1,2,4-Trichlorobenzene; CASRN 120-82-1

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR 1,2,4-Trichlorobenzene

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	05/01/1992
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	06/01/1989

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — 1,2,4-Trichlorobenzene
CASRN — 120-82-1
Last Revised — 05/01/1992

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
Increased adrenal weights; vacuolization of zona fasciculata in the cortex **Rat Reproductive Study** **Robinson et al., 1981**	NOAEL: 100 ppm (14.8 mg/kg/day) LOAEL: 400 ppm (53.6 mg/kg/day)	1000	1	1E-2 mg/kg/day

*Conversion Factors: Doses were based on actual water consumption and body weights provided by Robinson et al. (1981) for rats 83 days old.

I.A.2. Principal and Supporting Studies (Oral RfD)

Robinson, K.S., R.J. Kavlock, N. Chernoff and E. Gray. 1981. Multi- generation study of 1,2,4-trichlorobenzene in rats. J. Toxicol. Environ. Health. 8: 489-500.

The derivation of the oral RfD is based on a multigeneration reproductive study. At birth of the F0 generation, litters (17-23 litters/dose group) were randomly reduced to 4 males and 4 females. Male and female progeny were dosed with 0, 25, 100 or 400 ppm of 1,2,4-trichlorobenzene (TCB) in the drinking water. During the study maternal weights, litter size, neonate sex and weight, and 24-hour food and water intake were recorded. Blood samples and organs were collected on days 27 and 95 of age from selected rats from each group for chemistry determinations (i.e., glucose, BUN, creatinine, Na, K, Cl, uric acid, Ca, P, cholesterol, triglyceride, bilirubin, alkaline phosphatase, SGOT, SGPT, LDH, CPK, protein, globulin and albumin), and organ weights (i.e., liver, kidney, uterus, adrenals, lungs, heart and gonads). Similar procedures were performed with the F1 generation. The study ended when the F2 generation was 32 days old. Fertility (as indexed by conception rate of dams) of the F0 and F1 generation rats was not affected by treatment. A LOAEL was derived from a significant increase

(11% in males, 13% in females) in adrenal gland weights observed in the 400-ppm groups of males and females of the F0 and F1 generations.

The authors duplicated the increase in adrenal weights in an acute experiment in which preweanling females were given three daily i.p. injections of TCB. The acute experiment was performed to show that the adrenal enlargement was not due to either estrogenic properties of TCB or to long-term stress. The NOAEL was determined to be 100 ppm from the mid-dose group. The LOAEL was determined to be 400 ppm on the basis of increased adrenal gland weight.

A 1-month study, which repeated part of the Robinson et al. (1981) study, was performed by the U.S. EPA. Five rats/group were dosed with 53 mg/kg/day TCB (the LOAEL from the Robinson study) in corn oil by gavage. Microscopic examination of the TCB-treated rats showed moderate vacuolization of the zona fasciculata; the control group showed only slight vacuolization. Twenty-four hour urine and serum specimens were collected prior to post mortem examination. A 14% increase in absolute adrenal gland weight was observed and a 13% adrenal gland/body weight ratio was observed. This study indicated that the increase in adrenal gland weight observed by Robinson et al. (1981) could be associated with vacuolization of the zona fasciulata (Cicmanec, 1991). In addition, the treated rats had decreased serum corticosterone levels when compared with controls.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — An uncertainty factor of 10 was used to account for extrapolation from laboratory studies to humans. An additional factor of 10 was used to allow for sensitive subpopulations among humans. An additional factor of 10 was used to account for a lack of chronic studies. This results in a total uncertainty factor of 1000 for this substance.

MF — None

I.A.4. Additional Studies/Comments (Oral RfD)

Toxicokinetic studies by Smith and Carlson (1980) have shown that initially, adrenal glands have the highest concentration of TCB immediately following a single oral dose of radiolabeled compound. Later during the first week following dosing, only abdominal fat, kidney and liver showed higher concentrations than the adrenal gland. It has been demonstrated that dosing with pentachlorobenzene can induce increased adrenal weights in test rats (Linder et al., 1980). Inhalation studies with monochlorobenzene showed increased adrenal weights, attributed to vacuolization of the zona fasciculata, a significant adverse effect (Dilley, 1977). Other chlorinated aromatic compounds, including o-chlorotoluene and beta-chloronapthalene, have a

critical effect on adrenal gland weight. On the basis of this information for structurally similar compounds, the EPA determined that the occurrence of increased adrenal weights following administration of TCB is a significant adverse effect. Coate et al. (1977) reported a study in which rats, rabbits and cynomolgus monkeys were exposed by inhalation to TCB for 26 weeks at concentrations of 0, 25, 50 or 100 ppm (0, 186, 371 or 741 mg/cu.m) for 7 hours/day, 5 days/week. Thirty rats, 6 rabbits and 9 cynomolgus monkeys were assigned to each dose group.

