

4-Bromofluorobenzene
[CAS No. 460-00-4]

Review of Toxicological Literature

January 2005

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Prepared for
National Toxicology Program (NTP)
National Institute of Environmental Health Sciences (NIEHS)
National Institutes of Health
U.S Department of Health and Human Services
Contract No. N01-ES-35515

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January 2005

Abstract

4-Bromofluorobenzene (4-BFB) is a high production volume (HPV) chemical in the United States and Europe. It is produced by bromination of fluorobenzene in the presence of a catalyst. As a chemical in commerce, 4-BFB is listed on the Toxic Substances Control Act Inventory. Under the HPV Challenge Program, it appears to still be an "orphan" chemical. 4-BFB is used as an agrichemical intermediate, in organic syntheses, and as a tuning, internal, or surrogate standard for gas chromatography-mass spectrometry for the determination of volatile organic compounds in various media. 4-BFB was not detected in surface and subsurface soil, surface water, or sediment samples from the Defense Depot—Memphis, Tennessee National Priorities List site. In rats orally administered 4-BFB, 67% of the dose was recovered in the urine after 24 hours. Aromatic ring hydroxylation was a main pathway for urine excretion; phenolic metabolites were 75% of the total metabolites. In acute exposure studies, tremor, change in motor activity, ataxia and/or dyspnea were observed in rats treated orally or by inhalation. 4-BFB was irritating to rabbit eyes and skin and sensitizing to guinea pigs. No other toxicological data was identified.

Executive Summary

Basis for Nomination

4-Bromofluorobenzene (4-BFB) was nominated by the National Institute for Environmental Health Sciences (NIEHS) for toxicological studies because it is a high-production-volume (HPV) chemical with insufficient publicly available toxicological data. It is structurally similar to certain halogenated benzenes, such as bromobenzene and *p*-dichlorobenzene, the latter of which was found to be a rodent carcinogen in previous studies conducted by the National Toxicology Program (NTP).

Nontoxicological Data

4-BFB is a colorless to slightly yellow liquid with a boiling point between 152 and 155 °C and a melting point of -16 °C. It is stable under normal conditions but may release poisonous fumes of hydrogen bromide, hydrogen fluoride, carbon monoxide, and carbon dioxide when heated to decomposition. 4-BFB is an HPV chemical with annual production exceeding one million pounds in the United States and two million pounds in Europe. Analysis of 4-BFB is done via gas chromatography (GC).

Commercial Availability: In 1990, Diaz Chemical Corporation, Hoechst Celanese, and Rhone Poulenc, Inc. were reported as companies producing 4-BFB. In 1998, Diaz Chemical Corporation and Nipa Hardwicke, Inc. were the only companies listed. Diaz Chemical Corporation, currently operating as Diaz Intermediates Corporation, produces 99.9%-pure 4-BFB. A product with high purity ($\geq 99.0\%$) is also commercially available from Albemarle Corporation. It is available from Chem Service as a neat chemical standard with $\geq 98\%$ purity.

Production Processes: 4-BFB is produced by bromination of fluorobenzene in the presence of a catalyst. A "greener" commercial process for preparing fluorinated aromatic compounds in which water is generated as the only by-product was being developed by scientists at DuPont Central Research and Development.

Production Volume: Under the 1986 Inventory Update Rule (IUR), an aggregate production volume ranging between 10,000 lb (4535.9 kg) and 500,000 lb (226,800 kg) was reported for 4-BFB. In 1990, 1998, and 2002, volumes ranging between >1 million lb (453,600 kg) and 10 million lb (4,536,000 kg) were submitted by companies. In 1994, >500,000 lb (226,800 kg) to 1 million lb (453,600 kg) was reported.

Uses: 4-BFB is used as an agrichemical intermediate and in organic syntheses, such as the preparation of a Grignard reagent. It is apparently also used in the preparation of therapeutic drugs containing a 4-fluorophenyl moiety. 4-BFB is a suitable internal standard or surrogate spike for the determination of volatile organic compounds (VOCs) in water and fish, sediment, and soil, and in the analysis of hazardous air pollutants, air quality in car parking areas, total petroleum hydrocarbons, and industrial waste leachates. It is also used as a tuning, internal, or surrogate standard in several EPA GC methods (e.g., 500 series—methods for drinking water and the Contract Laboratory Program [CLP] method).

Environmental Occurrence and Persistence: The Defense Depot—Memphis, Tennessee (DDMT), a secured military supply, storage, and maintenance facility in operation from 1942 to 1997, National Priorities List (NPL) site was found to be of "no apparent public health hazard [to nearby residents] from 1989 to the present." 4-BFB was not detected in surface and subsurface soil, surface water, or sediment.

A microbial mixture (consisting of five pseudomonads, one klebsiella, four rhodococci, and two fungal strains) was found capable of completely degrading 4-BFB in 72 hours. For the biodegradation of

hazardous waste, rhodococci, widely distributed in soil and sludge, was tested. *Rhodococcus opacus* GM-14, however, failed to grow on 4-BFB after 14 days of incubation.

Human Exposure: No data for specific human exposures were found. Potential exposure to 4-BFB may occur for workers involved in the production of pharmaceuticals, pesticides, and other organics from 4-BFB.

Regulatory Status: As a chemical in commerce, 4-BFB is listed on the TSCA Inventory. Under the HPV Challenge Program, it appears to still be an orphan chemical (i.e., without sponsorship).

