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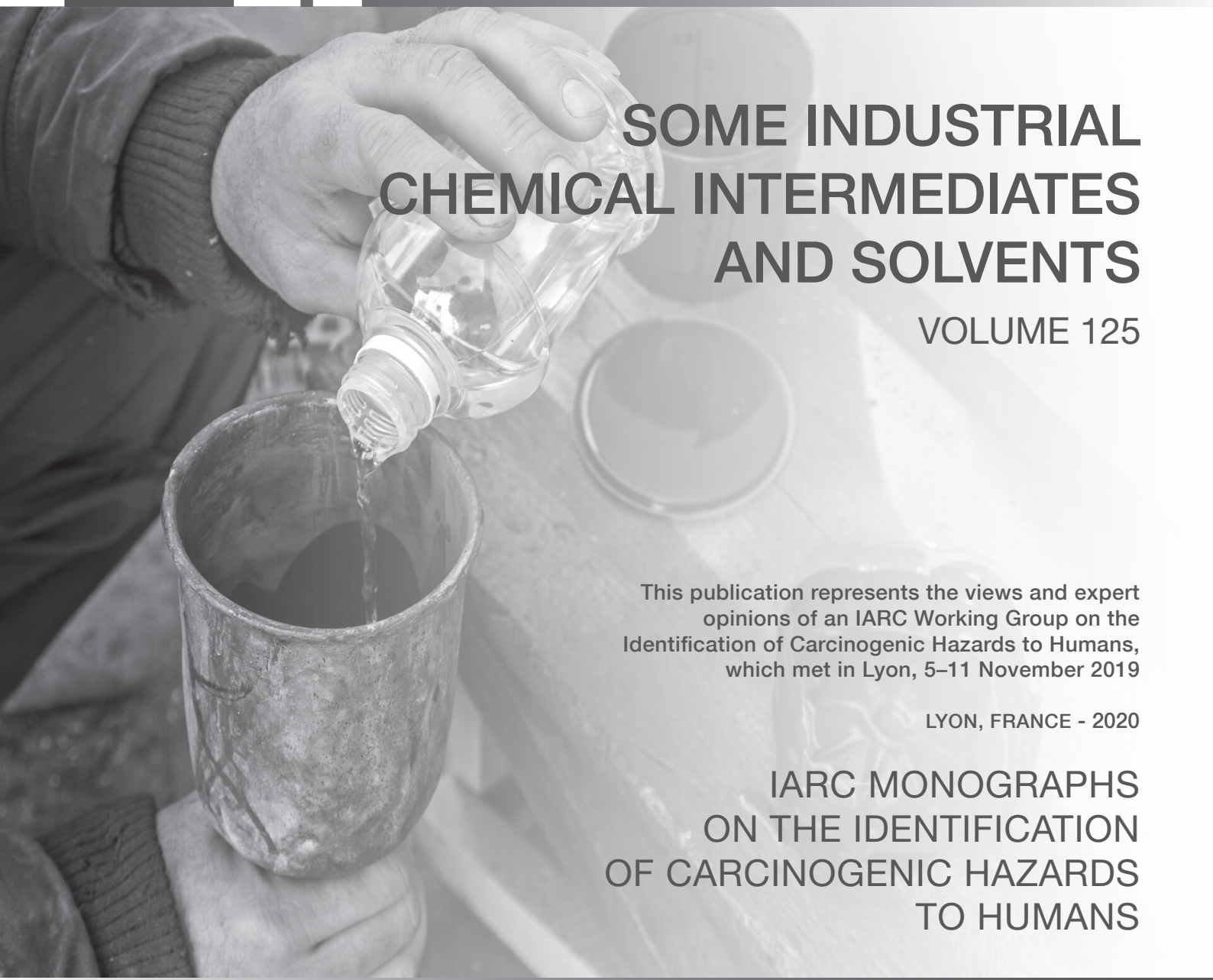

SOME INDUSTRIAL CHEMICAL INTERMEDIATES AND SOLVENTS

VOLUME 125

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International Agency for Research on Cancer

World Health Organization

4-CHLOROBENZOTRIFLUORIDE

1. Exposure Characterization

1.1 Identification of the agent

1.1.1 Nomenclature

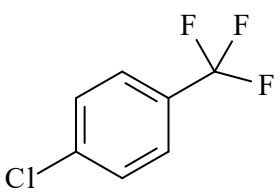
Chem. Abstr. Serv. Reg. No.: 98-56-6

Chem. Abstr. Serv. name: 1-chloro-4-(trifluoromethyl)benzene

Preferred IUPAC name: 1-chloro-4-(trifluoromethyl)benzene

Synonyms: 4-chlorobenzotrifluoride; 4-chloro-α,α,α-trifluorotoluene; *p*-chloro-α,α,α-trifluorotoluene; *p*-chlorobenzotri-fluoride; (*p*-chlorophenyl)trifluoromethane; *p*-chlorotrifluoromethylbenzene; *p*-chloro-(trifluoromethyl)benzene; *p*-trifluoromethylphenyl chloride; *p*-(trifluoromethyl)-chlorobenzene; 4-trifluoromethylchloro-benzene; 1-(trifluoro-methyl)-4-chlorobenzene; 4-chloro trifluoro-toluene.

1.1.2 Structural and molecular formulae, and relative molecular mass



Molecular formula: $C_7H_4ClF_3$

Relative molecular mass: 180.55

1.1.3 Chemical and physical properties of the pure substance

Description: clear, colourless liquid with a strong, aromatic, sweet pleasant odour (O'Neil, 2006; NTP, 2018)

Solubility (in water): 84.5 mg/L at 25 °C (predicted; NCBI, 2019)

Density (at 20 °C): 1.34 (NTP, 1992)

Vapour pressure: 7.63 mm Hg [1.02 kPa] at 25 °C (NCBI, 2019)

Vapour density: 6.24 (air = 1) (NTP, 1992)

Stability and reactivity: highly flammable (NCBI, 2019)

*Octanol/water partition coefficient (*P*):* log K_{ow} = 3.60 at 25 °C (NCBI, 2019)

Henry's law constant: 0.035 atm m^3 mol^{-1} [3.5 kPa m^3 mol^{-1}] at 25 °C (NCBI, 2019)

Melting point: –33 °C (NTP, 1992)

Boiling point: 139.3 °C (Lewis, 2007)

Flash point: 43 °C (O'Neil, 2006), 47 °C (NTP, 1992)

Conversion factor: 1 ppm = 7.38 mg/m^3 at 25 °C and 101.3 kPa.

1.2 Production and uses

1.2.1 Production process

4-Chlorobenzotrifluoride is synthesized from the reaction of 4-chlorotoluene and anhydrous hydrogen fluoride under atmospheric or high-pressure conditions (Boudakian, 1999). Alternatively, it can be produced by chlorination of benzotrifluoride and subsequent distillation of the isomer mixture (Albers & Kooyman, 1964; Maul et al., 1999).

1.2.2 Production volume

4-Chlorobenzotrifluoride is identified as a High Production Volume chemical by the Organisation for Economic Co-operation and Development (OECD) (OECD, 2009). Currently, there are several registered manufacturing plants in Europe, USA, and Asia (Chem Sources, 2019). In the European Union, the total volume manufactured and/or imported is listed as between 100 and 1000 tonnes per year (ECHA, 2019). The reported production/import in the USA was 10 000 000–50 000 000 lbs [4500–23 000 tonnes] in 2012–2015, of which most was imported (US EPA, 2016). In 2011, domestic production and import in the USA was reported to be approximately 29 000 000 lbs [~13 200 tonnes] (Lee et al., 2015; US EPA, 2016). In 1977, production of 4-chlorobenzotrifluoride in the USA was estimated to be between 4300 and 23 000 tonnes (NTP, 1992).

