Trifluoromethylbenzene

98-08-8

OVERVIEW

Prepared for the National Cancer Institute (NCI) for consideration by the Chemical Selection Working Group (CSWG) by Technical Resources International, Inc. under contract no. N02-07007.

Trifluoromethylbenzene came to the attention of the NCI Division of Cancer Biology (DCB) as the result of a review of high production chemicals in commerce that do not meet the criteria for inclusion in the United States (U.S.) Environmental Protection Agency (EPA) HPV Challenge Program. According to industry information, 10,000-50,000 metric tons of trifluoromethylbenzene are also used in the European Union.

Traditionally, trifluoromethylbenzene and substituted derivatives have uses as vulcanizing agents and intermediates in the production of dyestuffs, insulating fluids, herbicides, pharmaceuticals, antimicrobial agents, and the lampreycide, 4-nitro-2-(trifluoromethyl)phenol. The approval of trifluoromethylbenzene for a variety of cleaning applications as alternatives to ozone-depleting substances under EPA's Significant New Alternatives Policy (SNAP) Program accounts for much of its increased use. Trifluoromethylbenzene is marketed as one of the OXSOL® line of SNAP alternatives. The OXSOL® line was sold by Occidental Chemical Corporation to Makhteshim Agan Industries, Ltd. in 2002, and trifluoromethylbenzene is produced at their Milenia site in Brazil. Because of trifluoromethylbenzene's solvent uses in large scale industrial applications, a significant potential for occupational exposure and release into the environment exists.

Several studies give some information on the toxicities of trifluoromethylbenzene and monochlorotoluenes, also approved as SNAP alternatives. Trifluoromethylbenzene did not produce mutations in a battery of Ames assays or in the *Escherichia coli* WP2 uvrA assay. This chemical did not produce clastogenicity or polyploidy in a chromosome aberration assay and did not produce DNA damage in a *Bacillus subtilis* Rec-assay. No mitotic gene conversion occurred

in *Saccharomyces cerevisiae.* Thus, substantial information exists to indicate that this chemical is not genotoxic. However, in repeat dose toxicity tests, the central nervous system, kidney, and liver have been identified as target organs. Although information on structurally related chemicals suggests that a progressive set of lesions related to α_{2u}-globulin may have a role in male rats, gross effects, such as increased kidney weights, were also observed in female rats. Whether trifluoromethylbenzene is rapidly excreted or poses a risk from fluoride accumulation is unclear from the available literature.

Model projections and two acute studies raise concerns that trifluoromethylbenzene may pose a hazard to aquatic organisms.

NOMINATION OF TRIFLUOROTOLUENE TO THE NTP

Based on a review of the available literature and the recommendations of the Chemical Selection Working Group (CSWG) on December 15, 2004, NCI nominates this chemical for testing by the National Toxicology Program (NTP) and forwards the following information:

- The attached Summary of Data for Chemical Selection
- Copies of references cited in the Summary of Data for Chemical Selection
- CSWG recommendations to:

(1) Conduct studies to identify metabolites, with particular emphasis on the potential for accumulation of fluoride.

(2) Conduct subchronic (90 day) inhalational studies, focusing on the kidney as an endpoint.

(3) Consider the need for a 2-year carcinogenicity study based on the results of the subchronic study.

PRIORITY

High

COMMENTS

Studies to characterize the toxicity of trifluorotoluene are requested because of the high potential for human exposure, particularly in the workplace, the projected growth in the use of this

chemical as a SNAP alternative solvent, and the lack of information needed to ensure the safety of chronic exposure to this chemical both to humans and environmental organisms.

Whether mechanisms other than the male rat kidney tumor phenomenon associated with irreversible binding of the chemical to α_{2u}-globulin account for observed effects on the kidney needs to be determined. Based on these results, a two year chronic bioassay to determine the chronic toxicity and oncogenicity of this chemical may be required.

Trifluoromethylbenzene may be toxic if released to the environment, as suggested by limited results in aquatic species. More detailed testing to characterize the hazards posed to the environment would be appropriate.

INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

Dr. John Walker, Executive Director of the TSCA Interagency Testing Committee (ITC), and Ms. Norma Williams determined that this chemical had not been discussed by the ITC.

Dr. Boris Ionin from the Department of Bacterial Diseases of the Walter Reed Army Institute of Research provided translations of two Russian articles.

SUMMARY OF DATA FOR CHEMICAL SELECTION

CHEMICAL IDENTIFICATION

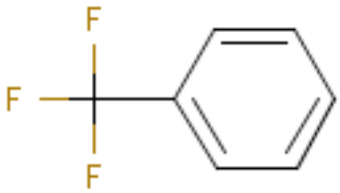
CAS Registry Numbers: 98-08-8

Chemical Abstracts Service Name: Benzene, (trifluoromethyl)- (9CI)

Synonyms and Trade Name: Trifluoromethylbenzene; □, □, □ -trifluorotoluene (IUPAC name); benzotrifluoride; benzylidyne fluoride; OXSOL® 2000; Phenylfluoro-form; trifluorotoluene; EINECS 202-635-0; USAF ma-16; UN 2338 (ChemFinder, 2004; ChemId, 2004; Milenia, 2002)

Structural Class: Substituted aromatic

Structure, Molecular Formula, and Molecular Weight:



$C_7H_5F_3$ Mol. wt.: 146.11

Chemical and Physical Properties:

Description: Water-white liquid (Lewis, 2002)

Boiling Point: 102.1 °C (Lewis, 2002)

Melting Point: 28.95-29.1 ºC (Lewis, 2002; Lide, 2003)

Density: 1.18 (Lewis, 2002)

Vapor Pressure: 53 hPa at 25 ºC (European Commission, 2000a); 31 mm Hg at 20 ºC (OxyChem, 1998)

Solubility: Miscible with ethanol, acetone, benzene, carbon tetrachloride, ether, n-heptane, insoluble in water (Lewis, 2002)

Water solubility at 25 ºC is 0.45 g/l (European Commission, 2000a, 2000)

Flash Point: 12.2 ^{o}C (closed cup) (Lewis, 2002)

