Chemical Information Profile

for

1-Chloro-4-(trifluoromethyl)benzene
[CAS No. 98-56-6]

Supporting Nomination for Toxicological Evaluation by the National Toxicology Program

June 2009

National Toxicology Program
National Institute of Environmental Health Sciences
National Institutes of Health
U.S. Department of Health and Human Services
Research Triangle Park, NC
http://ntp.niehs.nih.gov/

Data Availability Checklist for 1-Chloro-4-(trifluoromethyl)benzene [98-56-6]

Abbreviations: H = human; L = *Lepus* (rabbit); M = mouse; R = rat
Note: No judgement of whether the available data are adequate for evaluation of these endpoints in the context of human health hazard or risk assessment has been made.

ENDPOINT	H	M	R	L	ENDPOINT	H	M	R	L
ADME					**Developmental Toxicity**				
Absorption			X		Developmental abnormalities				
Distribution			X		Embryonic/fetal effects				
Metabolism			X		Newborn effects			X	
Excretion			X		**Carcinogenicity****				
Acute Toxicity (up to 1 week)					Dermal	X			
Dermal				X	Inhalation	X			
Inhalation		X	X		Oral	X			
Injection					**Anticarcinogenicity**				
Ocular				X	Anticarcinogenic effects				
Oral		X	X		**Genotoxicity**				
Subchronic Toxicity (1 to <26 weeks)					Cytogenetic effects	X			
Dermal					Microbial gene mutation	X			
Inhalation			X		Gene mutation *in vitro*		X		
Injection					Gene mutation *in vivo*				
Oral		X	X		Germ cell effects				
Chronic Toxicity (≥26 weeks)					**Neurotoxicity**				
Dermal					Behavioral activity			X	
Inhalation					Motor activity			X	
Injection					**Immunotoxicity**				
Oral					Immunotoxic effects				
Synergism/Antagonism					**Cardiovascular Toxicity**				
Synergistic effects					Cardiovascular effects				
Antagonistic effects					**Mechanistic Data**				
Cytotoxicity					Target Organs/Tissues		X	X	
Cytotoxic effects*					Endocrine modulation				
Reproductive Toxicity					Effect on enzymes				
Fertility effects			X		Modes of action				
Maternal effects			X		Effect on metabolic pathways			X	
Paternal effects			X		**Structure-Activity Relationships**	X	X	X	X

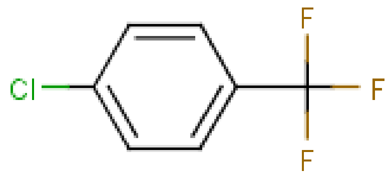
*effects observed in Salmonella, Chinese hamster ovary cells, L5178Y cells, and Balb/3T3 cells
**exposure route not defined in abstract; since occupational exposure, all routes are likely

The above table provides an overview of the data summarized in this profile. From left to right, column 1 and 6 list the endpoints and columns 2-5 and 7-10 identify the four species (human, rat, mouse, and rabbit) that were considered. An "**X**" is entered in each box that corresponds to an endpoint and species for which data are included in the profile. Blank cells indicate that no data were available in the literature.

1-Chloro-4-(trifluoromethyl)benzene Nomination Summary

Chemical Name: 1-Chloro-4-(trifluoromethyl)benzene **CAS RN:** 98-56-6

Formula: $C_7H_4ClF_3$ **Molecular Wt.:** 180.5



Basis for Nomination: 1-Chloro-4-(trifluoromethyl)benzene (PCBTF) was first nominated to the National Toxicology Program (NTP) by the National Cancer Institute in 1981. Subsequently, the NTP conducted two-week oral toxicity studies in rats and mice, absorption, disposition, metabolism, and elimination studies in male rats, and genotoxicity studies (http://ntp.niehs.nih.gov/go/TS-10472-T). In 2006, a representative from Kowa American Corporation nominated PCBTF, along with trifluoromethylbenzene [CAS No. 98-08-8], for more thorough toxicological testing because of the absence of Occupational Safety & Health Administration, The National Institute for Occupational Safety and Health, or American Conference of Governmental Industrial Hygienists exposure limits despite its expanded use (particularly with stricter clean air act regulations) and therefore greater potential for exposure to not only workers but the general public. Additionally, in public comments submitted in 2001 on the NTP Center for Evaluation of Risks to Human Reproduction draft Expert Panel Reports on 1-bromopropane and 2-bromopropane, the Executive Director of the Institute for Research and Technical Assistance requested evaluation of existing toxicology data for PCBTF to determine if chronic testing was warranted. The basis for their concern was its increasingly widespread use as a volatile organic compound exempt solvent, specifically in automobile body coatings and parts cleaning (http://cerhr.niehs.nih.gov/chemicals/bromopropanes/pubcomm/IRTA.PDF).