1.2.3 Uses

4-Chlorobenzotrifluoride was originally used as an industrial intermediate in the production of selected pesticides (Siegemund et al., 2008). Since the mid-1990s, 4-chlorobenzotrifluoride has been widely used as a solvent in many inks, paints, toners, and coatings due to its loading capacity for dissolving high volumes of ink (Wolf & Morris, 2006; NTP, 2018, ECHA, 2019). 4-Chlorobenzotrifluoride is extensively used in multiple dispersive applications in the automotive industry throughout the vehicle-manufacturing process, such as autobody coating formulations, thinners for coatings, repair and maintenance cleaning solvents, cosmetic stain removal, and aerosol rust inhibition (Wolf & Morris, 2006; Lee et al., 2015). Use as a dielectric fluid has also been reported (Lewis, 2007). 4-Chlorobenzotrifluoride is used as a component (at up to approximately 70%) in consumer products for cosmetic stain removal and aerosol, rust prevention, floor wax finishes, and sealers (HSDB, 2011; Lee et al., 2015).

1.3 Methods of measurement and analysis

1.3.1 Detection and quantification

Various methods for the determination and quantification of 4-chlorobenzotrifluoride in environmental samples are detailed in the literature (Table 1.1) (Kozlova & Kocherovskaia, 1986; Yost & Harper, 2000; NIOSH, 2003; Lava et al., 2013; Lee et al., 2015).

(a) Air

Active and passive sampling methods were evaluated by Lee et al. (2015). The passive sampling method used diffusive charcoal badges, while the active sampling method used coconut shell charcoal samplers. Active sampling has been carried out at a flow rate of 0.01–0.2 L/minute (NIOSH 1026 method). The extracts from both active and passive sampling were analysed by gas chromatography with flame ionization detection (NIOSH, 2003; Lee et al., 2015).

(b) Water

4-Chlorobenzotrifluoride was also extracted from water samples using a purge-and-trap extraction and concentration methodology. The extracts were analysed by gas chromatography

Table 1.1 Selected methods of analysis of 4-chlorobenzotrifluoride in various matrices

Sample matrix	Sample preparation	Assay method	Detection limit	Reference
Water	10 mL water sample was placed in 30 mL threaded bottles, 10 min in thermostat at 90 °C, injection of vapour phase into chromatograph	Vapour phase analysis method, GC-FID	4-Chlorobenzotrifluoride: 0.011 mg/L Toluene: 0.5 mg/L	Kozlova & Kocherovskaia (1986)
Water	20 mL of water was placed in 40 mL screw-top vials Purge and trap system with direct thermal desorption from the concentrator.	Vapour phase analysis method, GC-MS	0.002 µg/L	Lava et al. (2013)
Air	The samplers were desorbed by the introduction of 2 mL of carbon disulfide into the body of the sampler. The samplers were then shaken on a specially designed desorption shaker (SKC 226d-03) for 30 min	GC[a]	NA	Yost & Harper (2000)
Air	Coconut-shell charcoal sampler desorbed using 1.0 mL of carbon disulfide:methanol (99:1) solvent and allowed to stand for 30 min with occasional agitation	GC-FID	NR	NIOSH (2003)
Air	Coconut-shell charcoal sampler and diffusive charcoal badges were desorbed using 1.0 mL of carbon disulfide:methanol (99:1) solvent and allowed to stand for 30 min with occasional agitation	GC-FID	0.1–0.7 µg	Lee et al. (2015)

GC, gas chromatography; GC-FID, gas chromatography-flame ionization detection; GC-MS, gas chromatography-mass spectrometry; min, minute; NA, not applicable; NR, not reported.
[a] Detection method not reported.

and mass spectrometry, or gas chromatography with flame ionization detection, using low- to mid-polarity stationary phases (Kozlova & Kocherovskaia, 1986; Lava et al., 2013).

(c) Other matrices

No other specific methods for the detection of 4-chlorobenzotrifluoride in environmental matrices (e.g. dietary products, and soil) were identified in the literature.

1.3.2 Biomarkers of exposure

No data on biomarkers of exposure were available to the Working Group.

1.4 Occurrence and exposure

1.4.1 Environmental occurrence

4-Chlorobenzotrifluoride is not known to occur naturally in the environment; however, the substance may be released to the environment through various waste streams and from both indoor and outdoor use of products containing this chemical (ECHA, 2019). Environmental exposure to 4-chlorobenzotrifluoride may result from spillage or improper disposal in industrial settings (NTP, 2018).

(a) Air

If released to the atmosphere, 4-chlorobenzotrifluoride will exist solely as a vapour and it is expected to volatilize rapidly from water surfaces (Lyman et al., 1990; HSDB, 2011). Vapour-phase 4-chlorobenzotrifluoride will be

degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals (Atkinson et al., 1985); the half-life for this reaction in air is estimated to be 67 days (HSDB, 2011). 4-Chlorobenzotrifluoride is considered to have negligible photochemical reactivity (Atkinson et al., 1985; Young et al., 2008). 4-Chlorobenzotrifluoride does not contain chromophores that absorb at wavelengths > 290 nm and therefore is not expected to be susceptible to direct photolysis by sunlight (HSDB, 2011).

(b) Water

In a geographical area close to a major manufacturer in Holley, NY, USA, groundwater levels of 4-chlorobenzotrifluoride were reported to be 49 mg/L (US EPA, 2005). Industrial releases of 4-chlorobenzotrifluoride by a major manufacturer of the chemical in the early 1990s in Niagara Falls, NY, USA, resulted in detection of 4-chlorobenzotrifluoride in groundwater at up to 4.6 mg/L (US EPA, 2001). 4-Chlorobenzotrifluoride was detected in groundwater samples in Vicenza, Italy, at concentrations up to 1 mg/L, as a result of industrial contamination (Cacco & Ferrari, 1982). Water samples from Love Canal, NY, USA, have qualitatively tested positive for 4-chlorobenzotrifluoride (US EPA, 1982).

If released into water, 4-chlorobenzotrifluoride is expected to adsorb to suspended solids and sediment based upon the estimated soil absorption coefficient (K_{oc}). Volatilization from water surfaces is expected to be an important fate process based upon this compound's estimated Henry's law constant. Estimated volatilization half-lives for a model river and model lake are 4 hours and 5 days, respectively. An estimated bioconcentration factor of 110 suggests that the potential for bioconcentration in aquatic organisms is high. Hydrolysis is not expected to be an important environmental fate process since 4-chlorobenzotrifluoride lacks functional groups that hydrolyse under environmental conditions (HSDB, 2011).

(c) Soil and other matrices

4-Chlorobenzotrifluoride was detected in various media in a geographical area close to a major manufacturer in the 1980s, in sediment (up to 2 ppm) from the Bloody Run Creek, Niagara River watershed, and in fish (0.17–2.0 ppm) (Yurawecz, 1979; Elder et al., 1981).

If released to soil, 4-chlorobenzotrifluoride is expected to have low mobility based upon an estimated K_{oc} of 1600 (Swann et al., 1983). Volatilization from moist soil surfaces is expected to be an important fate process based upon the estimated Henry's law constant. 4-Chlorobenzotrifluoride may volatilize from dry soil surfaces based upon its vapour pressure. In an anaerobic screening test using digester sludge, 64% of the originally applied 4-chlorobenzotrifluoride was degraded in 59 days (HSDB, 2011).