Reactivity: Flammable, dangerous fire risk, with possible production of hydrogen fluoride and other organic fluorides (Lewis, 2002; Milenia, 2002)

O/W Partition Coefficient: Log Ko/w = 2.79-3.37 (calculated) (European Commission, 2000a); Log Ko/w = 3.01 (OxyChem, 2004)

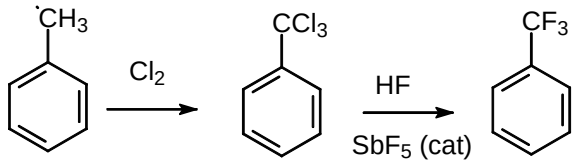
Technical Products and Impurities:

Trifluoromethylbenzene is available from the Aldrich division of Sigma-Aldrich at ≥99% purity (product no. T63703) and from the Acros Organics division of Fisher Scientific at 99+% purity (Fisher Scientific, 2004; Sigma-Aldrich, 2004). OXSOL® 2000, 99.5% minimum trifluoromethylbenzene, is available in the U.S. from the Makhteshim Agan North America Group (MANA) (Milenia, 2002).

EXPOSURE INFORMATION

Production and Producers:

Manufacturing Process. Trifluoromethylbenzene can be prepared industrially from toluene in two synthetic steps: free radical perchlorination of the methyl group followed by fluorine/chlorine exchange of the three chlorine atoms with anhydrous hydrogen fluoride. The chlorination step may be catalyzed by light of suitable wavelength and is carried out in the liquid phase. The fluoride/chloride exchange can be catalyzed by the presence of metal halides and is effected under a variety of conditions of temperature and pressure including liquid phase (high pressure and temperature), liquid phase (ambient pressure), or vapor phase (low pressure, high temperature) (Maul *et al.*, 1999).



Source: Adapted from Maul *et al.*, 1999

The specific process apparently used by Occidental Chemical Corporation was patented in 1984 (U.S. Patent No. 4,436,942). The process is carried out by passing the benzotrichloride vapors, together with gaseous HF, through a packed bed of particulate, pre-fluorinated, *gamma*-alumina, maintained at a temperature of 100 - 600 EC (Rader & Robota, 1984).

According to Makhteshim Agan Industries, Ltd, the Milenia site in Brazil uses the purification, acidity removal, and drying procedures developed for OXSOL® by Occidental Chemical Corporation (Islechem, 2004).

Prepared for NCI to support chemical nomination by Technical Resources International, Inc. under contract no. N02-CB-07007 (11/04; 9/05)

Producers and Importers. Chemical Sources International (2004) lists 24 U.S. suppliers of benzotrifluoride. ChemACX lists 9 suppliers selling 10 products; online vendors include Acros USA, Alfa Aesar, Fluorochem, and ICN (ChemACX, 2004).

According to recent issues of chemical directories, trifluoromethylbenzene is manufactured or distributed by Kowa American; Miteni S.P.A.; Occidental Chemical Corp./OxyChem; OxyChem; Rhodia, Inc.; and Spectrumchemical.com (Chemcyclopedia, 2004; Tilton, 2004).

OXSOL® 2000, which is the trifluoromethylbenzene solvent among a group of OXSOL® solvents, is a registered trademark of Milenia Agro Ciéncieas S.A., part of the Makhteshim Agan Industies, Ltd. Group. Milenia acquired the entire OXSOL® business from Occidental Chemical Company in 2002 (Makhteshim Agan Industries Ltd., 2002; Milenia, 2002).

Production/Import Levels:

Trifluoromethylbenzene is listed in the EPA Toxic Substances Control Act (TSCA) Inventory (EPA, 2004a).

The EPA 2002 Inventory Update Rule lists no reports for trifluoromethylbenzene production in the U.S. in 2002. Previous estimated production volume based on nonconfidential information supplied to EPA is as follows: 1986, 1990, and 1994, no production; and 1998, production of >1 to 10 million pounds (EPA, 2004b).

Trifluoromethylbenzene is listed as an HPV chemical in the European Union, meaning that >1,000 metric tons was produced or imported from 1990-1994. According to industry figures, 10,000 - 50,000 metric tons is used in the European Union (European Commission, 2000a). European producers are Clariant GmbH, Hoecst AG., MITENI S.P.A., and Rhone-Poulenc Chimie (European Chemicals Bureau, 2004; European Commission, 2000a).

For the 15-month period from March 8, 2003 to June 14, 2004, the Port Import/Export Reporting Service (PIERS) database reported three imports of benzotrifluoride with a cargo weight of 55,498 pounds (Dialog Information Services, 2004).

Use Pattern:

Historically, trifluoromethylbenzene has been used as a vulcanizing agent and as an intermediate in the manufacture of substituted trifluoromethylbenzenes. Trifluoromethylbenzene and related compounds are intermediates in the production of dyestuffs, insulating fluids, and several economically important classes of herbicides (e.g., fluometuron), pharmaceuticals, antimicrobial agents, and the lampreycide, 4-nitro-2-(trifluoromethyl)phenol (Antonova *et al.*, 1985; Chemical LAND21.com, 2004; HSDB, 2004; Lewis, 2002; Mazza *et al.*, 1986; Toxikologische Bewertung, 1993).

Trifluoromethylbenzene has gained commercial interest due to its solvency properties. Trifluoromethylbenzene is sold for a variety of cleaning applications as an alternative to ozone-depleting substances under EPA's Significant New Alternatives Policy (SNAP) Program, developed under section 612 of the Clean Air Act Amendments. It also has been demonstrated to be an effective replacement for methylene chloride in many reactions, giving similar yields (EPA, 2003; EPA, 2004c; Sherman *et al.*, 1998).

Trifluoromethylbenzenes and monochlorotoluenes, including p-chlorobenzotrifluoride, are substitutes for the following aerosol solvents: CFC-11 (trichloromonofluoromethane), CFC-113 (1,1,2-trichloro-1,2,2-trifluoroethane), MCF (methyl chloroformate), and HCFC-141b . These mixtures are also acceptable substitutes for CFC-113 and HCFC-141b (1,1-dichloro-1-fluoroethane) in non-aerosol cleaning and for CFC-113, HCFC-141b, and TCA (1,1,1-trichloroethane) in adhesives, coatings, and inks (EPA, 2003; EPA, 2004d,e,f).