PCBTF is used as an intermediate in the synthesis of dyes, pharmaceuticals, pesticides, insecticides, and herbicides, and as a solvent, mainly in paint and coating formulations. Occupational exposure to PCBTF can occur through inhalation and dermal contact during its production and use. Occidental Chemical Corporation (Niagara Falls, NY) reported workplace concentrations <1 ppm. Potential exposure of the general public is primarily from PCBTF-containing products and PCBTF in and around ground water. PCBTF (0.17-2.0 ppm) was found in fish from the Niagara River as well as in air samples collected from Niagara Falls (3 ppb). It was also detected (<1 ppm) in exhaled breath from Love Canal residents. In PCBTF-exposed rats, most of the treatment dose was expired as unchanged PCBTF. The remainder was excreted as metabolites in the urine (dihydroxybenzotrifluoride and 4-chloro-3-hydroxybenzotrifluoride glucuronides, as well as minor amounts of a mercapturic acid conjugate) and feces. The vehicle used for oral dosing of test animals was shown to affect both the absorption rate and maximum blood concentration, but not bioavailability, distribution or elimination. PCBTF acute toxicity was reported to be low (e.g., LC_{50} values of 20 and 22 mg/L in mice and rats, respectively; oral LD_{50} values of 11.5 g/kg in mice and up to 13 g/kg in rats; and dermal LD_{50} >2 mL/kg in rabbits). Rats exhibited clinical signs of toxicity in subchronic inhalation studies that included salivation, hyperactivity, tremors, and increased liver weight; a no-observed-effect-level of 51 ppm was reported in a 13 week inhalation study. In subchronic oral studies, mice exhibited hepatocellular hypertrophy and cholestasis, while rats showed a variety of toxic effects that included altered hematological parameters (males only), increased liver, kidney, and thyroid weights, centrilobular hypertrophy of the liver, hyaline droplet nephrosis, and cholestasis. The mean number of pups per litter, percentage of surviving pups, and pup weights were increased in rats exposed to PCBTF via gavage but no effect on dam weights were seen. Carcinogenicity studies in animals have not been reported, but one cohort mortality study of 4000 Niagara Plant workers reported increased respiratory and stomach cancers. PCBTF was cytotoxic to *Salmonella typhimurium*, and Chinese hamster ovary, mouse lymphoma L5178Y, and Balb/3T3 cells but was not mutagenic. It did induce an increase in sister chromatid exchange in L5178Y cells with and without metabolic activation. PCBTF was not neurotoxic in rats.

A. Chemical Information

Molecular Identification

Chemical Name: 1-Chloro-4-(trifluoromethyl)benzene (PCBTF)

CAS RN: 98-56-6

Synonyms: Toluene, *p*-chloro-α,α,α-trifluoro-(6CI, 7CI, 8CI); (*p*-Chlorophenyl)trifluoromethane; 4-Chloro-α,α,α-trifluorotoluene; 4-Chlorobenzotrifluoride; 4-Chlorobenzyltrifluoride; 4-Chloro(trifluoromethyl)benzene; 4-(Trifluoromethyl)chlorobenzene; 4-(Trifluoromethyl)phenyl chloride; 4-Chloro(trifluoromethyl)benzene; *p*-Chloro-α,α,α-trifluorotoluene; *p*-(Trifluoromethyl)chlorobenzene; *p*-Trifluoromethylphenyl chloride

Trade Names: Oxsol 100

Hill Formula: C7H4ClF3

Line Formula: Cl-C6H4-CF3

Smiles Notation: C1=CC(=CC=C1C(F)(F)F)Cl

PubChem CID: 7394

InChI: 1/C7H4ClF3/c8-6-3-1-5(2-4-6)7(9,10)11/h1-4H

Molecular Weight: 180.55

Purity of Commercial Products: 98-99% (ChemExper, 2008)

Additives in Commercial Products: Not available

Impurities in Commercial Products: Not available

Mammalian Metabolites: Glucuronides of dihydroxybenzotrifluoride and 4-chloro-3-hydroxybenzotrifluoride (HSDB, 2003a)

Biodegradation Products: 64% degradation over 59 days was estimated in an anaerobic screening test using digester sludge (HSDB, 2003a)

Environmental Transformation:

Air: PCBTF slowly degrades in the atmosphere by reaction with photochemically-produced hydroxyl radicals; the estimated half-life was 67 days (HSDB, 2003a). The primary product of atmospheric oxidation is 2-chloro-5-trifluoromethylphenol (*o*-CTFP; CAS RN: 40889-91-6; PubChem CID:123498) (Young et al., 2008).

Water: Estimated volatilization half-life - 4.0 hours for a model river (1 m deep, flowing 1 m/sec), 5.3 days for a model lake (1 m deep, flowing 0.5 m/sec), and 2.0 days for a model pond (2 m deep) (HSDB, 2003a). Aqueous photolysis of the primary atmospheric oxidation product, *o*-CTFP, produces 3,4-dihydroxybenzoic acid (protocatechuic acid, CAS RN: 99-50-3; PubChem CID:72) which is an approved food additive (Young et al., 2008).

Soil: Based on vapor pressure shown below, the potential for volatilization from dry soil may exist (HSDB, 2003a)

Physical-Chemical Properties

Physical State: water-white liquid with an aromatic odor (HSDB, 2003a)

Specific Gravity or Density Value: 1.3340 g/cm^3 @ 25 °C (Registry, 2008)

Boiling Point: 138.5 °C (ChemIDplus, undated; Registry, 2008)

Vapor Pressure: 7.63 mm Hg @ 25 °C (ChemIDplus, undated)

Solubility: 84.5 mg/L in water @ 25 °C [calculated] (ChemIDplus, undated)

Log P = Log K_{ow}: 3.600 [calculated] (ChemIDplus, undated); 3.458±0.277 @ 25 °C [calculated] (Registry, 2008)

Bioconcentration Factor(s) (species): 249.88 at pH 1-10 @ 25 °C [calculated] (Registry, 2008); 320 estimated from the log K_{ow} (above); suggests high potential for bioconcentration in aquatic organisms (HSDB, 2003a)

B. Exposure Potential

U.S. Annual Production
1986, 1990, 1994, 1998: >10 – 50 million pounds
2002: >1 – 10 million pounds
(U.S. EPA, 2009a [U.S. EPA IUR database; search by casno = 98566])

Worldwide Annual Production
Not available

Production Processes
- Reaction of 4-chloro-toluene with 2,4-dichlorotoluene (Maul et al., 1999).
- Reaction of bromine with 1-chloro-4-trifluoromethylcyclohex-1-ene in liquid phase at <190 °C (Tang, 1990 pat.).