1.4.2 Occupational and general population exposure

Exposure of humans to 4-chlorobenzotrifluoride can occur via inhalation, ingestion, and dermal absorption.

(a) Occupational exposure

Lee et al. (2015) reported collection of 28 personal and 8 area sample pairs at four vehicle-manufacturing sites, and 64 personal and 26 area sample pairs at three paint-manufacturing sites. The vehicle-manufacturing plants build helicopters, automobiles, or aircraft, and use 4-chlorobenzotrifluoride as a cleaning solvent, a primer, or a plastic-adhesion promoter. The workers at the paint-manufacturing plants use 4-chlorobenzotrifluoride in transferring to other containers, mixing or adding materials, and in the quality assurance laboratories. Overall, the geometric mean of personal exposures was reported to be 2.1 ppm (range, 0.1–12.2 ppm)

[~16 mg/m^3 (range, 0.7–90.1 mg/m^3)] at the vehicle-manufacturing plants and 0.7 ppm (range, 0.1–7.7 ppm) [~5.2 mg/m^3 (range, 0.7–57 mg/m^3)] at the paint-manufacturing plants (Lee et al., 2015).

(b) General population

No studies of exposure of the general population were identified by the Working Group. [The Working Group noted there is a high likelihood of exposure in consumers due to widespread use as a solvent in many formulations.]

1.5 Regulations and guidelines

The United States Environmental Protection Agency (US EPA) set 4-chlorobenzotrifluoride preliminary remediation goals for non-cancer end-points for air (73 µg/m^3), drinking-water (7.3×10^2 µg/L), and residential soil (1.2×10^3 mg/kg), and industrial soil (1.2×10^4 mg/kg) contamination related to superfund sites (US EPA, 2004, as cited in NTP, 2018). 4-Chlorobenzotrifluoride is considered by the state of New York, USA, as a "principal organic contaminant" and a maximum contaminant level has been established for drinking-water, ground water, and surface water at 5 µg/L (New York State Department of Health, 1998). No occupational or environmental air threshold limit values were identified by the Working Group.

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

See Table 3.1.

3.1 Mouse

Inhalation

In a study that complied with good laboratory practice (GLP), groups of 50 male and 50 female B6C3F$_1$/N mice (age, 5–6 weeks) were exposed to 4-chlorobenzotrifluoride (purity, > 99.5%) by whole-body inhalation for 6 hours per day, 5 days per week, for 104–105 weeks (NTP, 2018). The concentration in the exposure chamber was 0 (control), 100, 200, or 400 ppm. The survival rate for males at 400 ppm was significantly lower than for controls, and the survival rate of females at 400 ppm was non-significantly lower than for controls. Survival rates in males were 40/50 (control), 40/50 (100 ppm), 35/50 (200 ppm), and 28/50 (400 ppm); those in females were 38/50 (control), 33/50 (100 ppm), 37/50 (200 ppm), and 27/50 (400 ppm). The decreased survival rates in males and females at 400 ppm were attributed to increased number of deaths caused primarily by hepatocellular tumours. No significant difference in body-weight gain was observed in males. A significant increase in body-weight gain was observed in females for all exposed groups (> 10% increase at the end of the exposure period). All mice underwent complete necropsy and histopathological examination.

In males, the incidence of hepatocellular carcinoma was 8/50 (control), 19/50 (100 ppm), 16/50 (200 ppm), and 35/50 (400 ppm, with a significantly higher incidence of multiple tumours), and significantly increased in all exposed groups ($P < 0.05$, Poly-3 test). The incidence of hepatoblastoma was 1/50 (control), 1/50 (100 ppm), 1/50 (200 ppm), and 15/50 (400 ppm, with a significantly higher incidence of multiple tumours) and significantly increased at 400 ppm ($P < 0.001$, Poly-3 test). There were significant positive trends ($P < 0.001$, Poly-3 trend test) in the incidence of hepatocellular carcinoma and of hepatoblastoma. The incidence of hepatocellular adenoma was 25/50 (control), 24/50 (100 ppm),

Table 3.1 Studies of carcinogenicity with 4-chlorobenzotrifluoride in mice and rats treated by inhalation (whole-body exposure)

Species, strain (sex) Age at start Duration Reference	Purity (vehicle) Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Mouse, B6C3F$_1$/N (M) Age, 5–6 wk 104–105 wk NTP (2018)	Purity, > 99.5% (clean air) 0, 100, 200, 400 ppm 6 h/day, 5 days/wk 50, 50, 50, 50 40, 40, 35, 28	*Liver* Hepatocellular carcinoma 8/50, 19/50*, 16/50*, 35/50**	Trend: $P < 0.001$ (Poly-3 test) *$P < 0.05$ (Poly-3 test) **$P < 0.001$ (Poly-3 test)	Principal strengths: GLP study; study covered most of lifespan; males and females used; multiple-dose study Other comments: survival rate of males at 400 ppm was significantly decreased
		Hepatoblastoma 1/50, 1/50, 1/50, 15/50*	Trend: $P < 0.001$ (Poly-3 test) *$P < 0.001$ (Poly-3 test)	
		Hepatocellular adenoma 25/50, 24/50, 31/50, 29/50	NS	
		Hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (combined) 31/50, 37/50, 40/50*, 48/50**	Trend: $P < 0.001$ (Poly-3 test) *$P < 0.05$ (Poly-3 test) **$P < 0.001$ (Poly-3 test)	
Mouse, B6C3F$_1$/N (F) Age, 5–6 wk 104–105 wk NTP (2018)	Purity, > 99.5% (clean air) 0, 100, 200, 400 ppm 6 h/day, 5 days/wk 50, 50, 50, 50 38, 33, 37, 27	*Liver* Hepatocellular adenoma 12/50, 14/50, 24/50*, 34/50**	Trend: $P < 0.001$ (Poly-3 test) *$P = 0.004$ (Poly-3 test) **$P < 0.001$ (Poly-3 test)	Principal strengths: GLP study; study covered most of lifespan; males and females used; multiple-dose study Other comments: no significant effect of treatment on survival; historical incidence of Harderian gland adenocarcinoma for inhalation studies: 8/300 (2.7% ± 3.5%); range, 0–8%; all routes: 12/550 (2.2% ± 2.8%); range, 0–8%
		Hepatocellular carcinoma 7/50, 8/50, 12/50, 34/50*	Trend: $P < 0.001$ (Poly-3 test) *$P < 0.001$ (Poly-3 test)	
		Hepatoblastoma 0/50, 0/50, 1/50, 8/50*	Trend: $P < 0.001$ (Poly-3 test) *$P = 0.003$ (Poly-3 test)	
		Hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (combined) 18/50, 18/50, 29/50*, 46/50**	Trend: $P < 0.001$ (Poly-3 test) *$P = 0.008$ (Poly-3 test) **$P < 0.001$ (Poly-3 test)	

Table 3.1 (continued)