In non-aerosol solvent cleaning, EPA has historically applied SNAP only to large industrial cleaning applications (precision cleaning, electronics cleaning, and metals cleaning), including cold cleaning and vapor degreasing and defluxing. Typically, these applications

involve a bath of solvent. Metals cleaning involves a wide range of products from fully assembled aircraft down to small metal parts stamped out in large quantities. Electronics cleaning primarily involves the removal of flux residues from wiring assemblies on printed circuit boards after soldering. Precision cleaning applies to compositions for which an extremely high level of cleanliness is necessary, e.g., precision ball bearings for navigational devices (EPA, 2004c).

Human Exposure:

Occupational Exposure. No listing was found for trifluoromethylbenzene in the National Occupational Exposure Survey (NOES), which was conducted by the National Institiute for Occupational Safety and Health (NIOSH) between 1981 and 1983. Estimates from the NOES do not reflect recent changes in the use pattern of trifluoromethylbenzene. However, uses of trifluoromethylbenzene in large industrial cleaning applications (precision cleaning, electronics cleaning, and metals cleaning) suggest the likelihood of worker exposure.

Consumer Exposure. No information indicating that trifluoromethylbenzene is present in consumer products was identified in the available literature.

Environmental Exposure. Trifluoromethylbenzene's production and use may result in its release to the environment through various waste streams, resulting in human exposure (HSDB, 2004).

Trifluoromethylbenzene has been detected in water and sediment as the result of industrial uses:

- In the Niagara River (HSDB, 2004)
- At levels of 0.1-1 ppb in Bloody Run Creek downstream from the Hyde Park landfill in Niagara Falls, NY (HSDB, 2004; European Commission, 2000a)
- At levels of 0.5-2 ppm near the chemical land fill in Niagara Falls, NY (HSDB, 2004)

- At a concentration of <10 μg/l in 1 of 63 industrial effluent samples taken from Ohio, West Virginia, Pennsylvania, New Jersey, New York, Louisiana, Kentucky, Delaware, and Texas (HSDB, 2004).

Environmental Occurrence:

Terrestrial. Based on estimated values, trifluoromethylbenzene will have low mobility in soil. Volatilization of trifluoromethylbenzene may be important from both moist and dry soil surfaces. Trifluoromethylbenzene will not be susceptible to direct photolysis on soil surfaces based upon its lack of absorption of light at wavelengths >290 nm. Biodegradation of trifluoromethylbenzene will not be an important fate process in soil (HSDB, 2004).

Aquatic. Trifluoromethylbenzene is chemically stable in water, causing water to acquire the smell of bitter almonds. Biodegradation does not appear to be an important fate process in water. Trifluoromethylbenzene may volatilize from water surfaces with estimated half-lives for a model river and model lake of about 3.6 hours and 4.8 days, respectively. In open reservoirs, 40% of the original concentration remains after 4 hours; the loss is due to trifluoromethylbenzene's volatility. If released to water, trifluoromethylbenzene may adsorb to suspended solids and sediment but will not be susceptible to direct photolysis on water surfaces (Antonova *et al.*, 1985; HSDB, 2004).

Trifluoromethylbenzene will bioconcentrate in aquatic organisms (HSDB, 2004). Models also estimate that trifluoromethylbenzene would be moderately toxic to aquatic species (Milenia, 2002). The LC50 in *Brachydanio rerio* (fresh water fish) was reported to be 212 mg/l at 48 hr and 96 hr in a static system (European Commission, 2000a). The EC50 in *Daphnia magna* (*Crustacea*) (water flea) at 24 hr was reported to be 7-11 mg/l and about 58 mg/l (European Commission, 2000a; Verschueren, 2001).

Atmosphere. Trifluoromethylbenzene would exist in the vapor phase in the ambient atmosphere. Vapor-phase trifluoromethylbenzene is degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals; the half-life for this reaction in air is estimated to be about 35 days. Vapor-phase trifluoromethylbenzene is also degraded

in the atmosphere by reaction with ozone; the half-life for this reaction in air is estimated to be about 6.3 years. Particulate-phase trifluoromethylbenzene may be physically removed from the air by wet and dry deposition. Trifluoromethylbenzene will not be susceptible to direct photolysis (HSDB, 2004).

Regulatory Status:

No standards or guidelines have been set by NIOSH or the Occupational Safety and Health Administration (OSHA) for occupational exposure to or workplace allowable levels of trifluoromethylbenzene. Trifluoromethylbenzene was not on the American Conference of Governmental Industrial Hygienists (ACGIH) list of compounds for which recommendations for a Threshold Limit Value (TLV) or Biological Exposure Index (BEI) are made.

Under EPA's Significant New Alternatives Policy (SNAP) Program, section 612 of the Clean Air Act Amendments, a use restriction of 100 ppm is placed on trifluoromethylbenzene as an acceptable exposure limit (AEL) (EPA, 1999). Recovered nonusable trifluoromethylbenzene should be considered a RCRA Hazardous Waste (OxyChem, 1998).

TOXICOLOGICAL INFORMATION

Human Data:

No epidemiological studies or case reports investigating exposure to trifluoromethylbenzene and cancer risk in humans were identified in the available literature.

Trifluoromethylbenzene has been described as corrosive, a chemical that may cause eye and skin irritation with possible burns. It has also been reported to cause severe digestive tract irritation with possible burns (Fisher Scientific, 2003).

Animal Data:

No 2-year carcinogenicity studies of trifluoromethylbenzene in animals were identified in the available literature.

Acute Toxicity. The LC_{50} and LD_{50} values for trifluoromethylbenzene are listed in Table 1. Initial signs of toxicity observed in rats were short-term excitation, disturbances of coordination, and atonia, which gradually progressed to narcosis. Female rats were more sensitive than males (Toxikologische Bewertung, 1993).