Uses
(HSDB, 2003a; Maul et al., 1999)
- Intermediate in the synthesis of the following:
  - Dyes
  - Pharmaceuticals
  - Pesticides/insecticides
  - Herbicides (e.g., trifluralin and fluorodifen)
- Dielectric/functional fluid
- Solvent, particularly in paint and coating formulations:
  - Urethane systems [major coatings use area through 1998]
  - Epoxy, polyester, acrylic, silicone, ethyl silicate, phenolic varnish, vinyl butyral, melamine/urea formaldehyde, and nitrocellulose resin systems
  - Application areas: automotive refinishing, industrial, maintenance, metal furniture and appliances, wood furniture, marine coatings, aerospace, conformal coatings, and concrete sealers
  - Non-volatile organic compound universal diluent at the spray gun for modern high solids coatings
  - Metal cleaning, precision cleaning, adhesives, inks, and dye carriers

Occupational Exposure
Exposure may occur through inhalation and dermal contact at workplaces where PCBTF is produced or used (HSDB, 2003a). Occidental Chem. Co. (Niagara Falls, NY) reported workplace concentrations of <1ppm (U.S. EPA, 1985).

General Population Exposure
Potential exposure is primarily from PCBTF-containing products and PCBTF in ground water and surrounding soil. Water samples collected during a demineralization process were reported to be contaminated with PCBTF from the cation exchanger (Botta and Mantica, 1999). PCBTF was also found in residue of fish (0.17-2.0 ppm) from the Niagara River (Yurawecz, 1979 [PMID:422503]).

Foods and Beverages, Cosmetics, etc.: Not available

Ambient Environment

Preliminary Remediation Goals were reported for residential soil ($1.2x10^3$ mg/kg), industrial soil ($1.2x10^4$ mg/kg), ambient air (7.3 µg/m^3), and tap water ($7.3x10_2$ µg/L) (U.S.EPA, 2004).

Air Limit: Not available

Water Limit(s): 5 µg/L for groundwater (NY State Dept. of Environ. Conserv, 1999)

Soil Limit: Not available

Environmental Exposure in the United States: Detected at 3 ppb in 3 of 15 air samples from Niagara Falls, NY, and at <1ppb in exhaled breath from 5 of 9 Love Canal residents (U.S. EPA, 1985).

Levels in Tissues, Body Fluids, and Excreta: Not available

Environmental Occurrence

Natural Occurrence: Not applicable

U.S. Environmental Releases
Toxics Release Inventory: Not available
Hazardous Waste Sites: Yes _X_ No ____ No. of Facilities: at least 2 (Occidental Chemical Corporation and Diaz Chemical Corporation)
Industrial Releases (non-TRI substance): Mean concentrations released to soil and groundwater by Occidental Chemical Corporation (Niagara Falls, NY) were reported to be 217 µg/L (range: ND - 4,600 µg/L) (Wertz, 2001); 49,000 ppb were reported in groundwater from the Diaz Chemical Corporation site in Holley, NY (U.S. EPA, 2005).
Mobile Sources: Not available
Municipal and Hospital Waste Incineration: Not available
Concentrations in Environmental Media
Surface Water: Detected in water samples from Love Canal, NY, and Lake Ontario (HSDB, 2003a).
Groundwater: Found in the groundwater in Vicenza, Italy, at 1 mg/L due to improper chemical discharges (Cacco and Ferrari, 1982).
Industrial Wastewater: Detected in water samples from the Diaz Chemical Corporation Building C sump and wastewater pit (880 and 44 ppb, respectively) (U.S. EPA, 2005).
Municipal Waste/Sewage: Not available
Ambient Air: Concentrations in two household air samples in Holley, NY, ranged from 0.3 to 3 ppb (U.S. EPA, 2005).
Soils: Detected in sediment and soil samples from Love Canal, NY (Hauser and Bromberg, 1980; HSDB, 2003a); also identified in water (0.1-1 ppb) and sediment (0.5-2 ppm) samples from Bloody Run Creek, Niagara River Watershed (Niagara Falls, NY) (Elder et al., 1981).

C. Regulatory Information

U.S. Regulations

- In 1985 a decision issued by the U.S. EPA required no further testing of PCBTF for health effects, environmental effects, or chemical fate; U.S. EPA and Occidental Chemical Corporation data were reported to be adequate (U.S. EPA, 1985).
- PCBTF is listed on the TSCA Chemical Substances Inventory (Dialog, 2009). PCBTF is considered an orphan High Production Volume chemical and in 2006 was included in TSCA section 8(a) (Preliminary Assessment Information Reporting) and TSCA section 8(d) (Health and Safety Data Reporting [HaSDR]) rules (http://www.epa.gov/HPV/pubs/general/regactions.htm). Occidental Chem. Corp. (2007) submitted robust test summary data in response to the HaSDR rule.
- The U.S. EPA requires the submission of health and safety, environmental fate, and environmental effect studies on PCBTF when PCBTF is ≥90% by weight of test substance (U.S. EPA, 2008a). Chemical manufacturers and processors are required by the U.S. EPA to report production, use, and exposure-related information (U.S. EPA, 2008b).
- In 2009, the U.S. EPA proposed to amend the National Volatile Organic Compound Emission Standards for Aerosol Coatings (aerosol coatings reactivity rule), under the Clean Air Act. The proposed amendment would include PCBTF as a compound that could be used in an aerosol coating product (U.S. EPA, 2009b).

Exposure Limits (Standards and Criteria): Not available

European Union Scientific Committee Regulations

None available

Canadian Domestic Substances List (DSL) and Non Domestic Substances List (NDSL)

PCBTF is specified on the public portion of the DSL (published February 28, 2001), and no control measures are required. Substances on the DSL are not subject to a New Substance Notification under the 1999 Canadian Environmental Protection Act (Environment Canada, 2009).

D. Toxicological Information

General Toxicity

Human Studies: Exposure induces skin, eye, and respiratory irritation, depression of central nervous system, and dermatitis due to defatting of the skin. Other symptoms include coughing, wheezing, a burning sensation, laryngitis, shortness of breath, headache, nausea, vomiting, lung irritation, chest pain, and edema. PCBTF is destructive to mucous membrane tissues (CAMEO Chemicals, undated).

Animal Studies: Negative in skin and eye irritation studies in rabbits (Maul et al., 1999).

