DRAFT IRIS SUMMARY

0447
1,3-Dichlorobenzene; CASRN 541-73-1; 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 1,3-DICHLOROBENZENE

File First On-Line 09/01/1990

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

_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

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

Substance Name -- 1,3-Dichlorobenzene
CASRN -- 541-73-1
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.

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
	NOAEL: Not identified	3000	1	1 E -3
Thyroid lesions	LOAEL: 9 mg/kg-day			
Pituitary lesions	LOAEL: 147 mg/kg-day			
90-day rat gavage study McCauley et al. (1995)	BMDL: 3 mg/kg-day			

*Conversion Factors and Assumptions -- Incidence data for thyroid lesions (reduced follicular colloidal density) and pituitary lesions (cytoplasmic vacuolation in pars distalis) were analyzed by benchmark dose modeling. The lower 95% confidence interval on the benchmark dose (BMDL) associated with a 10% increased incidence was calculated for both types of lesions. The BMDLs for the thyroid and pituitary lesions were 1.9 and 3.3 mg/kg-day, respectively. The average of these values, 3 mg/kg-day (rounded from 2.6 mg/kg-day), was selected as the point of departure for the RfD, because the values are similar and the effects may be related to each other.

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

McCauley, P.T., M. Robinson, F.B. Daniel, and G.R. Olson (1995). Toxicity studies of 1,3-dichlorobenzene in Sprague-Dawley rats. Drug Chem. Toxicol. 18(2&3): 201-221.

The oral toxicity database for 1,3-dichlorobenzene is limited to one subchronic toxicity study in rats (McCauley et al., 1995) and one developmental toxicity study in rats (Ruddick et al., 1983). The developmental toxicity study is not a principal or supporting study because no effects were found at doses higher than LOAELs in the subchronic study (see Section I.A.4).

Groups of 10 male and 10 female Sprague Dawley rats were administered daily gavage doses of 0, 9, 37, 147, or 588 mg/kg of 1,3-dichlorobenzene in corn oil for 90 consecutive days (McCauley et al., 1995). Endpoints evaluated during the study included clinical signs and mortality (observed daily), body weight (measured weekly), and food and water consumption (measured weekly). At necropsy, blood was collected for hematology and serum chemistry analyses [erythrocytes, leukocytes, hemoglobin, hematocrit, mean corpuscular volume, glucose,

BUN, creatinine, AP, AST, ALT, cholesterol, LDH, and calcium levels], selected organs (brain, liver, spleen, lungs, thymus, kidneys, adrenal glands, heart, and gonads) were weighed, and comprehensive gross tissue examinations were conducted. Histological examinations were performed on all tissues that were examined grossly in all high-dose rats and one-half of control rats, as well as in the liver, thyroid, and pituitary glands from all animals treated with 9, 37, or 147 mg/kg-day. Inflammatory and degenerative lesions were graded on a relative scale from one to four depending on the severity (minimal, mild, moderate, or marked).

There were no compound-related deaths or overt clinical signs, although other effects occurred at all dose levels (McCauley et al., 1995). Body weight gain was reduced in both sexes at 588 mg/kg-day; final body weights were 24 and 10% lower than controls in males and females, respectively. The weight loss was progressive throughout the exposure period, and occurred despite increased food and water consumption in the same groups. Average daily food consumption was not significantly altered; however, food intake normalized to body weight was significantly increased (10-13%) in male and female rats in the 588 mg/kg-day group. Water consumption was increased (18%) in the 588 mg/kg-day group, and water consumption normalized for body weight was increased (18-23%) in the male rats at 147 and 588 mg/kg-day and female rats at 588 mg/kg-day. Relative testes and brain weights were significantly increased in males at 588 mg/kg-day, likely reflecting the decreased body weight at this dose. As discussed below, the histological and serum chemistry evaluations indicated that the thyroid, pituitary, and liver were sensitive targets at exposure levels as low as 9 mg/kg-day.