Changes in peripheral blood, liver, kidneys, stomach, and spleen were also observed following acute exposure to trifluoromethylbenzene. Transient decreases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities and serum ∃-lipoprotein were observed, replaced by increases after 1 to 3 days. Serum alkaline phosphatase (AP), liver, kidney, and heart lactate dehydrogenase (LDH), and stomach and duodenal succinate dehydrogenase (SDH) were also altered. Daily urine output and protein excretion in urine increased. At 10 and 45 days following acute exposure, histological examination revealed organ hypertrophy, especially severe in the liver and kidneys. Changes in the stomach, spleen, heart, and brain were more moderate (Antonova *et al.*, 1985).

Prepared for NCI to support chemical nomination by Technical Resources International, Inc. under contract no. N02-CB-07007 (11/04; 9/05)

Table 1. Acute Toxicity Values for Trifluoromethylbenzene

Species	Route of administration	LC_{50} (mg/m^3) or LD_{50} (mg/kg bw)
rats, 6/dose	oral (gavage); 14-day observation period	15,000
male rats	oral	23,000
Wistar rats, 5 males and 5 females	dermal (occlusive); neat substance on dorsal skin; 14-day observation period	>2,000 (no deaths at 2,000 mg/kg bw dose)
rats	inhalation (4 hr)	78,100
mice, 6/dose	oral (gavage); 14-day observation period	10,000
mice, albino males	intragastric	5,800 - 11,200
mice	inhalation (2 hr)	92,240

Source: Antonova, 1985; European Commission, 2000a; RTECS, 2003; Toxikologische Bewertung, 1993

Subacute Toxicity. When four drops of trifluoromethylbenzene were evenly distributed daily for 10 days to a 4 x 5 cm area of skin, mild dermatitis with thickening of the skin folds and slight flaking was observed (Toxikologische Bewertung, 1993).

Subchronic Toxicity.

In rats, intragastric administration of trifluoromethylbenzene 5 times a week for 45 days at doses of 50, 100, and 500 mg/kg was accompanied by a number of dose and duration dependent changes. The high-dose animals showed increased excitability. Serum AP activity, AST, LDH in liver, and catalase decreased. The relative liver weight increased; SDH activity in the stomach and duodenum increased, and LDH activity in the kidneys increased. Urine contained large quantities of protein and hippurates. In some animals, changes indicative of nephrotic processes in the kidney were observed. Morphological alterations in the stomach were characterized by local changes, including the presence of isolated cyst-like formations. Slight hypertrophy was observed in the liver upon examination, and functional changes were noted in the kidneys, lungs, and brain.

Administration of 100 mg/kg and 50 mg/kg doses produced a dose-related, milder response (Antonova *et al.*, 1985).

In a 6-month study, 425 albino rats of both sexes received 0.01, 0.1, 1, or 10 mg/l of trifluoromethylbenzene in drinking water. At the highest dose, animals showed an increase in excitability. Changes in β-lipoprotein content, AP, AST, and ALT in serum; liver catalase; and peroxidase in the blood were indicative of liver effects. Morphological changes included local irritation of the stomach and appearance of nuclear-nucleolar reaction and increased basophily of the cytoplasm, with hypertrophy in the liver. Exposure at 1 mg/l resulted in similar, but less pronounced changes. Morphological changes were described as compensatory in nature. No changes were observed in animals at the two lowest doses (Antonova *et al.*, 1985).

In a repeated dose toxicity test also designed to examine reproductive and developmental effects, Crj:CD (SD) rats, 12 per sex per dose, were gavaged with corn oil vehicle or 20, 100, or 500 mg/kg bw/day of trifluoromethylbenzene for approximately 49 days. At necropsy, renal hypertrophy and discoloration were observed in high dose males. Increased kidney weights were observed in males dosed at 100 mg/kg/day or greater and in females at 500 mg/kg bw/day. Increased liver weights were also observed in mid- and high-dose males. On histopathological examination, centrilobular hepatocyte hypertrophy was observed in both sexes, and hyaline droplets, necrosis, basophilic change and dilatation of the renal proximal tubules were observed in mid- and high-dose males (Japan Ministry of Health and Welfare, 1996).

Short-Term Tests:

Trifluoromethylbenzene has been examined in the Ames *Salmonella* assay by several investigators using similar techniques. In all cases, trifluoromethylbenzene did not demonstrate mutagenic activity.

Trifluoromethylbenzene dissolved in DMSO was negative in the Ames reversion assay at 100-2,500 μg/plate using TA98, TA100, TA1535, TA1537 and TA1538 and in the

TA100 strain using the preincubation assay at the same doses with and without Aroclor 1254-induced rat liver S-9 (Mazza *et al.*, 1986). It has been noted that the highest dose was not in the toxic range (Toxikologische Bewertung, 1993).

Trifluoromethylbenzene in DMSO was also negative in the Ames preincubation assay using TA97, TA98, TA100, TA1535, and TA1537 at doses ranging from 10-10,000 μg/plate with and without Aroclor 1254-induced rat or hamster liver S-9. The higher concentrations were in the toxic range (Zeiger *et al.*, 1988).

Trifluoromethylbenzene was not mutagenic in *S. typhimurium* TA98, TA100, TA1535, and TA1537 using the plate incorporation method and rat liver induced with phenobarbital and 5,6-benzoflavone. Doses were up to 1,000 μg/plate for TA1535 and TA1537 with and without activation and TA100 without activation and 2,000 μg/plate for TA98 with and without activation and TA100 with activation. Toxicity was observed at some of the higher doses (Japan Ministry of Health & Welfare, 1996).

In addition, trifluoromethylbenzene did not induce gene mutations in *Escherichia coli* WP2 uvrA using plate incorporation at doses up to 2,000 μg/plate (Japan Ministry of Health & Welfare, 1996).

Neither clastogenicity nor polyploidy were observed in a chromosomal aberration assay of Chinese hamster lung cells with and without phenobarbital and 5,6-benzoflavone-induced rat liver S-9 using continuous treatments up to 0.30 mg/ml and short-term treatments up to 1.5 mg/ml. Cytotoxicity was not observed (Japan Ministry of Health & Welfare, 1996).