- Inhalation of >28.4 mg/L (4 hours) caused death in rats (Hooker Chem. Co. 1979a; U.S. EPA, 1985). Clinical observations included muscle spasms and salivation during exposure and nasal discharge, lacrimation, and limb ataxia 14-days postexposure; decedents and survivors had lung and kidney discoloration and red foci in lungs.
- Single oral dose (5 mL/kg) in rats caused hypoactivity, tremors, ataxia, lacrimation, etc; decedents and survivors showed hemorrhagic areas in the thymus, white foci in lungs, and a solid mass in the uterus of one female (Hooker Chem. Co., 1979b).
- Dermal application (2 mL/kg) to rabbits for 24 hours produced erythema and edema that lasted up to 72 hours; decedents and survivors had pitted surfaces of kidneys, red foci in lungs, abscesses, and adhesion of pericardium to thoracic cavity wall (Hooker Chem. Co., 1978).

Chemical Disposition, Metabolism, and Toxicokinetics

Absorption and Clearance: One study for developing a PBPK model for inhaled PCBF reported that V_{max} (1038 nmol/hr/kg) and K_m (65.7 µmol/L) values from the metabolism of PCBTF to 3-OH-PCBTF by rat liver microsomes were not significantly altered by inhalation exposure of rats to PCBTF (10, 50, or 250 ppm for 13 weeks). These results indicate that PCBTF may not significantly induce rat liver CYP450 (Knaak et al., 1995 [PMID:7570677], 1998).

Human Studies: Partition coefficients for blood, fat, brain, and muscle have been determined (Abraham and Ibrahim, 2006; Abraham et al., 2005, 2006a,b).

Animal Studies:

- Single oral dose of [^{14}C]-PCBTF to rats (evaluation period not given); 62-82% expired unchanged; 3-4% and 14-15% was excreted in feces and urine, respectively. Urinary metabolites were glucuronides of dihydroxybenzotrifluoride and 4-chloro-3-hydroxybenzotrifluoride, with minor amounts of a mercapturic acid conjugate of PCBTF. Most of the radiolabel in the feces was unmetabolized. After 4 days ~1% of the unchanged dose remained in the body, predominantly in the fat (HSDB, 2003a; Occidental Chem. Corp., 1982).
- Average absorption half-life in male F344 rats dosed intragastrically was 17 minutes using α-cyclodextrin (CD) as the vehicle and 98 minutes with corn oil (CO) as the vehicle. The half-life after intravenous injection in 10% Tween 80 aqueous solution was 19 hours. Elimination constant, total body clearance and apparent volume of distribution were similar regardless of exposure route or vehicle. A significant differences was reported for time to reach maximum blood concentration, maximum blood concentration achieved (C_{max}), C_{max}-normalized dose, and absorption rate constant for CD versus CO (absorption was faster with CD). The bioavailability was complete for both vehicles and no statistical difference was observed in the area under the blood concentration versus time curves for either vehicle (Yuan et al., 1991 [PMID:1949027]).
- Partition coefficients for blood, fat, brain, and muscle have been determined (Abraham and Ibrahim, 2006; Abraham et al., 2005, 2006a,b).

Acute Exposures

LC_{50}/LD_{50} Values:	inhalation $LC_{50,}$ = 33 mg/L [rat] (Hooker Chem. Co., 1979a; U.S. EPA, 1985)
	inhalation LC_{50} = 22 mg/L [rat] (ChemIDplus, undated; RTECS, 2006a)
	inhalation LC_{50} = 20 mg/L [mouse] (ChemIDplus, undated; RTECS, 2006a)
	oral LD_{50} >5 mL/kg [rat] (Hooker Chem. Co., 1979b)
	oral LD_{50} = 6.8 g/kg [rat] (U.S. EPA, 1985)

oral LD_{50} = 13 g/kg [rat] (ChemIDplus, undated; RTECS, 2006a)
oral LD_{50} = 11.5 g/kg [mouse] (ChemIDplus, undated; U.S. EPA, 1985)
dermal LD_{50} > 2 mL/kg [rabbit] (Hooker Chem. Co., 1978)

Route:	inhalation
Species:	rat (Sprague-Dawley, 5 male and 5 female/dose)
Dose/Duration:	6.03, 20.8, 28.4, 39.1, and 66.7 mg/L for 4 hours
Observation Time:	14 days
Effects:	4, 6, and 8 animals exposed to 28.4, 39.1, and 66.7 mg/L, respectively, died; clinical observations during exposure included muscle spasms, labored breathing, excessive salivation and lacrimation, and mucoid nasal discharge; clinical observations 14-days postexposure included red and mucoid nasal discharge, excessive lacrimation, hypersensitivity to sound, limb ataxia, hair loss, and increased activity; necropsy of decedents and survivors showed lung discoloration, red foci in lungs, and kidney discoloration; no specific pathology was observed that was not observed in controls.
Source(s):	Hooker Chem. Co. (1979a); U.S. EPA (1985)

Route:	oral (gavage)
Species:	rat (Sprague-Dawley, 8 male and 8 female)
Dose/Duration:	5 mL/kg
Observation Time:	not provided
Effects:	2 males died; clinical observations included hypoactivity, tremors, ataxia, decreased limb tone, loss of righting reflex, lacrimation, hypothermia, hostility, and piloerection; necropsy of decedents and survivors showed hemorrhagic areas in thymus, white foci in (dark) lungs, and a solid mass in uterus of a female.
Source(s):	Hooker Chem. Co. (1979b)

Route:	dermal (occluded application)
Species:	rabbit (New Zealand White, 5 male and 5 female)
Dose/Duration:	2 mL/kg for 24 hours
Observation Time:	14 days
Effects:	1 female died; clinical observations included erythema and edema at 24 hours (effects gone by 72 hours); necropsy of decedents and survivors showed pitted surfaces of kidneys, scattered red foci on lungs, abscesses, and adhesion of pericardium with thoracic cavity wall; no significant lesions observed at application site in most test animals.
Source(s):	Hooker Chem. Co. (1978)