Species, strain (sex) Age at start Duration Reference	Purity (vehicle) Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Mouse, B6C3F$_1$/N (F) Age, 5–6 wk 104–105 wk NTP (2018) (cont.)		*Harderian gland* Adenoma 2/50, 6/50, 6/50, 8/50*	Trend: $P = 0.049$ (Poly-3 test) *$P = 0.041$ (Poly-3 test)	
		Adenocarcinoma 0/50, 0/50, 3/50, 0/50	NS	
		Adenoma or adenocarcinoma (combined) 2/50, 6/50, 9/50*, 8/50**	Trend: $P = 0.046$ (Poly-3 test) *$P = 0.026$ (Poly-3 test), **$P = 0.041$ (Poly-3 test)	
Rat, Hsd:Sprague-Dawley (M) Age, 6 wk 104–105 wk NTP (2018)	Purity, > 99.5% (clean air) 0, 100, 300, 1000 ppm 6 h/day, 5 days/wk 50, 50, 50, 50 25, 21, 15, 5	*Thyroid*: C-cell adenoma 2/50, 5/49, 3/49, 12/50*	Trend: $P < 0.001$ (Poly-3 test) *$P < 0.001$ (Poly-3 test)	Principal strengths: GLP study; study covered most of lifespan; males and females used; multiple-dose study Other comments: survival rate significantly decreased in males at 1000 ppm; incidence of bronchioloalveolar adenoma or carcinoma (combined) in historical controls for all routes in 2-year studies (incidence per study), 0/99 (0/50, 0/49)
		Lung Bronchioloalveolar adenoma 0/50, 2/50, 0/50, 1/50	NS	
		Bronchioloalveolar carcinoma 0/50, 0/50, 0/50, 2/50	Trend: $P = 0.032$ (Poly-3 test)	
		Bronchioloalveolar adenoma or carcinoma (combined) 0/50, 2/50, 0/50, 3/50	NS	
Rat, Hsd:Sprague-Dawley (F) Age, 6 wk 104–105 wk NTP (2018)	Purity, > 99.5% (clean air) 0, 100, 300, 1000 ppm 6 h/day, 5 days/wk 50, 50, 50, 50 23, 21, 25, 30	*Thyroid* C-cell adenoma 2/50, 8/50, 8/50, 14/50*	Trend: $P = 0.008$ (Poly-3 test) *$P = 0.003$ (Poly-3 test)	Principal strengths: GLP study; study covered most of lifespan; males and females used; multiple-dose study Other comments: no significant effect of treatment on survival; incidence of thyroid C-cell carcinoma in historical controls for all routes in 2-year studies (incidence per study), 0/99 (0/49, 0/50)
		C-cell carcinoma 0/50, 2/50, 0/50, 1/50	NS	
		C-cell adenoma or carcinoma (combined) 2/50, 10/50*, 8/50, 15/50**	Trend: $P = 0.009$ (Poly-3 test) *$P = 0.017$ (Poly-3 test), **$P = 0.002$ (Poly-3 test)	

Table 3.1 (continued)

Species, strain (sex) Age at start Duration Reference	Purity (vehicle) Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Rat, Hsd:Sprague-Dawley (F) Age, 6 wk 104–105 wk NTP (2018) (cont.)		*Adrenal medulla*: pheochromocytoma (benign) 0/49, 3/50, 4/50, 6/50* *Uterus* Adenocarcinoma 1/50, 1/50, 0/50, 5/50 Stromal polyp 7/50, 9/50, 16/50*, 12/50	*P = 0.035 (Poly-3 test) Trend P = 0.017 (Poly-3 test) *P = 0.047 (Poly-3 test)	

F, female; GLP, good laboratory practice; h, hour; M, male; NS, not significant; ppm, parts per million; wk, week.

31/50 (200 ppm), and 29/50 (400 ppm), respectively (not significant by Poly-3 pairwise or Poly-3 trend tests, but with a significantly higher incidence of multiple tumours at 200 ppm and 400 ppm). The incidence of hepatocellular adenoma, hepatocellular carcinoma or hepatoblastoma (combined) showed a significant positive trend ($P < 0.001$, Poly-3 trend test), and was significantly increased at 200 ppm ($P < 0.05$, Poly-3 test) and 400 ppm ($P < 0.001$, Poly-3 test).

In females, the incidence of hepatocellular adenoma was 12/50 (control), 14/50 (100 ppm), 24/50 (200 ppm), and 34/50 (400 ppm, with a significantly higher incidence of multiple tumours) and significantly increased at 200 and 400 ppm ($P \leq 0.004$, Poly-3 test). The incidence of hepatocellular carcinoma was 7/50 (control), 8/50 (100 ppm), 12/50 (200 ppm), and 34/50 (400 ppm, with a significantly higher incidence of multiple tumours) and significantly increased at 400 ppm ($P < 0.001$, Poly-3 test). The incidence of hepatoblastoma was 0/50 (control), 0/50 (100 ppm), 1/50 (200 ppm), and 8/50 (400 ppm) and significantly increased at 400 ppm ($P = 0.003$, Poly-3 test). The incidence of hepatocellular adenoma, hepatocellular carcinoma or hepatoblastoma (combined) was significantly increased at 200 and 400 ppm ($P \leq 0.008$, Poly-3 test). There were significant positive trends ($P < 0.001$, Poly-3 trend test) in the incidence of hepatocellular adenoma, hepatocellular carcinoma, and hepatoblastoma, and of hepatocellular adenoma, hepatocellular carcinoma or hepatoblastoma (combined).

In females, the incidence of Harderian gland adenoma was 2/50 (control), 6/50 (100 ppm), 6/50 (200 ppm), and 8/50 (400 ppm) and significantly increased at 400 ppm ($P = 0.041$, Poly-3 test) with a significant positive trend ($P = 0.049$, Poly-3 trend test). The incidence of Harderian gland adenoma or adenocarcinoma (combined) was 2/50 (control), 6/50 (100 ppm), 9/50 (200 ppm), and 8/50 (400 ppm) and significantly increased at 200 and 400 ppm ($P \leq 0.041$, Poly-3 test) with a significant positive trend ($P = 0.046$, Poly-3 trend test).

Regarding non-neoplastic lesions, there were significant increases in the incidence of centrilobular hepatocyte hypertrophy, eosinophilic foci, multinucleated hepatocyte, and hepatocyte necrosis in the liver, in groups of exposed males and females (NTP, 2018). [The Working Group noted this was a well-conducted GLP study with multiple doses, a high number of animals per group, and use of males and females.]

3.2 Rat

Inhalation

In a study that complied with GLP, groups of 50 male and 50 female Hsd:Sprague-Dawley rats (age, 6 weeks) were exposed to 4-chlorobenzotrifluoride (purity, > 99.5%) by whole-body inhalation for 6 hours per day, 5 days per week, for 104–105 weeks (NTP, 2018). The concentration in the exposure chamber was: 0 (control), 100, 300, or 1000 ppm. The survival rate was significantly decreased in males at 1000 ppm. Survival rates in males were 25/50 (control), 21/50 (100 ppm), 15/50 (300 ppm), and 5/50 (1000 ppm); those in females were 23/50 (control), 21/50 (100 ppm), 25/50 (300 ppm), and 30/50 (1000 ppm). The decreased survival rate in males at 1000 ppm was attributed to the increased number of deaths caused primarily by nephropathy. A decrease in body weight was observed in males at the highest dose (6% lower at the end of the exposure period) and females (10% lower at the end of the exposure period). All rats underwent complete necropsy and histopathological examination.

In males, the incidence of thyroid C-cell adenoma was 2/50 (control), 5/49 (100 ppm), 3/49 (300 ppm), and 12/50 (1000 ppm), and significantly increased at 1000 ppm ($P < 0.001$, Poly-3 test). There was a significant positive trend in the incidence of thyroid C-cell adenoma ($P < 0.001$, by Poly-3 trend test). The incidence

of bronchioloalveolar carcinoma occurred with a significant positive trend (P = 0.032, by Poly-3 trend test) and was 0/50 (control), 0/50 (100 ppm), 0/50 (300 ppm), and 2/50 (1000 ppm), respectively. The incidence of bronchioloalveolar adenoma or carcinoma (combined) was 0/50 (control), 2/50 (100 ppm), 0/50 (300 ppm), and 3/50 (1000 ppm), and not statistically different (by Poly-3 pairwise test or Poly-3 trend test). In historical controls, the incidence of bronchioloalveolar adenoma or carcinoma (combined) in males was 0/99.

