPA, 2000) and insufficient biological data to indicate otherwise, a 10% change in the incidence of the olfactory epithelial lesions was used as the BMR. The results of model fits, including benchmark concentrations (BMC_{10}) and the 95% lower bound on the benchmark concentration ($BMCL_{10}$), are presented in Appendix B.4 in the *Toxicological Review of Dichlorobenzenes* (U.S. EPA, 2006).

With the exception of the quantal quadratic model, all models provided an adequate fit of the data (as indicated by the χ^2 goodness-of-fit statistic, p>0.1). The log probit model provided the best fit to the data (as indicated by the lowest AIC) and was selected to estimate the BMC_{10} and $BMCL_{10}$ of 3.97 and 2.52 mg/m^3, respectively.

For changes in the testis of male mice, the HEC was calculated using the equations for a category 3 gas with extrarespiratory effects, as described by U.S. EPA (1994). The HEC for extrarespiratory effects produced by a category 3 gas is calculated by multiplying the duration-adjusted concentration with the ratio of blood:gas partition coefficients ($H_{b/g}$) in animals and humans (U.S. EPA, 1994). $H_{b/g}$ values were not available for 1,4-dichlorobenzene in mice and humans. In the absence of data on the blood/gas coefficients, a default value of 1 was used as the ratio of partition coefficients. The HEC values for the mouse were therefore 0, 3.6, 13.4, and 53.3 ppm, corresponding to HECs of 0, 22, 81, and 320 mg/m^3 for the 0, 20, 75, and 300 ppm groups, respectively. Incidence of the lesion was 27/49, 35/49, 42/50, and 41/49 in the 0, 20, 75, and 300 ppm groups, respectively. BMD analysis was performed on the data for mineralization of mouse testis using the dichotomous models in the Benchmark Dose Software, version 1.3.2, with a 10% change in incidence (the default assumption) being used as the BMR. These results are presented in Appendix B.5 in the *Toxicological Review of Dichlorobenzenes* (U.S. EPA, 2006).

Initial attempts to fit the testis data failed to generate an adequate fit (p>0.1). Data from the high-dose group were dropped to see if improved model fits could be achieved. As assessed by the χ^2 goodness-of-fit test, all models provided adequate fits to the data set that excluded data from the high-exposure group (χ^2 goodness-of-fit p-value > 0.1). The log logistic model provided the best fit to the data (as indicated by the lowest AIC); the BMC_{10} and $BMCL_{10}$ using this model were 4.78 and 2.26 mg/m^3, respectively.

A BMR of 10%, however, was associated with an exposure concentration that fell well below the experimental levels used in this study (i.e., outside the observable range); see

Appendix B.5 of the *Toxicological Review of Dichlorobenzenes* (U.S. EPA, 2006). To obtain a BMC within the observable range, it would have been necessary to use a BMR of approximately 40% excess risk of mineralization of the testes.

Because the BMC_{10} for changes to the olfactory epithelium was within the range of observable data, BMD modeling using this endpoint provided better resolution of the dose-response curve in the region of the benchmark response of 10% than did mineralization of the testes. The BMD analysis of the mouse testes data set, however, provided support for the $BMCL_{10}$ of 2.52 mg/m^3 as an appropriate point of departure for the RfC. Therefore, the $BMCL_{10}$ of 2.52 mg/m^3 based on eosinophilic changes to the olfactory epithelium was selected as the basis for the point of departure for the 1,4-dichlorobenzene RfC.

___I.B.3. UNCERTAINTY FACTORS

UF = 30

A threefold UF was 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 was addressed by the dosimetry adjustment (i.e., calculation of the HEC for time and concentration). Accordingly, only the pharmacodynamic area of uncertainty remained as a partial factor for interspecies uncertainty ($10^{0.5}$ or approximately 3).

A 10-fold UF was used to account for variation in sensitivity within human populations. As data were not available on variability within the human population with regard to sensitivity to 1,4-dichlorobenzene inhalation, a default value of 10 was applied.

A UF for database deficiencies was not needed based on the following. There are chronic inhalation toxicity studies of 1,4-dichlorobenzene in rats and mice (Aiso et al., 2005b; JBRC, 1995). The prenatal developmental toxicity of inhaled 1,4-dichlorobenzene has been sufficiently studied (Hayes et al., 1985; Hodge et al., 1977). A well-conducted two-generation reproductive study also exists (Tyl and Neeper-Bradley, 1989).