The study authors did not report the results of their statistical evaluation of the pathology data. Therefore, analysis of the lesion incidence data was conducted as part of the evaluation of the study in the Source Document (U.S. EPA, 2002), using the Fisher Exact test and a criterion of significance of $p \leq 0.05$. Histological examinations showed statistically significant increased incidences of reduced colloidal density in thyroid follicles that exceeded normal variability in male rats at $\geq$9 mg/kg-day and female rats at $\geq$37 mg/kg-day. (Incidences in the control to high dose groups were 2/10, 8/10, 10/10, 8/9 and 8/8 in males and 1/10, 5/10, 8/10, 8/10, and 8/9 in females). The authors did not explain why <10 animals were examined in the two high-dose groups. Depletion of colloid density in the thyroid was characterized by decreased follicular size with scant colloid and follicles lined by cells that were cuboidal to columnar. The severity of the colloid density depletion generally ranged from mild to moderate, increased with dose level, and was greater in males than females. For example, in the 147 and 588 mg/kg-day male groups, the severity was classified as moderate, as compared to mild for the females. Incidences of male rats with thyroid colloidal density depletion of moderate or marked severity were significantly increased at $\geq$147 mg/kg-day (0/10, 0/10, 2/10, 5/9, and 6/8). Pituitary effects included significantly increased incidences of cytoplasmic vacuolization in the pars distalis in male rats at $\geq$147 mg/kg-day (2/10, 6/10, 6/10, 10/10, and 7/7); the incidences in the 9 and 37 mg/kg-day groups were marginally increased ($p=0.085$). The vacuoles were variably sized, irregularly shaped, and often poorly defined, and the severity of the lesions (number of cells containing vacuoles) ranged from minimal to mild and generally increased with increasing dose level.

Incidences of male rats with pituitary cytoplasmic vacuolization of moderate or marked severity were significantly increased at 588 mg/kg-day (1/10, 0/10, 2/10, 3/9, and 7/7). The pituitary lesion was reported to be similar to "castration cells" found in gonadectomized rats and considered to be an indicator of gonadal deficiency. No compound-related pituitary lesions were observed in female rats. In possibly related changes, serum cholesterol was significantly ($p \leq 0.05$) increased in males at $\geq$9 mg/kg-day and females at $\geq$37 mg/kg-day in a dose-related manner, and serum calcium was significantly increased in both sexes at $\geq$37 mg/kg-day. The investigators suggested that these serum chemistry changes might reflect a disruption of hormonal feedback mechanisms, or target organ effects on the pituitary, hypothalamus, and/or other endocrine organs.

Hepatic effects occurred in both sexes at 147 and 588 mg/kg-day, including significant ($p \leq 0.05$) increases in relative liver weight (51 and 85% increases in males and 32 and 74% increases in females compared to controls) and incidences of liver lesions (McCauley et al., 1995). Absolute organ weights were not reported. The liver lesions were characterized by inflammation, hepatocellular alterations (characterized by spherical, brightly eosinophilic homogeneous inclusions), and hepatocellular necrosis. Liver lesions that were significantly increased included hepatocellular cytoplasmic alterations of minimal to mild severity in males at $\geq$147 mg/kg-day (incidences in the control to high dose groups were 1/10, 2/10, 1/10, 6/10 and 7/9) and females at 588 mg/kg-day (0/10, 2/10, 0/10, 1/10, and 7/9), and necrotic hepatocyte foci of minimal severity in both sexes at 588 mg/kg-day (1/10, 2/10, 1/10, 2/10, and 5/9 in males and 0/10, 0/10, 0/10, 3/10, and 5/9 in females). Other statistically significant liver-associated effects included significantly increased serum AST levels (90-100% higher than controls) in males at $\geq$9 mg/kg-day and females at $\geq$37 mg/kg-day. Serum cholesterol levels were significantly increased in males at $\geq$9 mg/kg-day and females at $\geq$37 mg/kg-day, but this change could be pituitary-related, as indicated above. Serum LDH levels were reduced in males at $\geq$9 mg/kg-day and BUN levels were reduced in both sexes at 588 mg/kg-day, but the biological significance of decreases in these indices is unclear. Relative kidney weight was increased in males at $\geq$147 mg/kg-day and females at 588 mg/kg-day, but there were no renal histopathological changes in any of the exposed animals. Other effects included hematological alterations consisting of significant increases in leukocyte levels in males at 147 mg/kg-day and females at 588 mg/kg-day, and erythrocyte levels in males at 588 mg/kg-day.