Trifluoromethylbenzene did not cause DNA damage in the *Bacillus subtilis* Rec-assay at concentrations of 500 - 10,000 μg/disk. This chemical also did not induce mitotic crossing-over (reciprocal recombination) or mitotic gene conversion (non-reciprocal recombination) in *Saccharomyces cerevisiae* at a concentration of 2,000 μg/ml with or without metabolic activation. The authors noted that water insoluble compounds might give rise to false negative results due to reduced diffusion in the water-based agar plates (Mazza *et al.*, 1986).

Metabolism:

In the 6-month rat study, animals exposed to trifluoromethylbenzene in drinking water at 10 mg/l, had a 200% increase in fluoride ion concentration in the urine. Fluorine content in teeth increased by 34%. Six month exposures at 1 mg/l resulted in a 45% increase in fluoride ion in the urine (Antonova *et al.*, 1985).

Intragastric administration of trifluoromethylbenzene 5 days a week for 45 days at 50-500 mg/kg resulted in only a very small fraction of the administered trifluoromethylbenzene being eliminated in the urine, suggesting to the authors that trifluoromethylbenzene is subject to accumulation in tissues associated with deposition of fluoride ion (Antonova *et al.*, 1985).

In rats administered a single oral dose of 1 mg/kg of the structurally related chemical, p-chlorotrifluoromethylbenzene, 3-4% and 14-15% of the carbon label were excreted in feces and urine, respectively. The major urinary metabolites were glucuronides of dihydroxybenzotrifluoride and 4-chloro-3-hydroxybenzotrifluoride, each representing 3-4% of the applied radioactive carbon. Minor amounts of a mercapturic acid conjugate of p-chlorobenzotrifluoride were also detected. p-Chlorobenzotrifluoride was rapidly expired by rats (62-82% of the applied dose) and was the major labeled residue in the feces. In general, levels of radioactive residues in tissues were low, but the small amount of radiolabel in the carcass 4 days after dosing was also identified as p-chlorobenzotrifluoride and was found predominantly in the fat (Quistad & Mulholland, 1983).

Discrepancies in the two studies could represent actual differences in metabolism because of the chloride moiety or experimental differences since one group measured fluoride and the other group measured radioactive carbon.

Other Biological Effects:

Reproductive and Developmental Toxicity Assays.

In a repeat dose/reproductive/developmental toxicity assay, trifluoromethylbenzene was administered to Crj:CD (SD) rats (12 males and 12 females) by gavage at 0 (corn oil), 20, 100, or 500 mg/kg/day. Males were administered trifluoromethylbenzene for 49 days and killed at 50 days. Females were administered trifluoromethylbenzene from 14 days before mating to day 3 of lactation and killed on day 4 of lactation. No effects were observed on the estrus cycle, copulation index, or fertility indices for males or females. Examination at delivery and during the lactation period did not reveal any effects related to the test article in terms of corpora lutea, implantations, litter and live newborns, gestational days, gestation index, stillborn index, or the sex ratio. No external anomalies were observed. Depression of body weight gain in offspring was apparent at all doses and decrease of the viability index on day 4 was noted in the high dose group (Japan Ministry of Health & Welfare, 1996).

In male and female rats exposed to 10 mg/l of trifluoromethylbenzene in drinking water for six months, reproductive function and offspring development were described as intact (Antonova *et al.*, 1985).

Central Nervous System (CNS) Changes.

Rats that received 500 mg/kg of trifluoromethylbenzene by intragastric administration 5 times a week for 45 days showed changes in the CNS manifested as increased excitability. In addition, 30% of the animals exhibited absence of narcotic sleep when treated with hexenal (Antonova *et al.*, 1985).

Toxic effects on the autonomic nervous system of frogs administered a subcutaneous dose of 870 mg/kg of trifluoromethylbenzene was also reported (RTECS, 2003).

Enzyme Induction.

Male rats were given 5 daily intraperitoneal injections of trifluoromethylbenzene at 1,000 mg/kg bw. The *in vitro* induction of microsomal liver enzymes in relation to detoxification of O-ethyl-O-p-nitrophenyl-phenylphosphonothionate (EPN) was measured. Pretreatment with trifluoromethylbenzene lead to a significant increase in EPN detoxification of p-nitroanisole and aminopyrine and a significant increase in the enzymes involved, O-demethylase and N-demethylase, respectively (Toxikologische Bewertung, 1993).

In Vitro Testing.

Sergeyeva and Turzhova (1992) developed an *in vitro* method for determining the lowest concentration of chemicals causing minimal change in the lipid spectrum (∃-lipoproteins, triglycerides, diene conjugates, and common lipids) of bovine serum. The $Lim_{in\ vitro}$ for trifluoromethylbenzene was approximately 7-fold greater than that of benzotrichloride and nearly identical to the $Lim_{in\ vitro}$ for carbon tetrachloride.

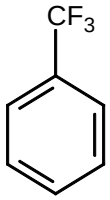
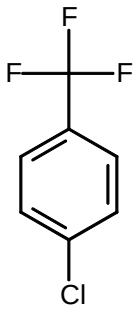
Structure-Activity Relationships:

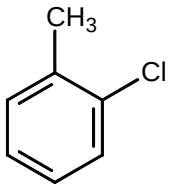
Based on availability of information, similarities in use patterns, and structural similarity, p-chloro- α, α, α -trifluorotoluene (CAS No. 98-56-6), 2-chlorotoluene (CAS No. 95-49-8), and 4-chlorotoluene (CAS No. 106-43-4) were chosen for an analysis of the possible toxic endpoints for trifluoromethyltoluene. This information is summarized in Table 2 below.

An additional related compound, benzotrichloride is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals. When administered by gavage, benzotrichloride induced squamous cell carcinomas of the forestomach and adenocarcinomas of the lung in female mice. Benzotrichloride was tested in three studies by skin application to female mice. It induced squamous cell carcinomas of the skin and lung in all three experiments, and upper digestive tract tumors (carcinomas of the lips, tongue, esophagus, or stomach) and lymphomas were observed in two of the three experiments. In a mouse-lung tumor bioassay, benzotrichloride increased the incidence of

lung adenomas. No data were available to evaluate the carcinogenicity of benzotrichloride, in humans (NTP, 2004).