A subchronic to chronic UF was unnecessary because the point of departure was derived from a chronic study.

A UF to account for the extrapolation from a LOAEL to a NOAEL was not applied because BMD modeling was used to determine the point of departure for derivation of the 1,4-dichlorobenzene RfC.

___I.B.4. ADDITIONAL STUDIES/COMMENTS

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 the findings are limited by a lack of adequate quantitative exposure information and/or verification that 1,4-dichlorobenzene was the sole causal factor (Reygagne et al., 1992; Miyai et al., 1988; Cotter, 1953). The hepatic, neurologic, and eye/nose irritation observations in humans were consistent with effects observed in animals exposed to high concentrations of the chemical.

Additional information on the inhalation effects of 1,4-dichlorobenzene in animals includes results from multispecies subchronic toxicity studies (Aiso et al., 2005a, Hollingsworth et al., 1956), a subchronic immunotoxicity study in guinea pigs (Suzuki et al., 1991), and chronic toxicity studies in rats and mice (Imperial Chemical Industries [ICI], 1980; Riley et al., 1980). One subchronic toxicity study (Asio et al., 2005a) exposed BDF_1 mice and F344 rats of both sexes (6 h/d and 5 d/wk) to inhalation of 25, 55, 120, 270 or 600 ppm (v/v) 1,4-dichlorobenzene vapor for 13 weeks. The exposure to 1,4-dichlorobenzene vapor retarded the growth rate in the male mice, and induced hepatotoxicity in the mice and rats of both sexes and renal and hematological toxicity in the male rates. Hepatotoxicity was characterized by increased liver weight, hepatocellular hypertrophy, and increased serum levels of total cholesterol. Liver necrosis and increased serum levels of AST and ALT were observed in the exposed mice, whereas these changes, which indicate hepatocellular death, did not occur in any of the exposed rats. Renal lesions occurred only in 1,4-dichlorobenzene-induced male rats. The NOAEL was 120 ppm for the hepatic endpoint in mice and for the renal endpoint in rats.

In another subchronic toxicity study rats, mice, guinea pigs, rabbits, and monkeys were exposed to 96 or 158 ppm for 7 hours/day, 5 days/week for 5–7 months (Hollingsworth et al., 1956). In additional experiments, animals were also exposed to 341 ppm for 6 months (rats and guinea pigs) or 798 ppm for 23–69 exposures (rats, guinea pigs, and rabbits). The experiments with rabbits and monkeys exposed to levels of 96 or 158 ppm were limited by small numbers of animals (one to two/group). Hepatic changes were observed, including increased relative liver weight and slight histologic alterations of questionable toxicological significance in rats at 158 ppm (no effects at 96 ppm), with more severe hepatic histopathology (e.g., cloudy swelling and necrosis) reported in guinea pigs at 341 ppm, and in rats, guinea pigs, and rabbits at 798 ppm. Other effects observed in the animals exposed to 798 ppm included eye irritation and frank signs of neurotoxicity (e.g., marked tremors). The subchronic immunotoxicity study found no effects in mice exposed to $\leq$50 ppm for 12 weeks (highest tested concentration, exposure schedule not specified) (Suzuki et al., 1991).

In the chronic studies (ICI, 1980; Riley et al., 1980), rats of both sexes and female mice were exposed to 75 or 500 ppm for 5 hours/day, 5 days/week for up to 76 weeks (rats) or 57 weeks (mice), followed by 32 weeks (rats) or 18–19 weeks (mice) without exposure. There were no exposure-related histopathologic changes in the nasal cavity or other tissues in either species. Liver and kidney weights were increased in rats of both sexes at 500 ppm (in females liver

weights were increased at ≥75 ppm after 26–27 weeks of exposure), but the toxicological significance is questionable due to the negative histopathology findings and the lack of related clinical chemistry effects. Evaluation of the mouse data is limited by insufficiencies in the available summary of the study.