The McCauley et al. (1995) study found that 1,3-dichlorobenzene caused toxic effects in rats at all tested dose levels, indicating that a NOAEL is not identifiable. Collectively, the data for male rats (which were more responsive than female rats) identify thyroid effects (reduced follicular colloidal density) and pituitary effects (cytoplasmic vacuolation in par distalis) as the critical effects, as summarized in Table I.A.2.1. Liver lesions (increased incidence of hepatocellular cytoplasmic alterations) occurred at higher dose levels than the lowest doses that induced thyroid and pituitary effects (Table I.A.2.1). Mean serum levels of AST and cholesterol were statistically significantly increased in all male exposed groups compared with control means, but other serum markers of liver damage such as activities of ALT and LDH were not

significantly increased in exposed groups (Table I.A.2.1). Because of this inconsistency, the observed statistically significant changes in AST and cholesterol are not considered to be biologically significant changes indicating liver damage. However, the observed histopathologic changes in the thyroid and pituitary are considered to be adverse. The vacuolation in the par distalis indicates cytotoxic effects in the pituitary, and the reduced follicular colloidal density in the thyroid is indicative of thyroid stimulation (Gershon and Nunez, 1988). In addition, McCauley et al. (1995) speculated that the elevated serum cholesterol concentrations may be related to pituitary damage, rather than liver damage. In the absence of data to indicate otherwise, the thyroid and pituitary effects are assumed to be critical effects relevant to humans who may chronically ingest 1,3-dichlorobenzene and are selected to serve as the basis of the RfD.

Table I.A.2.1. Liver, Thyroid, and Pituitary Effects Observed in Male Rats Orally Exposed to 1,3-Dichlorobenzene for 90 Consecutive Days (McCauley et al., 1995)

	Dose (mg/kg-day)				
Effects	0	9	37	147	588
mean serum AST (U/L) ±SD mean serum cholesterol (mg/dL) ±SD mean serum ALT (U/L) ±SD mean serum LDH (U/L) ±SD	43.7±37.7 73.5±1.4 46.8±7.7 1762±765	87.6±24.7[a] 96.6±1.7[a] 40.8±9.7 623±466	109.8±9.5[b] 111.1±1.6[a] 43.3±4.5 798±238	88.0±23.3[a] 157.9±12.5[a] 38.5±8.2 778±530	82.8±13.8[a] 89.5±1.5[a] 59.3±11.0 735±288
hepatocellular cytoplasmic alterations	1/10	2/10	1/10	6/10[c]	7/9[c]
thyroid, reduced follicular colloidal density	2/10	8/10[c]	10/10[c]	8/9[c]	8/8[c]
pituitary, cytoplasmic vacuolation in pars distalis	2/10	6/10[d]	6/10[d]	10/10[c]	7/7[c]

[a]Reported to be significantly higher ($p \leq 0.05$) than control mean by study authors.
[b]This value was not reported to be statistically significant by study authors.
[c]Significantly higher ($p<0.05$) than controls; Fisher Exact Test performed as part of study evaluation (U.S. EPA, 2002).
[d]Marginally higher ($p=0.085$) than controls; Fisher Exact Test performed as part of study evaluation (U.S. EPA, 2002).

Potential points of departure for the RfD were derived by benchmark dose analysis of the thyroid and pituitary data in Table I.A.2.1. All dichotomous models in the EPA Benchmark Dose Software (version 1.3.1) were fit to the male rat incidence data for: 1) reduced follicular colloidal density in the thyroid, and 2) cytoplasmic vacuolation in the pars distalis of the pituitary. For each variable, Akaike's Information Criteria (AIC) was used to select the best fitting model from which benchmark doses (BMDs) and their lower 95% confidence limits (BMDLs) were calculated, using a benchmark response (BMR) of 10% extra risk.