Subchronic Exposures

Route:	inhalation
Species:	rat (strain and sex not provided)
Dose/Duration:	1, 100, 250, 500, or 1000 ppm for 28 days
Observation Time:	not provided
Effects:	no deaths; at ≥500 ppm clinical signs included salivation, hyperactivity, and increased liver weight
Source(s):	Oxychem Co. (1993)

Route:	inhalation
Species:	rat (strain not provided, 10/sex/dose)
Dose/Duration:	100, 262.1, 492.3, and 1044 ppm for 6 hours/day, 5 days/week for 4 weeks

Observation Time:	not provided
Effects:	hyperactivity (dose related), tremors (1044 ppm), microscopic kidney and liver changes (≥262.1 and ≥100 ppm, respectively), and clinical chemistry parameter (≥492.3 ppm)
Source(s):	Occidental Chem. Corp. (1993)

Route:	inhalation
Species:	rat (Sprague Dawley, 10/sex/dose)
Dose/Duration:	0, 10, 51, or 252 ppm for 6 hours/day, 5 days/week for 13 weeks
Observation Time:	not provided
Effects:	no PCTB-related effects observed either during exposures or weekly clinical evaluations; no changes observed in body weight gain or measured hematological and clinical chemistry parameters; increase (11%) in relative liver weights in both sexes at highest dose tested correlated with centrilobular hypertrophy
Source(s):	Newton et al. (1998)
Notes:	NOEL (hepatocyte hypertrophy) = 51 ppm

Route:	oral (gavage)
Species:	mice ($B6C3F_1$, 5/sex/dose)
Dose/Duration:	0, 10, 50, and 400 mg PBCTF (in alpha-cyclodextrin [CD])/kg; 0, 10, 50, 400, and 1000 mg PBCTF (in corn oil [CO])/kg for 14 days
Observation Time:	15 days
Effects:	no tissue bioaccumulation with either vehicle; vehicle-independent hepatocellular hypertrophy and cholestasis
Source(s):	NTP (1992); Yuan et al. (1992 [PMID:1375921])

Route:	oral (gavage)
Species:	rat (Fischer-344, 15 male and 15 female)
Dose/Duration:	0, 10, 40, 150, or 500 mg/kg for 3 months
Observation Time:	not provided
Effects:	sex-specific effects observed (e.g., elevated alkaline phosphatase serum levels and altered hematological parameters in males); additional effects observed included increased liver, kidney, and thyroid weights, centrilobular hypertrophy of the liver at the high dose, and increased colloid in the thyroid gland
Source(s):	Elanco Products Co. (1983); U.S. EPA (1985)
Notes:	NOEL = 10 mg/kg

Route:	oral (gavage)
Species:	rat (Sprague-Dawley, 6/sex/dose)
Dose/Duration:	0, 10, 100, and 1000 mg/kg for 28 days
Observation Time:	not provided
Effects:	salivation observed in high-dose group; changes in blood chemistry observed in both sexes; hyaline droplet nephrosis, increase in relative kidney weight and in lipid vacuoles in adrenal cortex observed in males; increase in relative liver weights observed in both sexes
Source(s):	Macrì et al. (1987 [PMID:3679024])
Notes:	NOEL = 10 mg/kg/day

Route:	oral (gavage)
Species:	rat (F344/N, 5/sex/dose)

Dose/Duration:	0, 10, 50, and 400 mg PBCTF (in alpha-cyclodextrin [CD])/kg; 0, 50, 400, and 1000 mg PBCTF (in corn oil [CO])/kg for 14 days
Observation Time:	15 days
Effects:	1 high-dose female rat died, cause of death not determined; male rats receiving highest dose in CO had significantly lower body weights compared to controls; toxic nephropathy observed in male rats; hepatocyte hypertrophy and cytoplasmic vacuolization of the adrenal cortex observed in male and female rats; clinical pathology studies suggest mild anemia and cholestasis in rats; linear relationship between PCBTF kidney concentrations and alpha2u-globulin; clinical pathology studies suggest mild liver injury and cholestasis
Source(s):	NTP (1992); Yuan et al. (1992 [PMID:1375921])

Chronic Exposures
Not available
Synergistic/Antagonistic Effects
Not available
Cytotoxicity

- Cytotoxic to *Salmonella typhimurium* strains TA1535 and TA1537 at 10 µg/plate (HSDB, 2003a).
- Cytotoxic to Chinese hamster ovary (CHO) and mouse lymphoma L5178Y cells at concentrations ≥60 nL/mL (HSDB, 2003a).
- Dose-dependent decrease in relative survival (from 80% down to 50%) in Balb/3T3 cells after incubation for 72 hours (HSDB, 2003a).

Reproductive and Developmental Toxicity

Human Studies: Not available

Animal Studies: Male and female Sprague-Dawley rats (F_0; 20/sex/dose) were exposed via gavage to 0, 5, 15 or 45 mg/kg/day in corn oil starting 4 weeks prior to mating and continuing until litters (F_1) were weaned. F_1 pups (20/sex/dose) were treated orally with PCBTF for 90 days after weaning. The following significant changes were observed in treated versus control animals

- Increased mean number of pups per litter in the mid-dose group (females) and low-dose group (combined sexes), and in the percentage of surviving pups and pup weights in all dose groups
- Increased weight gain in F_1 male pups (all doses); decrease in female pups (high dose).
- Increased serum glutamic-pyruvic transaminase in F_1 females (mid-dose)
- Increased mean corpuscular volume but decreased hemoglobin in F_1 females (high-dose)
- Decreased corpuscular hemoglobin in all F_1 male treatment groups
- Decreased erythrocyte count F_1 females (low-dose)
- Increase in lung pathology (bronchopneumonia, adenomous hyperplasia, and inflammatory cell infiltrates) for all F_1 treatment groups.

No differences reported in dam weights, mortality, or urinalysis nor in F_1 mortalities, clinical chemistry, urinalysis, or organ weights for treated versus control groups (Hooker Chem. Co., 1981).

Carcinogenicity

Human Studies: Cohort mortality study of 4000 workers from a Occidental Chemical Corporation plant in Niagara showed increased respiratory and stomach cancers (Occidental Chem. Corp., 1983).