Additional data on effects of inhaled 1,4-dichlorobenzene were provided by reproduction studies in rats and mice (Tyl and Neeper-Bradley, 1989; Anderson and Hodge, 1976) and developmental toxicity studies in rats and rabbits (Hayes et al., 1985; Hodge et al., 1977). A two-generation reproduction study was conducted in male and female rats exposed to 66, 211, or 538 ppm for 6 hours/day, 5 days/week for 10 weeks before mating and subsequently through the F_1 generation (Tyl and Neeper-Bradley, 1989). There were no effects on reproductive parameters in either generation in the absence of parental toxicity. Systemic toxicity occurred at all dose levels in F_0 and F_1 adult rats (Tyl and Neeper-Bradley, 1989). Changes indicative of α_{2u}-globulin nephropathy were found in adult males of both generations at ≥66 ppm, but this syndrome is specific to male rats and not relevant to humans. Relative liver weights were increased in adult F_0 males at ≥66 ppm, F_1 males and F_0 females at ≥211 ppm, and F_1 females at 538 ppm; absolute liver weights were increased in adult F_0 males at ≥211 ppm, and in F_1 males and F_0 and F_1 females at 538 ppm. The increases in liver weight were more pronounced in males than in females and were statistically significant in these groups, but toxicological significance was questionable due to a lack of accompanying degenerative histopathologic effects. The only histopathologic finding in the liver was hepatocellular hypertrophy in both sexes and generations at 538 ppm. In the absence of other histopathologic lesions the liver effects were considered adaptive. Other effects at 538 ppm included clinical signs (e.g., tremors) in adults and increased stillbirths and perinatal mortality in F_1 and/or F_2 litters. The NOAEL and LOAEL were 211 and 538 ppm, respectively, based on the evidence for parental clinical signs and postnatal toxicity in the offspring. Anderson and Hodge (1976) found no effects on reproductive performance in male mice exposed for 6 hours/day for 5 days prior to weekly mating with unexposed females for 8 weeks. No maternal or 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 was 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, which was also maternally toxic as shown by body weight loss early in gestation (Hayes et al., 1985).

___I.B.5. CONFIDENCE IN THE CHRONIC 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 was generally well conducted and examined an array of endpoints. The experimental inhalation toxicity database for inhaled 1,4-dichlorobenzene is reasonably complete. The database includes chronic inhalation studies in two

species (rats and mice), a prenatal developmental toxicity study, and a two-generation reproductive study. Information on the systemic toxicity of subchronic inhalation exposure is available from a multiple species study, although the subchronic data are generally compromised by reporting insufficiencies.

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

Source Document -- U.S. EPA (2006)

This assessment was peer reviewed by a group of external scientists. Comments from the peer reviewers were evaluated carefully and considered by the Agency during the finalization of this assessment. A record of these comments is included in Appendix A of the *Toxicological Review of Dichlorobenzenes* (U.S. EPA, 2006).

Agency Completion Date -- __/__/__

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

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

1,4-Dichlorobenzene
CASRN – 106-46-7
Section II. Last Revised -- 00/00/0000

This section 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 and inhalation exposure. Users are referred to Section I of this file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS are described in the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) and the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b). The quantitative risk estimates are derived from the application of a low-dose extrapolation procedure, and are presented in two ways to better facilitate their use. First, route-specific risk values are presented. The “oral slope factor” is an upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a “unit risk” is an upper bound on the estimate of risk per unit of concentration, either per μg/L drinking water (see Section II.B.1.)

or per μg/m^3 air breathed (see Section II.C.1.). Second, the estimated concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000 is also provided.

__II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CHARACTERIZATION

Under the Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005a), 1,4-dichlorobenzene is considered likely to be carcinogenic to humans by both the oral and inhalation routes based on evidence of cancer in mice at multiple sites and by oral and inhalation exposure; tumors consisted of liver tumors, including hepatoblastomas (a rare type of hepatocellular carcinoma) in male and female mice by both oral and inhalation routes of exposure and bronchoalveolar tumors in female mice exposed by inhalation.

In the NTP (1987) gavage study, there was a positive dose-related trend for hepatocellular adenomas and carcinomas in male and female mice. Hepatoblastoma, an extremely rare form of hepatocellular carcinoma, also occurred in 4/50 high-dose male rats. NTP (1987) reported that only one hepatoblastoma had been observed among 6047 male and female control mice (vehicle and untreated controls combined).

In the 2-year inhalation bioassay of 1,4-dichlorobenzene (Aiso et al., 2005b; JBRC, 1995), investigators reported a statistically significant positive trend in hepatocellular adenomas and carcinomas in male and female mice, liver histiocytic sarcomas in male mice, and bronchoalveolar carcinoma in female mice. Consistent with the findings of the oral gavage NTP bioassay, Aiso et al. (2005b) observed a statistically significant increase in hepatoblastomas in male and female mice; the occurrence of this type of liver tumor was rare in JBRC historical control animals (10/1496 and 0/1498 male and female BDF1 mice, respectively).