For the thyroid incidence data, the Gamma, Multi-stage, Quantal-linear, and Weibull model runs obtained the same model (power parameters were restricted to be $\geq$1), which provided a better fit than the logistic, quantal-quadratic, or probit models (U.S. EPA, 2002). The chi-square goodness-of-fit statistics for all of these models indicated poor fits ($p<0.1$), but a graph of the observed incidences of thyroid lesions and Gamma-model-predicted incidences showed a reasonable visual fit (U.S. EPA, 2002). Thus, the BMD and BMDL predicted from the Gamma model, 4.09 and 1.9 mg/kg-day, respectively, were selected as the best benchmarks for thyroid lesions in male rats (U.S. EPA, 2002).

For the pituitary cytoplasmic vacuolation incidence data, the Gamma, Quantal-linear, and Weibull model runs obtained the same model (power parameters restricted $\geq$1), which provided a nearly equivalent fit as the Probit model. The other models fit the data less well, using the AIC as the fit indicator (U.S. EPA, 2002). The BMD and BMDL from the Gamma model were 4.08 and 2.10 mg/kg-day, whereas the BMD and BMDL from the Probit model were 7.79 and 4.46 mg/kg-day. Given the similarities of these BMDLs, their average, 3.3 mg/kg-day, is selected as the BMDL for pituitary cytoplasmic vacuolation in male rats.

Since the BMDLs for thyroid lesions (1.9 mg/kg-day) and pituitary lesions (3.3 mg/kg-day) are similar, and the effects may be related to each other, the point of departure for the RfD is selected as the average of these values, 3 mg/kg-day, rounded from 2.6 mg/kg-day.

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

UF = 3000. A total uncertainty factor of 3000 was applied to the average BMDL of 2.6 mg/kg-day: 10 for interspecies variability, 10 for interindividual variability, 10 for extrapolation from subchronic to chronic exposure, and 3 for database deficiencies.

A 10-fold uncertainty factor was used to account for uncertainty in extrapolating from rats to humans (i.e., interspecies variability). No information is available on the toxicity of ingested 1,3-dichlorobenzene in humans, or on differences that may exist between animals and humans in the disposition of, or response to, ingested 1,3-dichlorobenzene. In the absence of data to the contrary, the pituitary and thyroid effects observed in subchronically exposed rats are assumed to be relevant to humans chronically exposed to ingested 1,3-dichlorobenzene.

A 10-fold uncertainty factor was used to account for variation in sensitivity to 1,3-dichlorobenzene within human populations. There were no effects on developing fetuses of rat dams exposed to a dose of 200 mg/kg-day, suggesting that developmental effects from 1,3-dichlorobenzene, if they occur, would only occur at dose levels higher than those inducing thyroid or pituitary effects in subchronically exposed rats (9-147 mg/kg-day). However, this study was inadequately reported. The degree to which humans of varying gender, age, health status, or genetic makeup may vary in disposing of, or responding to, ingested 1,3-dichlorobenzene is unstudied. The rat subchronic toxicity study identified male rats as more

susceptible than females to the thyroid, pituitary, and liver effects of 1,3-dichlorobenzene, but additional information on possible gender differences in toxicokinetics or toxicodynamics is not available.

A 10-fold uncertainty factor was used to account for extrapolating from subchronic oral exposure to chronic oral exposure. Although the modes of action whereby 1,3-dichlorobenzene may produce cytotoxic effects on the pituitary and stimulate activity of the thyroid are unknown, it is plausible that with longer duration of exposure (i.e., chronic duration), lower exposure levels may induce the same effects.

A 3-fold uncertainty factor was used to account for deficiencies in the database. Some of the uncertainty in the database is addressed by the factors used for uncertainty in other areas (e.g., interspecies variability). The only information on the systemic toxicity of repeated oral exposure to 1,3-dichlorobenzene comes from the subchronic rat study reporting thyroid and pituitary effects at doses $\geq$9 mg/kg-day (McCauley et al., 1995). This is a well-designed study that investigated a large number of endpoints, including liver-associated enzymes and various other serum chemistry indices, hematology, and comprehensive histology that included the thyroid, pituitary and other endocrine tissues. A developmental toxicity study found no evidence for maternal toxicity or developmental toxicity in rats at a dose level of 200 mg/kg-day (Ruddick et al., 1983), but the data are not well reported. The oral-exposure database for 1,3-dichlorobenzene contains no chronic toxicity data and lacks assessments of developmental toxicity in a second animal species, reproductive toxicity in males or females, neurotoxicity and immunotoxicity.