Pulmonary function tests, operant behavior tests and opthalmoscopic examinations, as well as serum chemistry determinations (i.e., BUN, LDH isozymes, SGOT, SGPT, and alkaline phosphatase), were performed on monkeys. Microscopic examination of rat tissues were made at 4, 13 and 26 weeks. Although hepatocytomegaly, hepatic vacuolization, biliary hyperplasia, and granuloma formation were observed at 4 and 13 weeks, none of these changes were observed in rats killed at 26 weeks. Hyaline degeneration was present in the renal cortex at 4 and 13 weeks but not at 26 weeks. Adrenal glands were not examined. The authors felt that since it has not been shown that humans have a similar adaptive mechanism for long-term exposure, an occupational TLV of 5 ppm should be recommended on the basis of this study. A LOAEL was not established. No adverse effect was defined for rabbits or monkeys from this study.

Watanabe et al. (1977) reported the results of a subchronic inhalation study in which rats were exposed to TCB for 6 hours/day, 5 days/week for 90 days. The exposure concentrations tested were 0, 3 and 10 ppm (0, 22.3 and 74.2 mg/cu.m). The results showed a very weak sporatic increase in urinary porphyrins at 10 ppm. The 10-ppm exposure was considered a LOAEL and 3 ppm was considered a NOAEL.

Carlson (1977) reported a study in which induction of porphyria by hexachlorobenzene, dichlorobenzene and trichlorobenzene was investigated. Doses of 0, 50, 100 and 200 mg/kg/day of each compound were administered orally to female rats. Liver weights, hepatic porphyrins, and urinary porphyrins were determined at 30, 60, 90 and 120 days. The study demonstrated that hexachlorobenzene induced porphyria but that dichlorobenzene and trichlorobenzene did not.

In the study reported by Carlson and Tardiff (1976) male CD rats (6/dose) were dosed orally with TCB at 0, 10, 20 or 40 mg/kg/day. The investigators evaluated the effect upon weight gain, liver weight, hemoglobin, hematocrit and indicators of xenobiotic metabolism including cytochrome C reductase, detoxification, cytochrome P-450, glucoronyl transferase, benzopyrene hydroxylase and azoreductase activity. The dose of 10 mg/kg/day induced some enzymatic changes but did not affect liver-to-body weight ratios or blood parameters. For many of the enzymes tested change was dose-related. At 40 mg/kg/day, liver-to-body weight ratios were increased. Although enzyme induction is a sensitive endpoint, it is not an adverse effect. For this study 20 mg/kg/day is considered a NOAEL and 40 mg/kg/day is considered a LOAEL.

In the study reported by Kociba et al. (1981), male rats, rabbits and dogs were exposed to 0, 30 or 100 ppm (0, 223 or 742 mg/cu.m) for 44 days. No significant effects were observed for body weight gain, hematologic parameters, serum biochemical tests or microscopic appearance of tissues. A reversible increase in urinary excretion of porphyrins was noted. The authors interpreted this change as being a compound-specific physiologic effect rather than a sign of toxicity.

Smith et al. (1978) performed a study in which rhesus monkeys were dosed orally with 0, 25, 90, 125 and 173.6 mg/kg. The 25-mg/kg doses were nontoxic. Doses of 90 mg/kg caused hepatic induction as evidenced by a shift in the urinary pattern of chloroguanide metabolites and increased clearance of i.v. doses of labelled TCB. Doses of 173.6 mg/kg were lethal within 30 days. Monkeys receiving this dose exhibited severe weight loss and had fine tremors. At termination they had elevated levels of BUN, Na, K, CPK, SGOT, SGPT, LDH and ALK T'ase, hypercalcemia and hyperphosphatemia, but jaundice was not present. Clinical symptoms and biochemical changes were reversed when treatment was discontinued.

Kitchin and Ebron (1980) examined the maternal reproductive and hepatic effects of TCB upon CD-1 rats that were dosed with 0, 36, 120, 360 or 1200 mg/kg/day of TCB on days 9-13 of gestation. Among the treatment groups of 9 dams/group, alteration of embryonic parameters was noted only in the 360 mg/kg/day group. (All of the dams in the 1200 mg/kg/day group died.) The observed changes included significant retardation of all four growth criteria (i.e., head length, crown-rump length, somite number, and protein content). TCB did not cause increased resorptions, embryolethality or teratogenicity. This study also demonstrated significantly increased xenobiotic hepatic enzyme activity at 120 and 360 mg/kg/day.

In the development toxicity study of Black et al. (1983) pregnant Wistar rats received doses ranging from 75-600 mg/kg/day of 1,2,4-, 1,2,3-, and 1,3,5-TCB on days 6-15 of gestation. No abnormal teratogenic changes were observed except mild osteogenic changes. This paper was available only in abstract form and the dosage at which the changes were observed was not stated.

I.A.5. Confidence in the Oral RfD

Study — Medium
Database — Medium
RfD — Medium

A medium degree of confidence for the RfD is chosen since the multi- generation study of Robinson et al. (1981) provides sufficient data with multiple endpoints. The study used

appropriate group sizes. A medium to low confidence rating is given to the database since no chronic exposure study is available. Medium confidence in the RfD follows.