The increased incidence of male rat kidney tumors following oral exposure (NTP, 1987) was not considered relevant to humans because the mechanism (α_{2u}-globulin nephropathy) is specific to male rats.

Additional information on mode of action of 1,4-dichlorobenzene carcinogenicity is discussed in the *Toxicological Review for Dichlorobenzenes* (U.S. EPA, 2006).

___II.A.2. HUMAN CARCINOGENICITY DATA

Inadequate. The carcinogenicity of 1,4-dichlorobenzene in humans has not been investigated.

___II.A.3. ANIMAL CARCINOGENICITY DATA

Sufficient. Information on carcinogenicity in animals is available from chronic oral and inhalation studies in rats and mice (Aiso et al., 2005b; JBRC, 1995; NTP, 1987; ICI, 1980; Riley et al., 1980), as well as from subchronic initiation-promotion studies in rats (Umemura et al., 2000; Gustafson et al., 1998).

Chronic oral bioassays were conducted in rats and mice that were exposed to 1,4-dichlorobenzene doses of 107 or 214 mg/kg-day (male rats) or 214 or 429 mg/kg-day (female rats and mice of both sexes) for 103 weeks (NTP, 1987). Kidney tumors were induced in male rats, as shown by a dose-related increase in the incidence of renal tubular cell adenocarcinomas that was statistically significantly greater than controls in the high-dose group. Male rats additionally had a dose-related increase in the incidence of mononuclear cell leukemia that was statistically significant in the high-dose group, although the increase was considered marginal because it was comparable to the historical control incidence. No indication of carcinogenicity was found in female rats. Findings in mice included liver cancer in both sexes, as shown by positive dose-related trends for hepatocellular adenomas and carcinomas, with incidence in low-dose males and high-dose males and females significantly greater than in controls. Hepatoblastoma, an extremely rare form of hepatocellular carcinoma, also occurred in four high-dose male mice. The incidence of hepatoblastoma was increased, but did not reach statistical significance. Comparison to historical control incidence (01/1091 in vehicle control and 0/1784 in untreated control male mice, and 0/1092 in vehicle control and 1/2080 untreated control female mice) suggested that the finding was likely related to exposure. Other neoplastic findings included marginal increases in adrenal pheochromocytomas in male mice.

The only other information regarding 1,4-dichlorobenzene carcinogenicity in an oral exposure comes from two-stage studies that found no indication of kidney tumor initiation or liver tumor promotion by 1,4-dichlorobenzene in rats (Umemura et al., 2000; Gustafson et al., 1998). There was no kidney tumor initiating activity of 1,4-dichlorobenzene in rats that were orally administered 214 mg/kg-day for 13 weeks, followed by promotion with trisodium nitrilotriacetic acid for up to 39 weeks (Umemura et al., 2000). Preneoplastic foci in the liver were not increased in rats that were initiated with a single intraperitoneal injection of diethylnitrosamine, followed 2 weeks later by oral promotion with $\leq$58.8 mg/kg-day doses of 1,4-dichlorobenzene for 6 weeks (Gustafson et al., 1998).

Effects of chronic inhalation were investigated in rats of both sexes and female mice that were exposed to 75 or 500 ppm 1,4-dichlorobenzene for 5 hours/day, 5 days/week for up to 76 weeks (rats) or 57 weeks (female mice), followed by 36 weeks (rats) or 19 weeks (female mice) without exposure (ICI, 1980; Riley et al., 1980). There were no neoplastic or any other histopathologic changes in the liver, kidneys, or other tissues in rats or female mice. The adequacy of these studies for carcinogenicity evaluation is limited by failure to reach the maximum tolerated dose, less-than-lifetime exposure durations, and short observation periods in both species. The mouse study is further limited by lack of data in males (a group of male mice was terminated due to high early mortality from fighting and probable respiratory infection), as well as unavailability of a complete study report.