MF = 1. None.

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

No information is available on the toxicity of 1,3-dichlorobenzene in humans following oral exposure.

An oral developmental toxicity study of 1,3-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 via gavage 50, 100, or 200 mg/kg 1,3-dichlorobenzene 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 1,3-dichlorobenzene in rats. This NOAEL is higher than the LOAELs for subchronic toxicity (McCauley et al., 1995) discussed in Section I.A.2., indicating that the thyroid, pituitary and

other systemic effects are the most sensitive known endpoints for oral exposure to 1,3-dichlorobenzene.

___I.A.5. CONFIDENCE IN THE ORAL RfD

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

The overall confidence in this RfD assessment is low. The principal study is generally well-designed as it investigated a large number of endpoints (e.g., liver-associated enzymes and various other serum chemistry indices, hematology, and comprehensive histology including the thyroid, pituitary and other endocrine tissues), but warrants a medium level of confidence because relatively small numbers of animals were tested (10/sex/group) and a NOAEL was not identified. Confidence in the database is low because it is limited to information in one species (rat) from one subchronic study (the principal study) and one poorly reported developmental toxicity study. Overall confidence in the RfD is low due to the limitations of the database, particularly the lack of chronic toxicity and reproductive toxicity studies and assessments of subchronic and developmental toxicity in a second species.

___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 -- 1,3-Dichlorobenzene
CASRN -- 541-73-1

An RfC cannot be calculated for 1,3-dichlorobenzene due to inadequate data. No information is available on the systemic, reproductive, or developmental toxicity of inhaled 1,3-dichlorobenzene in humans or animals, indicating that the existing inhalation database is inadequate to support the derivation of an RfC for this isomer. As discussed in the Source Document (U.S. EPA, 2002), it is not feasible to derive an RfC from oral data on 1,3-dichlorobenzene. Because available mechanistic evidence suggests that hepatic metabolism to a reactive intermediate may be of considerable importance in toxicity, and the extent of hepatic metabolism is likely to vary dramatically following oral and inhalation exposures, a route-to-route extrapolation from the oral data is precluded. Derivation of an RfC for 1,3-dichlorobenzene by analogy to 1,2- or 1,4-dichlorobenzene also is not feasible (U.S. EPA, 2002). Inhalation data are inadequate for the derivation of an RfC for 1,2-dichlorobenzene, and available oral data strongly suggest that 1,4-dichlorobenzene is less acutely toxic than either of the other two isomers, and that target sites may vary between the isomers.

__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 -- 1,3-Dichlorobenzene
CASRN -- 541-73-1
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 1,3-dichlorobenzene*, under the draft revised guidelines for carcinogen risk assessment (U.S. EPA, 1999). These assessments are based on a lack of human and animal carcinogenicity data.

___II.A.2. HUMAN CARCINOGENICITY DATA

None.

___II.A.3. ANIMAL CARCINOGENICITY DATA

None.

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

The genotoxicity of 1,3-dichlorobenzene was evaluated in several *in vitro* and *in vivo* tests. Reverse mutations were not induced in assays using *S. typhimurium* or *E. coli* (Connor et al., 1985; Shimizu et al., 1983; Waters et al., 1982). Evidence of primary DNA damage was observed in *E. coli*, but not in *B. subtilis* or *S. cerevisiae* (Waters et al., 1982). 1,3-Dichlorobenzene did not cause an increase in replicative DNA synthesis in cultured human lymphocytes (Perocco et al., 1983). *In vivo*, micronucleus formation was increased in bone marrow cells of mice that were intraperitoneally exposed to 1,3-dichlorobenzene (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 -- 1,3-Dichlorobenzene
CASRN -- 541-73-1
Last Revised -- 00/00/0000

__VI.A. ORAL RfD REFERENCES

Gershon, M.D. and E.A. Nunez (1988). The thyroid gland. In Cell and Tissue Biology. A Textbook of Histology. Weis L, ed. 6th edition. pp. 1009-1020. Urban and Schwarzenberg, Baltimore.