Animal Studies: Not available

Anticarcinogenicity
Not available
Genetic Toxicity

Microbial Gene Mutation:

- Negative in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 with or without metabolic activation (S9) (e.g., Bignami and Crebelli, 1979; CCRIS, 1991; HSDB, 2003a; NTP, 2009a).
- Negative for gene conversion in *Saccharomyces cerevisiae* (HSDB, 2003a).

- Biological fluid from mice treated with PCBTF over 2 days was negative in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 (HSDB, 2003a).

Human Studies (*in vitro* and *in vivo*): Not available

Animal Studies (*in vitro* and *in vivo*):

Gene Mutation: Negative in mouse lymphoma cells at the thymidine kinase locus (HSDB, 2003a).

Cytogenetic Effects:

- Positive in L5178Y mouse lymphoma cells with and without S9 for increased sister chromatid exchange (SCE)/chromosome (0.02 µL/mL without S9; 0.0025, 0.01, and 0.02 µL/mL with S9) and SCE/cell with S9 (0.0025, 0.01, and 0.02 µL/mL) (HSDB, 2003a).
- Negative for chromosomal aberrations in CHO cells and for Balb/3T3 mouse cell transformation (HSDB, 2003a).
- Negative for chromosomal aberrations in Sprague-Dawley rat bone marrow (single gavage dose 0, 0.5, 1.7 or 5.0 mL/kg) (HSDB, 2003a).

Germ Cell Effects: Not available

Neurotoxicity

Human Studies: Not available

Animal Studies: No effect on motor activity or the nervous system, as measured by a battery of functional observational assessments (e.g., reactivity to stimuli, righting reflex, and landing foot splay) in rats after inhalation exposure (6 hours/day, 5 days/week for 13 weeks). No convulsions, tremors, or abnormal movements were noted (Newton et al., 1998).

Immunotoxicity

Not available

E. Mechanistic Data

Target Organs/Tissues

Human: Not available

Animal: Kidney and liver (BG Chemie, 1995 [species not identified]; NTP, 1992 [rats, mice])

Endocrine Modulation

Not available

Effect on Enzymes

Not available

Modes of Action

Human: Not available

Animal: Not available

Effect on Metabolic Pathways:

Activation: Inhalation exposure (10, 50, and 250 ppm; 6 hours/day for 90 days) produced a significant increase in total CYP450 content in female but not male rat liver microsomes at the 250 ppm dose. Analysis of specific CYP450s showed significant increases in CYP1A1, -1A2, -2B and -2E1, but not -3A, in male rats at the high dose. In female rats CYP1A1, -1A2, -2B and -3A, but not -2E1, were significantly elevated at the high dose. NOEL = 50 ppm (Pelosi et al., 1998).

Perturbation: Not available

Structure-Activity Relationships

QSAR studies with di-substituted benzene derivatives (general formula: 1-R-C_6H_4-4-X, where R = Cl, OH, NH_2, NO_2, or $N(CH_3)_2$ and X = a variety of groups including CF_3) evaluated correlations between structure and acute toxicity in *Photobacterium phosphoreum* using the Microtox test. Toxicity was correlated to Log P values when Cl was in the 1-position ($r^2 = 0.35$; n = 41). Toxicities were more highly correlated with the corresponding mono-substituted derivatives where R = H in the general formula, particularly when the R substituent is Cl ($r^2 = 0.71$; n = 35) (Kaiser, 1987).

Below are brief summaries of toxicological data for close PCBTF structural analogs. The availability of records from RTECS, HSDB, TSCA Inventory, and CAPLUS for additional analogs is provided in the table in the Appendix.

Isomers:

1-Chloro-3-(trifluoromethyl)benzene (MCBTF; CAS No. 98-15-7; PubChem CID:7374): No information on human effects was available. Low toxicity in rats reported after acute oral (LD_{50} >5 g/kg) and inhalation exposure (LC_{50} >23.6 g/m^3/4 hours). Toxic effects noted included muscle weakness and respiratory depression. MCBTF did not induce gene mutations or chromosomal aberrations. Based on structural similarities to PCBTF, similar effects on the liver and kidney may be expected (BG Chemie, 1997; CCRIS, 1994a; NTP 2009b; RTECS, 2002).

1-Chloro-2-(trifluoromethyl)benzene (OCBTF; CAS No. 88-16-4; PubChem CID:6921): Inhalation and skin absorption may affect the central nervous system, with possible narcosis. Low toxicity (LD_{50} = 1.6-2.0 and 2.9 g/kg) observed after acute oral administration to rats. Effects on lungs, liver, kidneys and adrenal glands, pancreas, and gut epithelium observed; all toxic effects (e.g., impairment of motor function and breathing) were reversed in animals after 6 days. OCBTF induced skin irritation in rabbits. It did not induce gene mutations or chromosomal aberrations. Time-weighted average and short-term exposure limit per the International Occupational Exposure Limits were set at 20 mg/m^3 and 60 mg/m^3 skin, respectively (BG Chemie, 1990; CCRIS, 1994b; NTP, 2009c; RTECS, 2006b).