In a more recent bioassay conducted according to Organization for the Economic Cooperation and Development (OECD) testing guidelines and in conformity with OECD Principles of Good Laboratory Practice, rats and mice were exposed to 0, 20, 75, or 300 ppm of 1,4-dichlorobenzene for 6 hours/day, 5 days/week for 104 weeks (Aiso et al., 2005b; JBRC, 1995). No evidence of compound-related tumor formation was reported in either sex of rats. In

male mice, increased incidences of hepatocellular carcinoma and histiocytic sarcoma were seen in animals exposed to the highest exposure concentration only. In females, increased incidences of hepatocellular carcinoma and combined bronchoalveolar adenoma and carcinoma were seen in high-dose animals only, while the incidence of hepatocellular adenoma was elevated in the low-exposure and high-exposure groups, but not in the mid-exposure group. The incidence of hepatoblastoma, a rare form of hepatocellular carcinoma, was statistically significantly increased in 300 ppm male and female mice.

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

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 *Toxicological Review of Dichlorobenzenes* (U.S. EPA, 2006). Negative results were reported in the majority of a variety of assays, including gene mutation in *Salmonella 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 (Tegethoff et al., 2000; Robbiano et al., 1999; Canonero et al., 1997; Morita et al., 1997; Miyagawa et al., 1995; Mohtashamipur et al., 1987; NTP, 1987). 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. Overall, the available genotoxicity data are insufficient to determine whether 1,4-dichlorobenzene is genotoxic.

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

___II.B.1. SUMMARY OF RISK ESTIMATES

____II.B.1.1. Oral Slope Factor—2×10^{-2} per mg/kg-day

The oral slope factor is derived from the LED_{50}, the 95% lower bound on the exposure associated with a 50% extra cancer risk, by dividing the risk (as a fraction) by the LED_{50}, and represents an upper bound, continuous lifetime exposure risk estimate:

LED_{50}, lower 95% bound on exposure at 50% extra risk —30.3 mg/kg-day
ED_{50}, central estimate of exposure at 50% extra risk—37.1 mg/kg-day

The slope of the linear extrapolation from the central estimate ED_{50} is 0.5/(37.1 mg/kg-

day) = 1×10^{-2} mg/kg-day.

The slope factor for 1,4-dichlorobenzene should not be used with exposures exceeding the point of departure (30 mg/kg-day), because above this level the fitted dose-response model better characterizes what is known about the carcinogenicity of 1,4-dichlorobenzene.

____II.B.1.2. Drinking Water Unit Risk*—5×10^{-7} per µg/L

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Lower Bound on Concentration Estimate*
10^{-4} (1 in 10,000)	200 µg/L
10^{-5} (1 in 100,000)	20 µg/L
10^{-6} (1 in 1,000,000)	2 µg/L

* The unit risk and concentration estimates assume water consumption of 2 L/day by a 70 kg human.

____II.B.1.3. Extrapolation Method

Multistage model with linear extrapolation from the point of departure LED_{50}). See the *Toxicological Review of Dichlorobenzenes* (U.S. EPA, 2006) for more details of the extrapolation method applied.

___II.B.2. DOSE-RESPONSE DATA

Tumor type – hepatocellular adenoma or carcinoma
Test species – mouse, $B6C3F_1$, male
Route – gavage

Incidence of liver tumors in male mice exposed to 1,4-dichlorobenzene by gavage

Administered dose (mg/kg-day)[a]	Human equivalent dose (mg/kg-day)	Incidence of adenoma or carcinoma[b]
0	0	17/46
214	33	22/40
429	66	40/42

[a] Doses are average daily doses in the study adjusted by 5/7 for a 5 day/week dosing schedule.
[b] Denominators were adjusted for early mortality.

Source: NTP (1987).

___II.B.3. ADDITIONAL COMMENTS

- Animals dying before the first appearance of liver tumors during the first year of exposure 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.

- Doses were converted to human equivalent doses on the basis of:

  $$\text{HED (mg/kg-day)} = \text{Dose in animals (mg/kg-day)} \times (BW_a/BW_h)^{0.25}.$$

- For the male mouse data the lower 95% bound of the BMD_{10} ($BMDL_{10}$) was well below the range of observed data. Consequently, the cancer slope factor was based on a point of departure more consistent with the lower range of observed data, in this case the $BMDL_{50}$.

___II.B.4. DISCUSSION OF CONFIDENCE

The cancer slope factor is based on an NTP study that used an adequate number of test animals and dose levels, and included a comprehensive histopathologic examination.