Table 2. Analysis of the Toxicological Information on Chemicals Structurally Related to Trifluoromethylbenzene

Compound/CAS No.	Genotoxicity	Other Information
Trifluoromethylbenzene (CAS No. 98-08-8) 	Negative in an extensive battery of standard tests for mutagenicity, clastogenicity, and DNA damage	Two separate rat studies of 45-day to 6 month duration show that the liver and kidney are target organs; these effects were dose-related and more severe in males than in females.
4-Chloro- α, α, α-trifluorotoluene (CAS No. 98-56-6) 	*S. typhimurium* TA98, TA100,TA1535, and TA1537 w/wo S-9: negative (Benigni *et al*., 1982) *Aspergillus nidulans* mitotic segregation system: negative (Benigni *et al*., 1982) Epithelial-like human cells - induction of unscheduled DNA synthesis: positive (induced detectable levels of ^{3}H-TdR incorporation ((Benigni *et al*., 1982) *In vitro/in vivo* urinary assay (urine collected from mice given the chemical), the mouse lymphoma assay, *Saccharomyces* strain D_4, and *E. coli* W3110/po;A+ and P3478/polA- were all negative (EPA, 1985) *In vitro* testing in Chinese hamster ovary (CHO) cells and *in vitro* testing in the rat bone marrow cytogenic assay were negative (EPA, 1985) Produced sister chromatid exchanges in CHO cells (Toxikologische Bewertung, 1995) Not mutagenic in host-mediated assay, in rec assay in *Bacillus subtilis*, and in the mitotic crossing-over test in *Saccharomyces cerevisiae* (Toxikologische Bewertung, 1995)	F344/N rats and B6C3F$_1$ mice; gavage once a day for 14 days: dose-related accumulation in kidney linearly related to kidney levels of α_{2U}-globulin; dose-related hyaline droplet nephropathy (male rats only); hepatocyte hypertrophy and cytoplasmic vacuolization of the adrenal cortex (male and female rats); hepatocellular hypertrophy, cholestasis, and mild liver injury (mice) (Yuan *et al.*, 1991; NTP, 1992) Fischer 344 rats; gavage at 10, 40, 150, or 500 mg/kg bw/day for 90 days: dose related increases in blood urea nitrogen, total bilirubin, alkaline phosphatase, and induction of hepatic enzymes; increased liver and kidney weights; liver hypertrophy and mild proteinuria. Effects more pronounced in males (EPA, 1985; Toxikologische Bewertung, 1995) Sprague-Dawley rats; gavage daily for 28 days at 0, 10, 100, and 1,000 mg/kg bw/day; males showed significant dose-dependent increases in blood cholesterol and triglycerides, hyaline droplet nephrosis, increased relative kidney weight, and increase in lipid vacuoles in adrenal cortex at the highest dose. Both males and females showed significant increase in relative liver weight at the highest dose (Macrì *et al.*, 1987). Male rats (undefined strain): inhalation

Compound/CAS No.	Genotoxicity	Other Information
		at 5.5-440 mg/m^3 24 hr/day for 4 months; top two concentrations led to effects on almost all parameters studied, including hematological parameters, cholinesterase and LDH, motor activity, and muscle power, even though body weights were not affected (Toxikologische Bewertung, 1995)
2-Chlorotoluene (CAS No. 95-49-8) 	*S. typhimurium* TA98, 100, 102, 104 1535, 1537, 1538 w/wo S-9: negative (CCRIS, 2004; European Commission, 2000b) *E coli* wp2uvra and wp2uvra/pkm101 w/wo S-9: negative (CCRIS, 2004; European Commission, 2000b) CHO cells cytogenetic assay w/ wo S-9: negative for chromosomal aberrations (European Commission, 2000b) Mouse lymphoma cell line, L5178Y TK+/- w/wo S-9: negative (European Commission, 2000b) Sprague Dawley rats, gavage, single dose and five doses - did not induce chromosomal aberrations in rat bone marrow cells (European Commission, 2000b) *In vitro* transformation of Balb/3T3 cells - negative (European Commission, 2000b)	Weaning Harlan rats (20 males, 20 females/group): at 80 and 320 mg/kg/day males developed increases in adrenal, heart, and testes weights. No histological changes were observed (IRIS, 1990)
4-Chlorotoluene (CAS No. 106-43-4) 	*S. typhimurium* TA97, TA98, 100, 102, 104, 1535, 1537, and 1538 w/wo S-9: negative (CCRIS, 2004; European Commission, 2000c) *S. typhimurium* TA1535/pSK 1002 w/ wo S-9 (umu test): negative (European Commission, 2000c) *E coli* wp2uvra and wp2uvra/pkm101 w/wo S-9: negative (CCRIS, 2004) CHO cells cytogenetic assay w/wo S-9: negative for chromosomal aberrations (European Commission, 2000c)	In a subchronic (90-day) study, Sprague-Dawley rats, 10/dose/sex, dosed at 0, 50, 200, or 800 mg/kg bw by gavage 7 days a week: results were as follows: at high dose, 4/10 males and 2/10 females died early; all males had abnormalities in kidneys (pale area, mottled appearance, dilated renal pelvis and or granular/pitted/rough texture; males and females had centrilobular hypertrophy of hepatocytes, chronic progressive nephropathy characterized by degeneration and regeneration of the tubular epithelial cells, interstitial fibrosis and mononuclear cell infiltrates