Congeners:

1-Chloro-4-(trichloromethyl)benzene (PCBTC; CAS No. 5216-25-1; PubChem CID:21277):

- After a single oral dose of 1.4 mg/kg in rats, most was excreted in urine (77-87%); major urinary metabolite was 4-chlorohippuric acid (BG Chemie, 1994; Quistad et al., 1985).
- Time-weighted average and short-term exposure limit per the International Occupational Exposure Limits was set as 0.01 mg/m^3 and 0.05 mg/m^3 skin, respectively (RTECS, undated).
- Produced moderate to high acute toxicity, depending on exposure route: oral LD_{50} = 614–1350 mg/kg [rat], 700 mg/kg [mouse]; dermal LD_{50} = 1900 mg/kg [rat], >2000 mg/kg [rabbit]; inhalation LC_{50} = 125 mg/m^3 [rat, mouse]. Structural changes to trachea and/or bronchi were observed in inhalation studies (BG Chemie, 1994; ChemIDplus, undated).
- Repeated oral administration for 14 days in rats reduced body weight gain and feed intake and induced body weight loss, gastrointestinal disturbances, dehydration, impaired breathing, ataxia, and spasms. The NOEL was 1.25 mg/kg and doses >150 mg/kg led to animal death. Repeated oral administration for 90 days reduced leukocyte and lymphocyte counts. Effects on the testes and liver were also observed (BG Chemie, 1994).
- Inhalation studies in rats exposed for 30 days induced airway irritation at the highest test concentration (100 mg/m^3). Effects on the respiratory tract, spleen, thymus, testes, and endometrium were observed at the lowest concentration (4 mg/m^3). Longer inhalation exposure (4 months) induced weight loss and affected the nervous system, liver, kidneys, lungs, and blood in rats and guinea pigs (BG Chemie, 1994).
- Skin corrosive and slight eye irritant in rabbits; induced skin sensitization in guinea pigs (BG Chemie, 1994).
- Positive in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* with S9 (BG Chemie, 1994).
- Induced chromosomal aberrations in CHO cells with and without S9 (CCRIS, 2005).
- Long-term oral or dermal exposure in mice induced a dose-dependent increase in tumor incidence in studied organs and tissues (BG Chemie, 1994).
- Not embryotoxic or teratogenic in rats after inhalation exposure (BG Chemie, 1994).

1,2-Dichloro-4-(trifluoromethyl)benzene (3,4-DCBTF: CAS No. 328-84-7; PubChem CID:9481):

- Repeated exposure may cause dermatitis and overexposure to vapors may cause nose and throat irritation; it is slightly irritating to eyes and skin (HSDB, 2003b).
- Decreases isolated rat liver mitochondrial respiration (Schiller, 1980).

- Negative in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538; *E. coli* strains W3110/POL A+ and P3478/POL A-; and *Saccharomyces cerevisiae*. Negative for mutation at the thymidine kinase locus in mouse lymphoma cells. No increase in transformation of BALB/3T3 cells (HSDB, 2003b; HPVIS, 2009).
- Positive for SCE in L5178Y mouse lymphoma cells with metabolic activation. Induced unscheduled DNA synthesis in EuE cells (HSDB, 2003b; HPVIS, 2009).
- No mutagenic material was identified in the urine of male mice exposed to 3,4-DCBTF (HPVIS, 2009).
- Induced skin and eye irritation in rabbits (HSDB, 2003b; HPVIS, 2009).
- Shows low to moderate acute toxicity, depending on route of exposure: oral LD_{50} = 1.15 g/kg, ~2 ml/kg, 1.96 ml/kg (F), and 2.225 ml/kg (M) [rat]; dermal LD_{50} >5 g/kg [rabbit], >5 ml/kg [rat]; inhalation LC_{50} >15860 mg/m^3 and >2000 ppm/hour [rat]). Oral administration produced salivation, chromorhinitis, tremors, lethargy, body rigidity, and diarrhea. Pathology studies showed hemorrhagic lungs and darkened liver (ChemIDplus, undated; HSDB, 2003b; HPVIS, 2009).
- Rat subchronic studies showed changes in organ weights and effects on kidneys (HPVIS, 2009)
- No effect on reproduction at doses up to 45 mg/kg (Maul et al., 1999).
- Liver and kidneys are likely target organs (Maul et al., 1999).

<u>2,4-Dichloro-1-(trifluoromethyl)benzene</u> (2,4-DCBTF; CAS No. 320-60-5; PubChem CID:9443):

- Showed low acute toxicity: oral LD_{50} >10 g/kg [rabbit], >25 g/kg, >2.6 g/kg [rat]; dermal LD_{50} >2 g/kg [rabbit]; and inhalation LC_{50} > 5mg/L (ChemIDplus, undated; Occidental Chem. Corp., 1992).
- Did not induce skin or eye irritations or skin sensitization (Occidental Chem. Corp., 1992).
- Repeated exposure (90 days) increased liver weights at highest tested concentration (10%) (Occidental Chem. Corp., 1992).
- Repeated dermal exposure (28 days) reduced ovary weight at ≥500 mg/kg (Occidental Chem. Corp., 1992).
- Repeated inhalation exposure (28 days) increased liver and lung weight and the numbers of pulmonary macrophages, hepatocytomegaly, and centrilobular hepatocytes (Occidental Chem. Corp., 1992).