In females, the incidence of thyroid C-cell adenoma was 2/50 (control), 8/50 (100 ppm), 8/50 (300 ppm), and 14/50 (1000 ppm) and significantly increased at 1000 ppm (P = 0.003, Poly-3 test). There was a significant positive trend in the incidence of thyroid C-cell adenoma (P = 0.008, Poly-3 trend test). The incidence of thyroid C-cell carcinoma was 0/50 (control), 2/50 (100 ppm), 0/50 (300 ppm), and 1/50 (1000 ppm). In historical controls, the incidence of thyroid C-cell carcinoma for all routes of 2-year studies was 0/99 in females (incidence per study: 0/49, 0/50). The incidence of thyroid C-cell adenoma or carcinoma (combined) was significantly increased according to Poly-3 pairwise test at 100 ppm (P = 0.017) and 1000 ppm (P = 0.002), and Poly-3 trend test (P = 0.009).

In females, the incidence of benign pheochromocytoma in the adrenal medulla was significantly increased at 1000 ppm (P = 0.035, Poly-3 test). The incidence of adenocarcinoma in the uterus occurred with a significant positive trend (P = 0.017, Poly-3 trend test). The incidence of stromal polyp in the uterus was significantly increased at 300 ppm (P = 0.047, Poly-3 test).

Regarding non-neoplastic lesions, there was a significant increase in the incidence of chronic inflammation of the lung in all groups of exposed males and females, lung fibrosis in all groups of exposed males and in females at 300 and 1000 ppm, and adrenal medullary hyperplasia in females at 300 and 1000 ppm (NTP, 2018). [The Working Group noted this was a well-conducted GLP study conducted with multiple doses, a high number of animals per group, and use of males and females.]

4. Mechanistic Evidence

4.1 Absorption, distribution, metabolism, and excretion

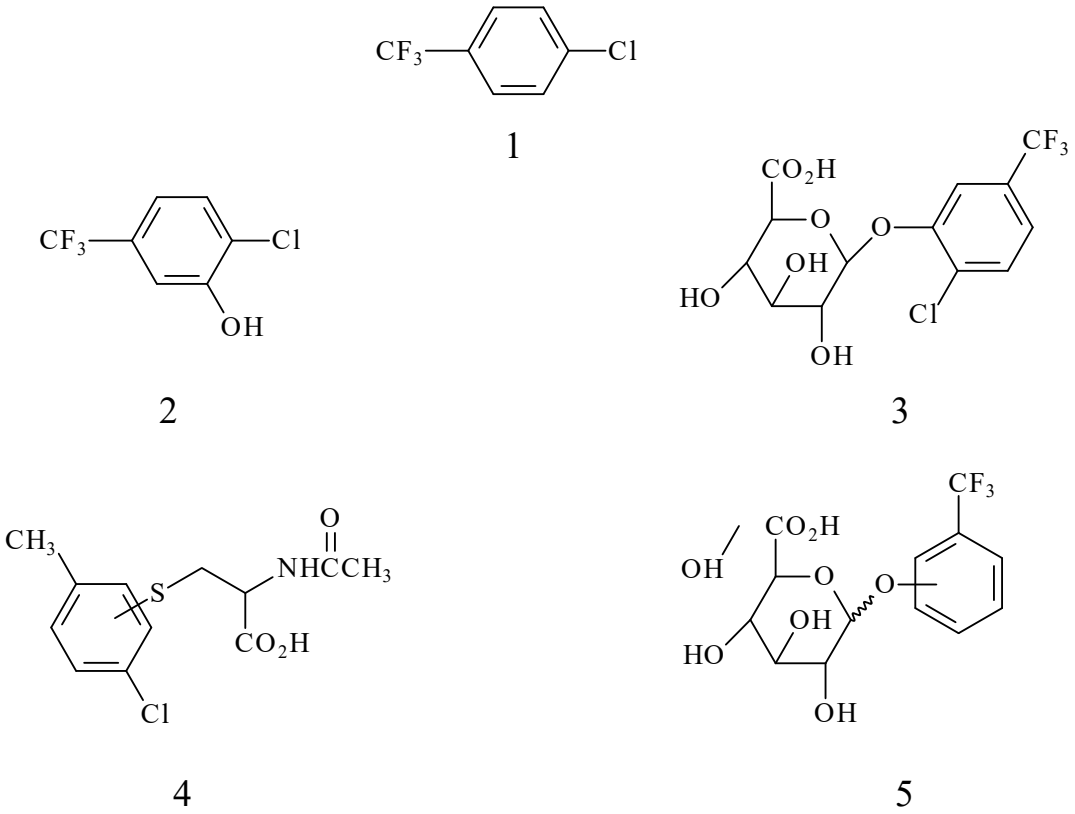
4.1.1 Humans

No direct data on absorption, distribution, metabolism, and excretion were available to the Working Group. Indirect evidence of absorption and distribution was provided by laboured breathing, dizziness, drowsiness, coughing, shortness of breath, chest pain, and oedema after exposure to 4-chlorobenzotrifluoride by inhalation (CAMEO-Chemicals, 2018).

4.1.2 Experimental systems

The absorption, distribution, metabolism, and excretion of 4-chlorobenzotrifluoride was assessed in rats in a study reported by Quistad & Mulholland (1983) and US EPA (1983a). In male and female Sprague-Dawley rats given a single oral dose of 4-chloro[trifluoromethyl-^{14}C]benzotrifluoride at 1 mg/kg body weight (bw), 62–82% of the administered dose was transported to the lungs and rapidly exhaled, while the remainder of the radiolabel was excreted in the urine (14–15%) and faeces (3–4%). 4-Chlorobenzotrifluoride was the major ^{14}C-labelled residue in the faeces. The major urinary metabolites were glucuronides of dihydroxybenzotrifluoride and 4-chloro-3-hydroxybenzotrifluoride (each representing 3–4% of the administered radiolabel); a minor amount of mercapturic acid *N*-acetyl-*S*-[chloro-(trifluoromethyl)phenyl]cysteine (0.1–0.2% of the administered radiolabel) was also observed (see Fig. 4.1). Less than 1% of the administered

Fig. 4.1 4-Chlorobenzotrifluoride and its observed metabolites in rats



(1) *p*-Chloro-α,α,α-trifluorotoluene [4-chlorobenzotrifluoride]; (2) 4-chloro-3-hydroxybenzotrifluoride; (3) glucuronide of chemical 2; (4) mercapturic acid conjugate of chemical 1; (5) glucuronide of dihydroxybenzotrifluoride.
Reprinted with permission from Quistad & Mulholland (1983). Metabolism of *p*-chlorobenzotrifluoride by rats. *J Agric Food Chem*. 31:585–589. Copyright (1983) American Chemical Society.

dose of 4-chlorobenzotrifluoride was found in tissues, mainly in fat, 4 days after dosing.

Bioavailability was shown to be complete in male F344 rats given a single oral dose of 4-chlorobenzotrifluoride (10, 50, or 400 mg/kg bw) (Yuan et al., 1991). The blood concentration increased proportionally with the administered dose.