McCauley, P.T., M. Robinson, F.B. Daniel, and G.R. Olson (1995). Toxicity studies of 1,3-dichlorobenzene in Sprague-Dawley rats. Drug Chem. Toxicol. 18(2&3): 201-221.

Ruddick, J.A., W.D. Black, D.C. Villeneuve, and V.E. Valle (1983). A teratological evaluation following oral administration of trichloro- and dichlorobenzene isomers to the rat. Teratology 27(2): 73A-74A.

U.S. EPA. (2002). Toxicological Review of Dichlorobenzenes in Support of Summary Information on the Integrated Risk Information System (IRIS). National Center for Environmental Assessment, Washington, DC. Available online from http://www.epa.gov/iris.

__VI.B. INHALATION RfC REFERENCES

U.S. EPA. (2002). Toxicological Review of Dichlorobenzenes in Support of Summary Information on the Integrated Risk Information System (IRIS). National Center for Environmental Assessment, Washington, DC. Available online from http://www.epa.gov/iris

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__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Connor, T.H., J.C. Theiss, H.A. Hanna, D.K. Monteith, and T.S. Matney (1985). Genotoxicity of organic chemicals frequently found in the air of mobile homes. Toxicol. Lett. 25: 33-40.

Mohtashamipur, E., R. Triebel, H. Straeter, and K. Norpoth (1987). The bone marrow clastogenicity of eight halogenated benzenes in male NMRI mice. Mutagenesis 2(2): 111-113.

Perocco, P., S. Bolognesi, and W. Alberghini (1983). Toxic activity of seventeen industrial solvents and halogenated compounds on human lymphocytes cultured *in vitro*. Toxicol. Lett. 16: 69-85.

Shimizu, M., Y. Yasui, and N. Matsumoto (1983). Structural specificity of aromatic compounds with special reference to mutagenic activity in *Salmonella typhimurium* - a series of chloro- or fluoro-nitrobenzene derivatives. Mutat. Res. 116: 217-238.

U.S. EPA (1986). Guidelines for Carcinogen Risk Assessment. Federal Register 51(185):33992-34003.

U.S. EPA. (1999) Guidelines for Carcinogen Risk Assessment. Review Draft, NCEA-F-0644, July 1999. Risk Assessment Forum.

U.S. EPA. (2002). Toxicological Review of Dichlorobenzenes in Support of Summary Information on the Integrated Risk Information System (IRIS). National Center for Environmental Assessment, Washington, DC. Available online from http://www.epa.gov/iris

Waters, M.D., S.S. Sandhu, V.F. Simmon, K.E. Mortelmans, A.D. Mitchell, T.A. Gorgenson, D.C.L. Jones, R. Valencia, and N.E. Garrett (1982). Study of pesticide genotoxicity. Basic Life Sci. 21: 275-326.

_VII. REVISION HISTORY

Substance Name -- 1,3-Dichlorobenzene
CASRN -- 541-73-1

Date	Section	Description
09/01/1990	II.	Carcinogen assesment on-line
09/01/1990	VI.	Bibliography on-line
01/01/1992	IV.	Regulatory Action section on-line
08/01/1992	I.A.	Oral RfD now under review
08/01/1995	I.A.	EPA's RfD/RfC and CRAVE workgroups were discontinued in May, 1995. Chemical substance reviews that were not completed by September 1995 were taken out of IRIS review. The IRIS Pilot Program replaced the workgroup functions beginning in September, 1995.
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 1,3-Dichlorobenzene.

_VIII. SYNONYMS

Substance Name -- 1,3-Dichlorobenzene
CASRN -- 541-73-1
Last Revised -- 00/00/0000

41-73-1
Benzene, 1,3-dichloro-
Benzene, m-dichloro-
1,3-Dichlorobenzene
m-DCB
m-Dichlorobenzene
m-Dichlorobenzol
HSDB 522
m-Phenylene dichloride
NSC 8754