Compound/CAS No.	Genotoxicity	Other Information
	Mouse lymphoma cell line, L5178Y TK+/- w/wo S-9: negative (European Commission, 2000c) NMRI mouse, *in vivo* micronucleus assay, no evidence of a clastogenic effect (European Commission, 2000c) *Saccharomyces cerevisiae* D3, negative for mitotic recombination (European Commission, 2000c)	(10/10 males, 9/10 females, 2/10 control males, 0/10 control females); hyperplasia of the zona fasciculata in the adrenal glands (European Commission, 2000c). In a 90-day study in Charles River rats gavaged at 100, 300, or 1,000 mg/kg bw/day, results were as follows: No treatment related alterations in any of the hematological parameters tested; blood chemistry studies showed no effect; no gross or histopathologic abnormalities observed; at the highest dose, excessive urination with a transient increase in albumin (European Commission, 2000c) In a 90-day study of Beagle dogs receiving capsules of 30-300 mg/kg bw/d, no treatment related abnormalities were described (European Commission, 2000c) In a 6 month study in rats administered p-chlorotoluene at 0.01-1.0 mg/kg bw/day, at the highest dose, changes in hematological parameters, decreased blood-urea level, disturbances of carbohydrate metabolism, capillary hyperemia and low-grade hemorrhages, and alterations in the brain, liver, kidney, and lung were observed (European Commission, 2000c)

References

Antonova, V.I., Salmina, Z.A., Budilova, L.V. & Petrova, N.A. (1985) [Hygenic standardization of benzofluoride for Water Resevoirs]. *Gig. Sanit.,* **2**, 86-87. Russian.

Benigni, R., Bignami, M., Conti, L., Crebelli, R., Dogliotti, E., Falcone, E. & Carere, A. (1982) In vitro mutational studies with trifluralin and trifluorotoluene derivatives. *Ann. Ist. Super. Sanità*, **18**(1), 123-126

Bignami, M. & Crebelli, R. (1979) A simplified method for the induction of 8-azaguanine resistance in *Salmonella typhimurium*. *Toxicol.Lett.*, **3**(3), 169-175

Budavari, S., ed. (2001) *The Merck Index*, 13th ed., Whitehouse Station, NJ, Merck & Co., Inc., p 190

CCRIS (2004) Trifluoromethylbenzene, 2-Chlorotoluene, and 4-Chlorotoluene. *Chemical Carcinogenesis Research Information System*. Record nos. 2808, 7785, 6000.. National Library of Medicine, Bethesda, MD. Accessed through [http://toxnet.nih.gov] Searched November 27, 2004

ChemACX (2004) Benzotrifluoride [98-08-9]. *Search results*. [http://chemacx. cambridgesoft.com/ChemACX/index.asp] Searched June 18, 2004

Chemcyclopedia (2004) Chemcyclopedia Search Result Page. [http://www.mediabrains.com/ client/chemcyclop/BG1/search.asp] Searched November 24, 2004

ChemFinder (2004) ChemFinder.Com Search Result Page. [http://chemfinder.cambridgesoft. com/result.asp]. Searched November 24, 2004

Chemical LAND21.com (2004) Benzotrifluoride [http://www.chemicalland21.com/] Searched November 27, 2004

Chemical Sources International (2004) *All Chemical Suppliers for: Benzotrifluoride.* [http://www.chemsources.com] Searched June 18, 2004

ChemID (2004) Benzotrifluoride. *ChemIDplus*. National Library of Medicine, Bethesda, MD. [Record No. 98088]. [http://chem.sis.nlm.nih.gov/chemidplus/] Searched October 25, 2004

Dialog Information Services (2004) *Search for benzotrifluoride*. PIERS Imports (US Ports) (File 573), Palo Alto, CA, [Record no 4036037] Searched November 11, 2004

EPA (1985) 4-Chlorobenzotrifluoride; Decision not to test. *Fed. Reg.*, **50**(202), October 18, 1985, 42216-42221

EPA (1999) Protection of stratospheric ozone. 40 CFR Part 82, *Fed. Reg.*, **64**(109), June 8, 30410-30415

EPA (2003) Substitute Aerosol Solvents and Propellants Under SNAP as of August 25, 2003. *SNAP Information.* U.S. Environmental Protection Agency, Air and Radiation, Global Programs Division. [http://www.epa.gov/ozone/snap] Searched October 25, 2004

EPA (2004a) Substance list CAS No. 98-08-8. Benzene, trifluoromethyl-. *Substance Registry System*. U.S. Environmental Protection Agency. Available through [http://oaspub.epa.gov/srs/] Searched November 27, 2004

EPA (2004b) Search results: search by CAS No. for 98088. *Inventory Update Rule.* U.S. Environmental Protection Agency. [http://www.epa/gov/cgi-bin/iursrch3_2002.cgi] Searched November 8, 2004

EPA (2004c) Questions and answers on alternative solvents. *Alternatives*. U.S. Environmental Protection Agency. [http://www.epa.gov/Ozone/snap/solvents/qa.html] Searched October 25, 2004

EPA (2004d) Substitutes in metals cleaning. *Alternatives*. U.S. Environmental Protection Agency. [http://www.epa.gov/Ozone/snap/solvents/lists/metals.html] Searched October 25, 2004

EPA (2004e) Substitutes in electronics cleaning. *Alternatives*. U.S. Environmental Protection Agency. [http://www.epa.gov/Ozone/snap/solvents/lists/electron.html] Searched October 25, 2004

EPA (2004f) Substitutes for ODS in aerosol solvent propellants. *Alternatives*. U.S. Environmental Protection Agency. [http://www.epa.gov/Ozone/snap/saerosol/list/electron.html] Searched October 25, 2004

European Chemicals Bureau (2004) Result for CAS#: 98-08-8. *ESIS (European Chemical Substances Information System).* [http://ecb/jrc/it/esis-pgm/esis_response.php] Searched October 25, 2004)

European Commission (2000a) Existing chemical substance ID: 98-08-8. *IUCLID Dataset.* 39 p

European Commission (2000b) Existing chemical substance ID: 95-49-8. *IUCLID Dataset.* 55 p

European Commission (2000c) Existing chemical substance ID: 106-43-4. *IUCLID Dataset.* 47 p

Fisher Scientific (2003) alpha,alpha,alpha-Trifluorotoluene, 99+%. *Material Safety Data Sheet*. [https://fscimage.fishersci.com/msds/07328.htm] Searched October 25, 2004