The concentration of 4-chlorobenzotrifluoride in fat was ~10–33-fold that in the blood, liver, kidney, lung, or muscle in female Sprague-Dawley rats exposed via nose-only inhalation at a concentration of 50 ppm after exposure by whole-body inhalation for 13 weeks (Newton et al., 1998).

Levels of 4-chlorobenzotrifluoride were quantified in male and female F344/N rats and B6C3F$_1$ mice treated orally for 14 days at doses of 10, 50, 400, or 1000 mg/kg bw (NTP, 1992; Yuan et al., 1992). 4-Chlorobenzotrifluoride was detected in the blood, liver, and kidney of male and female rats, with kidney levels in males ~10-fold those in females; on the other hand, the substance could not be quantified in blood, kidney, and liver in the females and in most male mice (NTP, 1992; Yuan et al., 1992).

4.2 Evidence relevant to key characteristics of carcinogens

This section summarizes the evidence for the key characteristics of carcinogens (Smith et al., 2016), including whether 4-chlorobenzotrifluoride is genotoxic; or alters cell proliferation, cell death, or nutrient supply. Insufficient data were available for the evaluation of other key characteristics of carcinogens.

4.2.1 Is genotoxic

Table 4.1, Table 4.2, Table 4.3, and Table 4.4 summarize the studies evaluated that report genetic and related effects of 4-chlorobenzotrifluoride.

(a) Humans

No data in exposed humans were available to the Working Group.

In human epithelial-like cells in vitro, 4-chlorobenzotrifluoride at 1–10 µL/mL induced unscheduled DNA synthesis in a dose-responsive manner (Carere & Morpurgo, 1981; Benigni et al., 1982; see Table 4.1).

(b) Experimental systems

(i) Non-human mammals in vivo

See Table 4.2.

NTP (2018) investigated *Ctnnb1* and *Hras* mutations in hepatocellular carcinoma, either arising spontaneously or induced, in male and female B6C3F$_1$/N mice after chronic exposure to 4-chlorobenzotrifluoride by whole-body inhalation at 0, 100, 200, or 400 ppm. Genetic mutations in *Ctnnb1* and *Hras* are common in hepatocellular tumours in mice. No effect on *Ctnnb1* mutations was found on hepatocellular carcinoma in mice exposed to 4-chlorobenzotrifluoride compared with the control animals. On the other hand, a statistically significant difference in the frequency of *Hras* mutation (in the negative direction) was observed between hepatocellular carcinoma arising spontaneously and hepatocellular carcinoma resulting from chronic exposure to 4-chlorobenzotrifluoride at 400 ppm. [The Working Group noted that the lack of a dose–response relationship in the frequency of *Hras* mutations suggests that these were spontaneous lesions, rather than treatment-related.]

A single dose of 4-chlorobenzotrifluoride administered by gavage at 0.5, 1.7, or 5 mL/kg bw did not induce chromosomal aberrations in bone marrow cells of male or female Sprague-Dawley rats (US EPA, 1983b). After exposure to 4-chlorobenzotrifluoride at 2000 ppm by inhalation for 3 months, there was no effect on micronucleus formation in immature or mature peripheral blood erythrocytes in male or female Sprague-Dawley rats (NTP, 2018), while in B6C3F$_1$ mice a weak effect was seen in males, and no effect was detected in females (NTP, 2018).

Urine collected from male CD1 mice treated orally with 4-chlorobenzotrifluoride did not cause mutagenicity in *Salmonella typhimurium* strains TA1535, TA100, TA1537, and TA98 (US EPA, 1979b).

(ii) Non-human mammalian cells in vitro

See Table 4.3.

4-Chlorobenzotrifluoride did not induce gene mutations in L5178Y mouse lymphoma cells (US EPA, 1978a), or cause chromosomal aberration in Chinese hamster ovary (CHO) cells (US EPA, 1983c); however, sister-chromatid exchanges were found in L5178Y mouse lymphoma cells after treatment with 4-chlorobenzotrifluoride, with and without metabolic activation (US EPA, 1979a).

(iii) Non-mammalian experimental systems

See Table 4.4.

4-Chlorobenzotrifluoride did not induce mutagenicity in any of the tested strains of *Salmonella typhimurium* (TA1535, TA100, TA1537, TA1538, and TA98) with or without metabolic activation (US EPA, 1978b; Bignami &

Table 4.1 Genetic and related effects of 4-chlorobenzotrifluoride in human cells in vitro

End-point	Tissue, cell line	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Unscheduled DNA synthesis	Epithelial-like human cells	+	NT	1 µL/mL	Purity, NR	Carere & Morpurgo (1981); Benigni et al. (1982)

HIC, highest ineffective concentration; LEC, lowest effective concentration, NR, not reported; NT, not tested.
[a] +, positive.

Table 4.2 Genetic and related effects of 4-chlorobenzotrifluoride in non-human mammals in vivo

End-point	Species, strain (sex)	Tissue	Results[a]	Dose (LED or HID)	Route, duration, dosing regimen	Reference
Hras mutation (codon 61)	Mouse, B6C3F$_1$ (M, F)	Hepatocellular carcinoma (M, F)	– [b]	400 ppm	Whole-body inhalation, 2 years, 6 h/day, 5 days/wk, at 100, 200 or 400 ppm	NTP (2018)
Ctnnb1 mutation (codons 15–46)	Mouse, B6C3F$_1$ (M, F)	Hepatocellular carcinoma (M, F)	– [c]	400 ppm	Whole-body inhalation, 2 years, 6 h/day, 5 days/wk, at 100, 200, or 400 ppm	NTP (2018)
Chromosomal aberration	Rat, Sprague-Dawley (M, F)	Bone marrow cells	–	5 mL/kg	Gavage, 0.5, 1.7, 5.0 mL/kg bw, collection 6, 24, and 48 h after single treatment	US EPA (1983b)
Micronucleus formation	Rat, Sprague-Dawley (M, F); mouse, B6C3F$_1$/N (F)	Peripheral blood erythrocytes	–	2000 ppm	Inhalation, daily, for 3 mo	NTP (2018)
Micronucleus formation	Mouse, B6C3F$_1$/N (M)	Peripheral blood erythrocytes	± [d]	2000 ppm	Inhalation, daily, for 3 mo	NTP (2018)
Mutagenicity of urine	Mouse, CD1 (M)	Host-mediated assay; Ames test in *Salmonella typhimurium* strains TA1535, TA100, TA1537, and TA98	–	500 mg/kg bw per day	Gavage, 2 days	US EPA (1979b)

bw, body weight; F, female; h, hour; HID, highest ineffective dose; LED, lowest effective dose; M, male; mo, month; ppm, parts per million; wk, week.
[a] +, positive; –, negative; ±, equivocal.
[b] *Hras* mutation frequency in hepatocellular carcinomas of animals at 400 ppm (mutation observed in 29% of tissues assayed) was significantly lower ($P < 0.01$) than the mutation frequency in spontaneous hepatocellular carcinomas in the chamber-control animals (mutation in 73% of assayed tissues). No statistical difference at lower doses.
[c] *Ctnnb1* mutation frequency in hepatocellular carcinomas of animals at all doses up to 400 ppm was not significantly different from the mutation frequency in spontaneous hepatocellular carcinomas in the chamber-control animals.
[d] Effect considered equivocal by the Working Group.