Reactive Moieties: Not available

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Search Strategy

STN International files MEDLINE, AGRICOLA, CABA, EMBASE, ESBIOBASE, BIOTECHNO, IPA, BIOSIS, TOXCENTER, and NTIS were searched simultaneously on March 5, 2008. The search terms included the CAS RN, synonyms, a trade name that appeared in the REGISTRY record, and abbreviations seen in a few abstracts. The abbreviation CTT was not specific enough for an unrestricted search such as this and was not used. The history of the search session is reproduced below. The set of synonyms, including those with zero hits in this set of databases, was saved as a query for possible future use in other databases such as the environmental sections of CAPLUS.

```
L1            20 S (O OR 1)(W)CHLORO(W)(4 OR P OR PARA)(W)TRIFLUOROMETHYL(W)BENZENE
L2            87 S (P OR 4 OR PARA)(W)CHLORO(4A)TRIFLUOROTOLUENE
L3             0 S (P OR 4 OR PARA)(W)CHLOROPHENYL(W)TRIFLUOROMETHANE
L4             0 S (O OR 1)(W)TRIFLUOROMETHYL(W)(4 OR P OR PARA)(W)CHLOROBENZENE
L5             2 S (O OR 1)(W)CHLORO(W)(P OR PARA OR 4)(W)TRIFLUOROMETHYLBENZENE
L6           138 S (PARA OR P OR 4)(W)CHLOROBENZOTRIFLUORIDE
L7             6 S TRIFLUORO(W)(P OR PARA OR 4)(W)CHLOROTOLUENE
L8            13 S (PARA OR P OR 4)(W)TRIFLUOROMETHYL(W)CHLOROBENZENE
L9             9 S (PARA OR P OR 4)(W)CHLOROTRIFLUOROMETHYLBENZENE
L10            0 S PARACHLOROTRIFLUOROMETHYLBENZENE
L11            0 S (PARA OR 4 OR P)(4A)TRIFLUOROCHLOROTOLUENE
L12            6 S OXSOL(W)100
L13            0 S 4(W)CHLOROBENZYLTRIFLUORIDE OR 4(W)CHLOROBENZYL(W)TRIFLUORIDE
L14           23 S PARACHLOROBENZOTRIFLUORIDE
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L15           1 S (4 OR P OR PARA)(W)TRIFLUOROMETHYLPHENYL(W)CHLORIDE
L16         104 S TFCB OR PCBTF OR CTFT
L17           6 S (PARA OR P OR 4)(4A)(CHLOROTRIFLUOROTOLUENE)
L18           0 S PARACHLOROTRIFLUOROTOLUENE
L19         206 S 98-56-6
L20         323 S L1-L18
L21         356 S L20 OR L19
                SET DUPORDER FILE
L22         234 DUP REM L21 (122 DUPLICATES REMOVED)
                SAVE L21 X0520NAMES/Q
L23         234 SORT L22 1-234 TI
                SAVE L23 X0520BIOMED/A
```
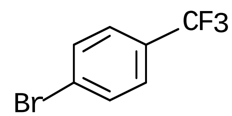
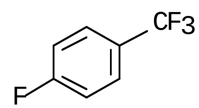
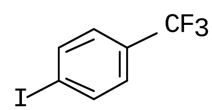
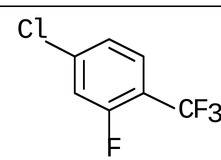
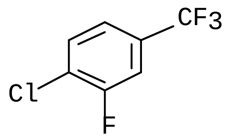
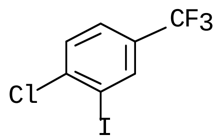

Additional duplicates were removed by comparing the titles sorted in alphabetical order. Answer numbers for 78 selected titles were grouped by subjects addressed in a typical dossier and printed in full in a subsequent online session.

On April 24, 2009, using the same strategy but with the limitation to publication years 2008 and 2009, the search was repeated to identify new data published since the previous draft profile was written. Five records (four TOXCENTER and one MEDLINE record) pertaining to QSAR studies were download; one of acute toxicity in rats, three of environmental fate, and one of the prediction of the air-to-blood partition coefficient. Most of the other references identified related to the use of PCBTF in synthesis processes, especially synthesis of pharmaceuticals.

Appendix. Several PCBTF Analogs and Their Record Availability in RTECS, HSDB, TSCA Inventory, and CAPLUS

Chemical or Trade Name	CAS RN	Structure	PubChem CID	RTECS	HSDB	TSCA Inventory	Records in CAPLUS
Benzene, 1-bromo-4-(trifluoromethyl)- (CA INDEX NAME) OTHER CA INDEX NAMES: Toluene, p-bromo-α,α,α-trifluoro- (6CI, 7CI, 8CI) OTHER NAMES: 1-Bromo-4-(trifluoromethyl)benzene 4-(Trifluoromethyl)bromobenzene 4-Bromobenzotrifluoride p-(Trifluoromethyl)bromobenzene p-Bromo(trifluoromethyl)benzene p-Bromobenzotrifluoride	402-43-7		67827	-	-	x	1160
Benzene, 1-fluoro-4-(trifluoromethyl)- (CA INDEX NAME) OTHER CA INDEX NAMES: Toluene, p,α,α,α-tetrafluoro- (6CI, 7CI, 8CI) OTHER NAMES: 1-Fluoro-4-(trifluoromethyl)benzene 4-(Trifluoromethyl)fluorobenzene 4-Fluorobenzotrifluoride p-(Trifluoromethyl)fluorobenzene p-Fluoro(trifluoromethyl)benzene p-Fluorobenzotrifluoride	402-44-8		67873	-	-	x	244
Benzene, 1-iodo-4-(trifluoromethyl)- (CA INDEX NAME) OTHER CA INDEX NAMES: Toluene, α,α,α-trifluoro-p-iodo- (8CI) OTHER NAMES: 1-Iodo-4-(trifluoromethyl)benzene 4-(Trifluoromethyl)iodobenzene 4-Iodobenzotrifluoride p-(Trifluoromethyl)iodobenzene p-Iodo(trifluoromethyl)benzene p-Iodobenzotrifluoride	455-13-0		67993	-	-	x	447
Benzene, 4-chloro-2-fluoro-1-(trifluoromethyl)- (CA INDEX NAME) OTHER NAMES: 4-Chloro-2-fluorobenzotrifluoride	94444-59-4			-	-	-	6

Chemical or Trade Name	CAS RN	Structure	PubChem CID	RTECS	HSDB	TSCA Inventory	Records in CAPLUS
Benzene, 1-chloro-2-fluoro-4-(trifluoromethyl)- (CA INDEX NAME) OTHER CA INDEX NAMES: Toluene, 4-chloro-α,α,α,3-tetrafluoro- (8CI) OTHER NAMES: 1-Chloro-2-fluoro-4-(trifluoromethyl)benzene 3-Fluoro-4-chlorobenzotrifluoride 4-Chloro-3-fluorobenzotrifluoride	32137-20-5			-	-	-	16
Benzene, 1-chloro-2-iodo-4-(trifluoromethyl)- (CA INDEX NAME) OTHER CA INDEX NAMES: Toluene, 4-chloro-α,α,α-trifluoro-3-iodo- (7CI, 8CI) OTHER NAMES: 1-Chloro-2-iodo-4-trifluoromethylbenzene 2-Chloro-1-iodo-5-trifluoromethylbenzene	672-57-1		69596	-	-	-	24