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — U.S. EPA, 1985

Other EPA Documentation — U.S. EPA, 1988

Agency Work Group Review — 02/26/1986, 05/26/1988, 09/11/1991, 12/12/1991

Verification Date — 12/12/1991

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for 1,2,4-Trichlorobenzene conducted in November 2001 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

I.A.7. EPA Contacts (Oral RfD)

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

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

Substance Name — 1,2,4-Trichlorobenzene
CASRN — 120-82-1

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — 1,2,4-Trichlorobenzene
CASRN — 120-82-1
Last Revised — 06/01/1989

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 ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing 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 Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). 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

Classification — D; not classifiable as to human carcinogenicity

Basis — A dermal exposure study in mice was found inadequate for drawing conclusions as to carcinogenicity in humans.

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

Inadequate. Yamamoto et al. (1982) applied 1,2,4-trichlorobenzene in acetone to the dorsal skin of Slc.ddy mice twice weekly for 2 years. The solution of 1,2,4-trichlorobenzene was 60% for the high dose and 30% for the low dose and the volume applied was 0.03 mL/application. Each treated group contained 75 animals of each sex. There were 50 vehicle control animals for each

sex. Growth rates in treated and control mice were comparable through 83 weeks. Mean survival days were significantly reduced in the 60% 1,2,4- trichlorobenzene groups of males and females and also in the 30% treatment group of females. All males and treated females showed as poor as 60% survival by week 40.

Histopathology showed some organ sites had increased nonneoplastic lesions. All 75 animals in the treated groups and all 50 in the control groups appear to have been examined. Increases in nonneoplastic lesions (i.e., amyloid) were reported in lung, liver, kidney, adrenal, spleen and lymph node of the male high-dose group and in all these organs except lymph node of the female high-dose group.

No single tumor type was increased significantly over the control incidence; there was no significant difference in total tumor incidence between treated and control groups. Among males, nine different tumors were found in the high-dose group as compared with two in the low-dose and two in the control group. In females there were 11 different tumors in the high-dose group as compared with 3 in the low-dose and 8 in the control group. However, no adjustment was made for reduced survival, and there was no indication of the time to first tumor appearance. The authors do not state whether these tumors were all found in different individual animals or whether these were multiple tumors in the same animal. This study has several limitations. Although male mice were housed individually, female mice were group-housed. The animals were only treated twice a week, and no pharmacokinetic studies were performed. There was a low survival rate; 80% of the control mice and 90% of the treated mice died before the end of the study.

II.A.4. Supporting Data for Carcinogenicity

Results of two reports on mutagenicity tests with Salmonella typhimurium test strains were negative (Schoeny et al., 1979; Lawlor et al., 1979). Grover and Sims (1965) reported trichlorobenzene to be a metabolite of gamma- hexachlorocyclohexane (Lindane) which is a possible or probable human carcinogen. The authors isolated 2,4,5- and 2,3,5-trichlorophenol, which are metabolites of trichlorobenzene, from urine of Lindane treated rats. This suggested that dehydrochlorination via trichlorobenzene is one metabolic pathway of gamma-hexachlorocyclohexane.

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not available.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not available.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1988

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 10/19/1988

Verification Date — 10/19/1988

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for 1,2,4-Trichlorobenzene conducted in November 2001 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

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

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — 1,2,4-Trichlorobenzene
CASRN — 120-82-1

VI.A. Oral RfD References

Black, W.D., V.E.O. Valli, J.A. Ruddick and D.C. Villeneuve. 1983. The toxicity of three trichlorobenzene isomers in pregnant rats. Toxicologist. 3(1): 30. (Abstract)

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Smith, E.N. and G.P. Carlson. 1980. Various pharmacokinetic parameters in relation to enzyme-

inducing abilities of 1,2,4-trichlorobenzene and 1,2,4- tribromobenzene. J. Toxicol. Environ. Health. 6(4): 737-749.

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Wantanabe, P.G., H.O. Yankel and R.J. Kociba. 1977. Subchronic Toxicity Study of Inhaled 1,2,4-Trichlorobenzene in Rats. Internal Report. Toxicology Research Laboratory. Dow Chemical Co., Midland, MI.

VI.B. Inhalation RfC References

None.

VI.C. Carcinogenicity Assessment References

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VII. Revision History

Substance Name — 1,2,4-Trichlorobenzene
CASRN — 120-82-1

Date	Section	Description
06/01/1989	II.	Carcinogen summary on-line
10/01/1989	I.A.	Oral RfD withdrawn pending further review
05/01/1992	I.A.	Oral RfD summary replaced; RfD changed
12/03/2002	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — 1,2,4-Trichlorobenzene
CASRN — 120-82-1
Last Revised — 01/31/1987

- 120-82-1
- BENZENE, 1,2,4-TRICHLORO-
- 1,2,4-Trichlorobenzene
- Trichlorobenzene, 1,2,4-
- TROJCHLOROBENZEN
- UN 2321
- unsym-TRICHLOROBENZENE