Table 4.3 Genetic and related effects of 4-chlorobenzotrifluorotoluene in non-human mammals in vitro

End-point	Species, tissue, cell line	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Gene mutation, *Tk* locus	L5178Y mouse, lymphoma	–	–	50 nL/mL		US EPA (1978a)
Sister-chromatid exchange	L5178Y mouse, lymphoma cells	+	+	2.5 nL/mL		US EPA (1979a)
Chromosomal aberration	Chinese hamster ovary cells	–	–	130 nL/mL	Purity, NR	US EPA (1983c)

HIC, highest ineffective concentration; LEC, lowest effective concentration, NR, not reported; Tk, thymidine kinase.

[a] +, positive; –, negative.

Table 4.4 Genetic and related effects of 4-chlorobenzotrifluoride in non-mammalian experimental systems

Test system (species, strain)	End-point	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Salmonella typhimurium TA1535, TA100, TA1537, TA1538, and TA98	Reverse mutation	–	–	10 µL/plate	Purity, NR	US EPA (1978b)
Salmonella typhimurium TA1535 and TA100	Reverse mutation (induction of 8-azoguanine resistance)	–	NT	150 µg/plate		Bignami & Crebelli (1979)
Salmonella typhimurium TA1535, TA100, TA1537, and TA98,	Reverse mutation	–	–	0.4 µL/plate	Purity, NR	Carere & Morpurgo (1981); Benigni et al. (1982)
Salmonella typhimurium TA1535, TA100, TA1537, and TA98	Reverse mutation	–	–	1000 µg/plate	Purity, 96%	Haworth et al. (1983)
Salmonella typhimurium TA1535, TA100, TA1537, TA1538, and TA98	Reverse mutation	–	–	2500 µg/plate	Purity, NR	Mazza et al. (1986)
Salmonella typhimurium TA100 and TA98	Reverse mutation	–	–	5000 µg/plate (–S9) 6000 µg/plate (+S9)	Purity, NR	NTP (2018)
Escherichia coli WP2 *uvrA*/pKM101	Reverse mutation	–	–	5000 µg/plate (–S9) 6000 µg/plate (+S9)	Purity, NR	NTP (2018)
Escherichia coli W3110 polA$^+$ and P3478 polA$^-$	Reverse mutation	–	–	10 µL/plate	Purity, NR	US EPA (1978b)
Saccharomyces cerevisiae D4	DNA repair	–	–	10 µL/plate	Purity, NR	US EPA (1978b)
Saccharomyces cerevisiae 6117	Gene conversion and mitotic crossing over	–	–	2000 µg/mL	Purity, NR	Mazza et al. (1986)
Aspergillus nidulans	Mitotic recombination, spot test	–	NT	2.5 µL/plate, 2500 µg/plate	Purity, NR	Carere & Morpurgo (1981); Benigni et al. (1982)
Bacillus subtilis	DNA damage and repair	–	NT	10 000 µg/disc	Purity, NR	Mazza et al. (1986)

HIC, highest ineffective concentration; LEC, lowest effective concentration, NR, not reported; NT, not tested.

[a] –, negative.

Crebelli, 1979; Carere & Morpurgo, 1981; Benigni et al., 1982; Haworth et al., 1983; Mazza et al., 1986; NTP, 2018). It also gave consistently negative results in *Escherichia coli WP2 uvrA*/pKM101 and *E. coli W3110* polA+ and *P3478* polA– (NTP, 2018; US EPA, 1978b).

4-Chlorobenzotrifluoride did not induce genetic alterations in DNA repair in *Saccharomyces cerevisiae* strains D4 (US EPA, 1978b) and 6117 (Mazza et al., 1986), or mitotic recombination in *Aspergillus nidulans* (Carere & Morpurgo, 1981; Benigni et al., 1982), or DNA damage and repair in *Bacillus subtilis* (Mazza et al., 1986).

4.2.2 Alters cell proliferation, cell death, or nutrient supply

No data in humans were available to the Working Group.

Regarding repeated-dose treatment by the oral route, the results of a 14-day study in male and female F344/N rats and $B6C3F_1$ mice treated by gavage showed that 4-chlorobenzotrifluoride induced a consistent increase in liver and kidney weights, and adrenal cortex cytoplasmic vacuolization (NTP, 1992). These findings were confirmed in a 28-day study in Sprague-Dawley rats in which oral treatment with 4-chlorobenzotrifluoride caused increases in the relative weight of the liver and kidney (Macrì et al., 1987). In a 90-day study in Fischer 344 rats, 4-chlorobenzotrifluoride (0, 10, 40, 150, or 500 mg/kg bw per day, by gavage) increased the weight of the liver and kidney and caused centrilobular hypertrophy in the liver, effects that were generally dose-related (US EPA, 1983e).

Repeated-dose studies performed by the inhalation route confirmed some of the effects observed after oral administration. In a 13-week toxicity study in male and female $B6C3F_1$/N mice (NTP, 2018), exposure to 4-chlorobenzotrifluoride by whole-body inhalation resulted in increased absolute liver weight (≥ 250 ppm, in males and females), and significantly increased incidence of central lobular hepatocyte hypertrophy (≥ 250 ppm in males, ≥ 500 ppm in females), and hepatocyte necrosis and multinucleated hepatocytes (both lesions: ≥ 500 ppm in males, ≥ 1000 ppm in females). In $B6C3F_1$/N mice exposed to 4-chlorobenzotrifluoride by inhalation for up to 105 weeks (NTP, 2018), significant increases in the incidence of centrilobular hepatocyte hypertrophy, eosinophilic foci, multinucleated hepatocyte, and hepatocyte necrosis were reported in the liver of both males and females.

In a 28-day study in Sprague-Dawley rats treated by whole-body inhalation (6 hours per day, 5 days per week, at 100, 250, 500, or 1000 ppm), a significant increase in liver and kidney weights was observed, as well as in the frequency of hepatocellular hypertrophy (US EPA, 1993). Severity of effects was higher in males than in females. In a 90-day study in Sprague-Dawley rats treated by whole-body inhalation (6 hours per day, 5 days per week, at 10, 50, and 250 ppm (US EPA, 1994; Newton et al., 1998), an increase in relative liver weights, which correlated with hepatocellular hypertrophy, was found in males and females at the highest dose. Hypertrophy was not observed in the 90-day recovery animals. [The Working Group noted that liver enlargement is likely to be an indication of enzyme induction (see Section 4.2.3) rather than cell proliferation.] In a 13-week toxicity study in male and female Hsd:Sprague-Dawley rats (NTP, 2018), exposure to 4-chlorobenzotrifluoride by whole-body inhalation resulted in increased liver weight (≥ 125 ppm in males) and significantly increased incidence of centrilobular hepatocyte hypertrophy (≥ 250 ppm in males, ≥ 1000 ppm in females). In Hsd:Sprague-Dawley rats exposed to 4-chlorobenzotrifluoride by inhalation for up to 105 weeks (NTP, 2018), significant increases in the incidence of adrenal medullar hyperplasia and atypical hyperplasia of the endometrium were reported in females.

4.2.3 Evidence on other key characteristics of carcinogens

Modulation of metabolism enzymes provided evidence for receptor-mediated effects. A 13-week study in male and female Sprague-Dawley rats exposed to 4-chlorobenzotrifluoride by inhalation at 250 ppm, but not 10 or 50 ppm, resulted in increases of 5- and 2-fold in hepatic microsomal activity and levels of cytochrome P450 CYP2B in males and females, respectively, and an increase of 2-fold in levels of CYP1A1 and CYP1A2 in both males and females. CYP2E1 increased marginally in males exposed to 4-chlorobenzotrifluoride at 50 or 250 ppm, while CYP3A increased by 3-fold in females exposed at the highest dose only (Pelosi et al., 1998). When administered for 90 days by gavage to rat Fischer 344 at a dose of 10, 40, 150, or 500 mg/kg bw per day, 4-chlorobenzotrifluoride caused the induction of hepatic *para*-nitroanisole *O*-demethylase activity in males at the two higher doses and in females at the highest dose (US EPA, 1983d).