This assessment used one dose-response model, the multistage model, to characterize the potential risk to human populations from 1,4-dichlorobenzene exposure. The full extent of uncertainty in model selection cannot be quantified. The uncertainty associated with the model that was considered, however, can be quantified. In addition, there is uncertainty concerning the mode(s) of action. Sufficient information to support a nonlinear low-dose extrapolation is not available. However, there is some uncertainty regarding whether linear low-dose extrapolation provides a reasonable estimate of low-dose risk.

Parameter uncertainty can be assessed through confidence intervals analysis. Each description of parameter uncertainty assumes that the underlying model and associated assumptions are valid. Uncertainty in the animal dose-response data can usually be assessed through the ratio of benchmark doses to their lower bounds. For the oral slope factor, this ratio was less than a factor of two.

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

___II.C.1. SUMMARY OF RISK ESTIMATES

____II.C.1.1. Inhalation Unit Risk—4×10^{-6} per $\mu g/m^3$

The inhalation unit risk is derived from the LEC_{10}, the 95% lower bound on the exposure associated with a 10% extra cancer risk, by dividing the risk (as a fraction) by the LEC_{10}, and represents an upper bound, continuous lifetime exposure risk estimate:

LEC_{10}, lower 95% bound on exposure at 10% extra risk—22.6 mg/m^3 (male mouse); 22.9 mg/m^3 (female mouse)
EC_{10}, central estimate of exposure at 10% extra risk—31.6 mg/m^3 (male mouse); 41.3 mg/m^3 (female mouse)

The slope of the linear extrapolation from the central estimate EC_{10} is $0.1/(31.6 \times 10^3$ μg/m^3) = 3×10^{-6} μg/m^3.

The unit risk for 1,4-dichlorobenzene should not be used with exposures exceeding the point of departure (23 mg/m^3), because above this level the fitted dose-response model better characterizes what is known about the carcinogenicity of 1,4-dichlorobenzene.

Air Concentrations at Specified Risk Levels:

Risk Level	Lower Bound on Concentration Estimate
10^{-4} (1 in 10,000)	25 μg/m^3
10^{-5} (1 in 100,000)	2.5 μg/m^3
10^{-6} (1 in 1,000,000)	0.25 μg/m^3

____II.C.1.2. Extrapolation Method

Multistage model with linear extrapolation from the point of departure (LEC_{10}). See the *Toxicological Review of Dichlorobenzenes* (U.S. EPA, 2006) for more details of the extrapolation method applied.

___II.C.2. DOSE-RESPONSE DATA

Tumor type – hepatocellular adenoma or carcinoma
Test animals – mouse, Crj:BDF1, male and female
Route – inhalation

Incidence data for tumors in mice exposed by inhalation						
Administered concentration (ppm)	Equivalent continuous concentration (ppm)	Human equivalent continuous concentration (ppm)	Male mouse tumor incidence			Female mouse tumor incidence
			Adenoma	Carcinoma	Adenoma or Carcinoma	Adenoma or Carcinoma
0	0	0	13/49 (27%)	12/49[a] (24%)	20/49[a] (40%)	4/50[a] (8%)
20 ppm	3.6	3.6	9/49 (18%)	17/49 (34%)	21/49 (42%)	13/50 (26%)
75 ppm	13.4	13.4	7/50 (14%)	16/50 (32%)	18/50 (36%)	7/49 (14%)
300 ppm	53.3	53.3	13/49 (26%)	38/49 (76%)	41/49 (82%)	45/50 (90%)

Source: Aiso et al., 2005b; JBRC, 1995.

___II.C.3. ADDITIONAL COMMENTS

In addition to hepatocellular adenomas and carcinomas, there were statistically significantly increasing trends for the incidence of hepatic histiocytic sarcomas in male mice and bronchoalveolar adenomas or carcinomas in female mice in the JBRC (1995) study. A quantitative analysis was performed of all three tumor types.

All of the data sets (hepatocellular tumors, hepatic histiocytic sarcoma, and bronchoalveolar adenoma or carcinoma) displayed dose-response patterns where the mid-exposure response was lower than the low-exposure response. Except for the male mouse carcinomas, this behavior was strong enough that combining the low and mid-exposure groups was considered in order to facilitate modeling. In all of these cases, the incidences in the low- and mid-exposure groups were not statistically significantly different, as determined by Fisher's exact test (p>0.05). Therefore, dose-response modeling for all but hepatocellular tumors in male mice was performed after combining the two lower exposed groups to result in an average dose of 47.5 ppm, and by adding both the tumor incidences and the numbers of animals at risk.