Fisher Scientific (2004) a,a,a-Trifluorotoluene 99+%. Acros Organics Product Search. [https://www1.fishersci.com] Searched October 25, 2004

HSDB (2004) HSDB (2004) *Hazardous Substances Data Bank*. [Record no. 2077]. Bethesda, MD, National Library of Medicine. Searched November 27, 2004

IRIS (1990) o-Chlorotoluene CASRN: 95-49-8. *Integrated Risk Information System*. U.S. Environmental Protection Agency, Office of Research and Development. Available through ChemID. [http://toxnet.nlm.nih.gov/cgi-bin/sis/search/] Searched November 27, 2004

IsleChem (2004) OXSOL®. [http://www.islechem.com/oxsol/oxsol.htm] Searched October 29, 2004

Japan Ministry of Health & Welfare. Trifluoromethylbenzene. *Toxicity Testing Reports of Environmental Chemicals.* [http://wwwdb.mhlw.go.jp/ginc/dbfile1/file/file98-08-8.html] Searched October 25, 2004

Lide, D.R., ed. (2003) Trifluoromethylbenzene. *CRC Handbook of Chemistry and Physics*, Version 2003, (On CD-Rom), Boca Raton, FL, CRC Press LLC

Lewis, R.J., ed. (2002) Benzotrifluoride. *Hawley's Condensed Chemical Dictionary*, 14th ed., (on CD-ROM), NY, John Wiley & Sons, Inc.

Macri, A., Ricciardi, C., Stazi, A.V., Mantovani, A., Vendramin Macri, C., Piccioni, A., Badellino, E., Bianchi, M.P., Pepe, M. & Ceccabtu, M. (1987) Subchronic oral toxicity of 4-chloro-alpha, alpha, alpha-trifluorotoluene in Sprague-Dawley rats. *Food Chem. Toxicol*. **25**(10), 781-786

Makhteshim Agan Industries Ltd. (2002) Subsidiary of Makhteshim-Agan Acquires Oxsol Product Line from Occidental Chemical Company. Press Release

Maul, J.J., Ostrowski, P.J., Ublacker, G.A., Linclau, B. & Curran, D.P. (1999) Benzotrifluroide and derivatives: Useful solvents for organic synthesis and fluorous synthesis. *Topics Curr. Chem*., **206**, 79-105

Mazza, G., DaCarro, C., Bonferoni, C. & Bonferoni, B. (1986) Studies on the mutagenic activity of trifluoromethylbenzene and twelve derivatives in microbial short-term assays. *Farmaco., Ed., Prat*., **41**(7), 215-225

Milenia (2002) OXSOL® 2000, *Material Safety Data Sheet*. [http://wwwislechem.com/rdfs/2000msds.pdf]

NTP (1992) Toxicity Studies of p-Chloro-a,a,a Trifluorotoluene (CAS NO: 98-56-6) Administered in Corn Oil and a-Cyclodextrin to F344.N Rats and B6C3F$_1$ Mice in 14-Day

Comparative Gavage Studies. TOX-14. Available from search of [http://ntp.nih.gov] as of September 30, 2005

NTP (2004) Benzotrichloride. *10th Report on Carcinogens*. U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program. [http://ehp.niehs.nih.gov/roc/toc10.html] Searched November 27, 2004

OxyChem (1998) Benzotrifluoride. *Material Safety Data Sheet*. Occidental Chemical Corporation, Dallas, TX, 13 p

Quistad, G.B. & Mulholland, K.M. (1983) Metabolism of p-chlorotrifluoromethylbenzene by rats. *J. Agric. Food Chem.,* **31**(1), 585-589

Rader, C.G. & Robota, S. (1984) Process for the catalyzed fluorinatin of haloalkyl aromatic compounds. U.S. Patent No. 4,436,942, March 13, 1984. [http://patft.uspto.gov/netac.gi/] Searched November 26, 2004

RTECS (2003) Toluene, alpha,alpha,alpha-trifluoro. *Registry of Toxic Effects of Chemical Substances*. MDL Information Systems, Inc., Elsevier Science, Inc.

Sergeyeva, M.G. & Ye.B. Turzhova (1992) [A method of rapid evaluation of chemical substances using biotesting., Scientific Resaerch Institute for Hygiene and Occupational Pathology, St. Petersburg (Translation from the Russian**)**

Sherman, J., Chin, B., Huibers, P.D.T, Garcia-Valls, R. & Hatton, T.A. (1998) Solvent replacement for green processing. Environ. Hlth. Perspect., **106**(Suppl. 1), 253-271

Sigma-Aldrich (2004) Search Results: CAS Number: 98-08-8. [https://www.sigmaaldrich.com/cgi-bin/hsrun/Suite7] Searched June 18, 2004

Tilton, H., ed. (2004). *OPD 2005 Chemical Buyers Directory*, New York, Schnell Publishing Co., p 105

Toxikologische Bewertung (1993) Benzotrifluoride. Heidelberg, Berufsgenossenschaft der chemischen Industrie,**75**, 27-33 [English translation]

Toxikologische Bewertung (1995) p-Chlorobenzotrifluoride. Heidelberg, Berufsgenossenschaft der chemischen Industrie, **272** (1995), 25 p [English translation]

Verschueren, K. (2001) Trifluoromethyl)benzene. *Handbook of Environmental Data on Organic Chemicals*. 4th ed., John Wiley & Sons. New York, NY, 2115-2116

Yuan, J., Jameson, C.W., Goehl, T.J., Elwell, M.R., Leininger, J.R., Thompson, M.B., Corniffe, G. & Carlton, T. (1992) Application of molecular encapsulation for toxicology studies: comparative toxicity of p-chloro-alpha, alpha, alpha-triflurortoluene in alpha-cyclodextrin

vehicle versus corn oil vehicle in male and female Fischer 344 rats and B6C3F1 mice. *Fund. Appl. Toxicol*., **18**(3), 460-470

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T. & Mortelmans, K. (1988) Salmonella mutagenicity tests: IV Results from the testing of 300 chemicals. *Environ. Molec. Mutagen*. **11**(Suppl. 12), 1-158