No changes in total or specific immunoglobulin IgM antibody activity to sheep erythrocytes were observed in a study that, in part, addressed immune suppression in female $B6C3F_1$ mice exposed dermally to 6–100% (v/v) 4-chlorobenzotrifluoride for 14 days (25 µL/ear) (Franko et al., 2011). In BALB/c mice, dermal exposure to 4-chlorobenzotrifluoride (75% and 100%, v/v) for three consecutive days significantly increased production of interferon-gamma (IFNγ) protein by stimulated draining lymphoid cells, but did not alter the immune response to a T-cell-dependent antigen (Franko et al., 2011). In female BALB/c mice, no treatment-related elevations in total or specific IgE were observed.

4-Chlorobenzotrifluoride failed to induce cell transformation in BALB/3T3 mouse cells (US EPA, 1980; US EPA, 1983e). In a study of chronic toxicity in Hsd:Sprague-Dawley rats exposed to 4-chlorobenzotrifluoride by inhalation for up to 105 weeks (NTP, 2018), significant increases in the incidence of chronic inflammation of the lung and of lung fibrosis were reported in males and females.

4.3 Other relevant evidence

Several studies reported effects related to α_{2u}-globulin in the kidney of male rats. In particular, kidney nephropathy, combined with a dose-dependent increase in kidney α_{2u}-globulin, was reported in a 14-day study in male F344/N rats treated by gavage (NTP, 1992). 4-Chlorobenzotrifluoride also increased the incidence of hyaline droplet-associated necrosis in the kidney in a 28-day study in Sprague-Dawley rats treated orally (Macrì et al., 1987). In a 90-day study in Fischer 344 rats treated by gavage, 4-chlorobenzotrifluoride increased the incidence of tubular degeneration in the kidneys (males only) in a dose-related manner (US EPA, 1983d). In a study in Sprague-Dawley rats treated by inhalation, intracytoplasmic eosinophilic granules were reported in the kidney (male only) after administration of 4-chlorobenzotrifluoride (6 hours per day, 5 days per week, for 4 weeks, at a dose of 100, 250, 500, or 1000 ppm) (US EPA, 1993). While such data can be informative interpreting the relevance to humans of kidney tumours observed in rodents (IARC, 1999), 4-chlorobenzotrifluoride did not induce kidney tumours in rodents (see Section 3).

4.4 Data relevant to comparisons across agents and end-points

The analysis of the bioactivity in vitro of the agents reviewed in *IARC Monographs* Volume 125 was informed by data from high-throughput screening assays generated by the Toxicity Testing in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast) research programmes of the Government of the USA (Thomas et al., 2018). 4-Chlorobenzotrifluoride was one of thousands

of chemicals tested across the large assay battery of the Tox21 and ToxCast research programmes as of 1 September 2019 (US EPA, 2019). Detailed information about the chemicals tested, assays used, and associated procedures for data analysis is publicly available (US EPA, 2019). [The Working Group noted that the metabolic capacity of the cell-based assays is variable, and generally limited, as acknowledged in Kavlock et al. (2012).]

Among the 428 assays in which 4-chlorobenzotrifluoride (at concentrations of up to 100 μM) was tested, it was found to be inactive in almost all assays. Active responses were observed in 10 assays (US EPA, 2019). For nuclear receptors, borderline activity (potency of < 50%, or half-maximal activity concentration, AC_{50}s, less than the lowest concentration tested) was found for estrogen receptor α (ERα) agonism and constitutive androstane receptor (CAR). For cell viability, 4-chlorobenzotrifluoride was shown to be cytotoxic in human HEPG2 and HEK293 cells at AC_{50}s of 0.001–0.01 μM.

5. Summary of Data Reported

5.1 Exposure data

4-Chlorobenzotrifluoride is a High Production Volume chemical widely used as a solvent and diluent for inks, paints, toners, and coatings. It is also extensively used in dispersive applications in the automotive industry. Additional applications may include its use as a major component in industrial and consumer formulations such as cleaners, degreasers, stain removers, rust inhibitors, and floor wax finishes and sealants. One study reported occupational exposures in paint- and vehicle-manufacturing facilities. The general population may be exposed via consumer products and contaminated water and fish; however, published studies documenting actual exposure levels were not available to the Working Group.

5.2 Cancer in humans

No data were available to the Working Group.

5.3 Cancer in experimental animals

In one well-conducted study that complied with good laboratory practice (GLP) in male and female mice treated by whole-body inhalation, 4-chlorobenzotrifluoride significantly increased the incidence, with a significant positive trend, of hepatocellular carcinoma and hepatoblastoma in males and females. The incidence of hepatocellular adenoma was significantly increased, with a significant positive trend, in females but not in males. The combined incidence of hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma was significantly increased in males and females, with a significant positive trend. The incidence of Harderian gland adenoma and of Harderian gland adenoma or adenocarcinoma (combined) was significantly increased in females, with a significant positive trend.

In one well-conducted study that complied with GLP in male and female rats treated by whole-body inhalation, 4-chlorobenzotrifluoride significantly increased the incidence, with a significant positive trend, of thyroid C-cell adenoma in males and females, and of thyroid C-cell adenoma or carcinoma (combined) in females, and there was a significant positive trend in the incidence of bronchioloalveolar carcinoma in males. In females, there was a significant increase in the incidence, with a significant positive trend, of benign pheochromocytoma of the adrenal medulla. There was a significant positive trend in the incidence of uterine adenocarcinoma and of uterine stromal polyp in females.

5.4 Mechanistic evidence

No direct data on absorption, distribution, metabolism, or excretion in humans were available, but a study of other adverse effects in exposed humans indirectly confirmed absorption and distribution upon inhalation exposure. Several studies in rats exposed orally or by inhalation report the detection of 4-chlorobenzotrifluoride in multiple organs, mainly in fat.

There is suggestive evidence that 4-chlorobenzotrifluoride alters cell proliferation, cell death, or nutrient supply, based on a dose-related increase in the incidence of atypical hyperplasia in the endometrium in rats exposed chronically by inhalation. Regarding whether 4-chlorobenzotrifluoride is genotoxic, the findings were largely negative in rats and mice in vivo and in the Ames test, with the only positive results in single tests in vitro of unscheduled DNA synthesis in human cells and of sister-chromatid exchange in rodent cells. For other key characteristics of carcinogens, there is a paucity of available data. 4-Chlorobenzotrifluoride was largely inactive in the assay battery of the Toxicity Testing in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast) research programmes.

6. Evaluation and Rationale

6.1 Cancer in humans

There is *inadequate evidence* in humans regarding the carcinogenicity of 4-chlorobenzotrifluoride.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of 4-chlorobenzotrifluoride.

6.3 Mechanistic evidence

There is *inadequate mechanistic evidence.*

6.4 Overall evaluation

4-Chlorobenzotrifluoride is *possibly carcinogenic to humans (Group 2B).*

6.5 Rationale

The evaluation of 4-chlorobenzotrifluoride as Group 2B is based on *sufficient evidence* of cancer in experimental animals. The evidence on cancer in humans is *inadequate* as no data were available. The *sufficient evidence* of carcinogenicity in experimental animals is based on the induction of malignant neoplasms in two species. The mechanistic evidence was *inadequate.*

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