Human equivalent exposures were estimated following the EPA RfC methodology (U.S. EPA, 1994). According to this methodology, 1,4-dichlorobenzene behaves as a category 2 gas, water soluble, with systemic and point of contact effects. For category 2 gases, HEC values are calculated using methods for category 1 gases for portal-of-entry effects and category 3 gas methods for systemic effects (U.S. EPA, 1994). Thus, for liver tumors, the HEC was calculated using the equations for a category 3 gas with extrarespiratory effects (U.S. EPA, 1994), by multiplying the duration-adjusted concentration by the ratio of blood:gas partition coefficients ($H_{b/g}$) in animals and humans; in the absence of published partition coefficients, a default value of 1 was used for the ratio. For the bronchoalveolar tumors in female mice, the HECs were calculated using the rules for a category 1 gas (U.S. EPA, 1994), where HEC = duration-adjusted concentration × $RGDR_{(PU)}$, where RGDR is the regional gas dose ratio (equal to 3.4).

In order to gain some understanding of the total risk from multiple tumor sites in male mice in the JBRC study (Aiso et al., 2005b; JBRC, 1995), a sum of risks across tumor sites (hepatocellular adenoma or carcinoma and histiocytic sarcoma) was considered. A statistically appropriate approach was used to sum the maximum likelihood estimates of unit potency across these tumor sites for male mice, assuming independence of the tumor sites. The resulting upper bound on the summed risks was less than 10% higher than the risk estimated from hepatocellular carcinomas alone. Consequently, adding the risks did not impact the unit risk estimate significantly in this instance.

For female mice, summing the risks from two sites (hepatocellular adenomas or carcinomas and bronchoalveolar adenomas or carcinomas) similarly did not change the estimated risk from hepatocellular adenomas or carcinomas substantially.

___II.C.4. DISCUSSION OF CONFIDENCE

The inhalation unit risk is based on a chronic 2-year bioassay that used an adequate number of test animals and dose levels, and included a comprehensive histopathologic examination.

This assessment used one dose-response model, the multistage model, to characterize the potential risk to human populations from 1,4-dichlorobenzene exposure. The full extent of uncertainty cannot be quantified; however, the uncertainty associated with the model that was considered can be quantified. In addition, there is uncertainty concerning the mode(s) of action. Sufficient information to support a nonlinear low-dose extrapolation is not available. However, there is some uncertainty regarding whether linear low-dose extrapolation provides a reasonable estimate of low-dose risk.

Parameter uncertainty can be assessed through confidence intervals analysis. Each description of parameter uncertainty assumes that the underlying model and associated assumptions are valid. Uncertainty in the animal dose-response data can usually be assessed through the ratio of benchmark doses to their lower bounds. For the inhalation unit risk, while the model was fit through the center of the dose-response data for each tumor site, the data were more uncertain than the model fits suggest. As a rough assessment of the uncertainty in these data, multistage models fit to the female mouse hepatocellular tumors, alternately omitting the low and mid-exposure groups, led to benchmark concentrations (BMCs) which varied by fivefold and BMCLs which varied by fourfold (results not shown), while the ratio between BMCs and BMCLs remained at approximately twofold. There was no information that supported ignoring either of these groups, however. Consequently the recommended unit risk includes all of the exposure groups.

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

___II.D.1. EPA DOCUMENTATION

Source Document -- U.S. EPA (2006)

This assessment was peer reviewed by a group of external scientists. Comments from the peer reviewers were evaluated carefully and considered by the Agency during the finalization of this assessment. A record of these comments is included in Appendix A of the *Toxicological Review of Dichlorobenzenes* (U.S. EPA, 2006).

___II.D.2. EPA REVIEW

Agency Completion Date -- __/__/__

___II.D.3. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

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

_VI. BIBLIOGRAPHY

1,4-Dichlorobenzene
CASRN – 106-46-7
Section VI. Last Revised -- 00/00/0000

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_VII. REVISION HISTORY

1,4-Dichlorobenzene
CASRN – 106-46-7
File First On-Line 01/01/1994

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.A., I.B., II.	Added RfD and cancer assessments, revised RfC assessment

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_VIII. SYNONYMS

1,4-Dichlorobenzene
CASRN -- 106-46-7
Section VIII. 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