Toxicological Data

No information regarding short-term/subchronic or chronic exposure, synergistic/antagonistic effects, cytotoxicity, reproductive or teratological effects, carcinogenicity, or genotoxicity was available.

Chemical Disposition, Metabolism, and Toxicokinetics: In male Wistar rats orally administered 4-BFB (87.5 mg/kg [500 μ mol/kg] body weight), 67% of the dose was recovered in the urine after 24 hours. Aromatic ring hydroxylation was a main pathway for urine excretion; phenolic metabolites were 75% of the total metabolites. The regioselectivity of aromatic ring hydroxylation (C2/6:C3/5) was 74:26. Hydroxylation at the positions ortho to the bromine was only 40% of that predicted by molecular orbital theory, presumably due to steric hindrance. Pretreatment of rats with various cytochrome P450 inducers showed very little influence of the P450 enzyme on the regioselectivity of the aromatic hydroxylation.

Acute Toxicity: The oral LD₅₀ values for rats ranged from 2248 to 3788 mg/kg (12.84-21.64 mmol/kg). The four-hour LC₅₀ value was 18 g/m³ (2500 ppm). Tremor, change in motor activity, ataxia and/or dyspnea were observed in the studies. 4-BFB (doses not provided) was irritating to rabbit eyes and skin. In albino rabbits, application of 0.5 mL to the semi-occluded intact skin for four hours produced a primary irritation index of 0.33.

Immunotoxicity: In the Magnusson and Kligman guinea pig maximization test, 4-BFB (dose n.p.) was a mild sensitizer; it produced a 20% sensitization rate.

Structure-Activity Relationships

In this section, results from NTP studies for two structurally related analogues, *p*-dichlorobenzene and bromobenzene, are presented.

1,4-Dichlorobenzene [CAS No. 106-46-7]

1,4-Dichlorobenzene is used as an insecticidal fumigant, germicide, chemical intermediate, and space deodorant for restrooms and garbage; in dyes and pharmaceuticals; and for moth control.

Short-Term or Subchronic Studies: In 13-week gavage studies in Fischer 344 rats, 1,4-dichlorobenzene (300-1500 mg/kg) decreased survival and weight gain and increased the liver weight-to-brain weight ratio, serum cholesterol levels, and urinary porphyrins. Degeneration and necrosis of hepatocytes, hypoplasia of the bone marrow, lymphoid depletion of the spleen and thymus, and epithelial necrosis of the nasal turbinates were reported for both males and females. In males only, renal tubular cell degeneration and increases in the kidney weight-to-brain weight ratio and blood urea nitrogen level were observed. Additionally, there were reductions in serum triglycerides, hematocrit, red blood cell count, and hemoglobin level.

In B6C3F₁ mice, 1,4-dichlorobenzene (85-1800 mg/kg) reduced survival, body weight gain, white blood cell count and increased the liver weight-to-brain weight ratio. Hepatocellular degeneration and

hepatocellular cytomegaly were also observed in the animals. In males only, serum cholesterol levels and serum protein and triglycerides were increased.

Carcinogenicity: In two-year gavage studies, there was clear evidence of carcinogenicity with 1,4-dichlorobenzene in male Fischer 344 rats and in male and female B6C3F₁ mice.

Genotoxicity: 1,4-Dichlorobenzene was not mutagenic in the *Salmonella* or micronucleus test. It failed to induce chromosome aberrations or sister chromatid exchanges (SCEs) in Chinese hamster ovary cells and produced inconclusive results in the mouse lymphoma assay.

Bromobenzene [CAS No. 108-86-1]

Bromobenzene, used as a chemical intermediate, solvent, and motor oil additive, is a classic hepatotoxicant. Its hepatotoxicity is strongly correlated with covalent binding of reactive metabolites to cellular proteins. In mice and rats, a decrease in glutathione (GSH) levels was observed. Bromobenzene was negative for mutagenicity in the *Salmonella* test. It was also negative for the induction of chromosome aberration but weakly positive for induction of SCEs. Short-term toxicity studies (i.e., 13-week inhalation and gavage studies) have been conducted by the NTP in Fischer 344 rats and B6C3F₁ mice, but no results were available.

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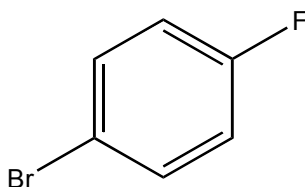
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1.0 Basis for Nomination

4-Bromofluorobenzene (4-BFB) was nominated by the National Institute for Environmental Health Sciences (NIEHS) for toxicological studies because it is a high-production-volume (HPV) chemical with insufficient publicly available toxicological data. It is structurally similar to certain halogenated benzenes, such as bromobenzene and *p*-dichlorobenzene, the latter of which was found to be a rodent carcinogen in previous studies conducted by the National Toxicology Program (NTP).

2.0 Introduction

4-Bromofluorobenzene
[460-00-4]



The CAS Registry Number for generic bromofluorobenzene (i.e., unspecified for position of the bromine and fluorine atoms) is 30135-88-7.

2.1 Chemical Identification and Analysis

4-BFB (C₆H₄BrF; mol. wt. = 175.01) is also called:

Benzene, 1-bromo-4-fluoro- (7CI, 8CI, 9CI)
1-Bromo-4-fluorobenzene
4-Bromo-1-fluorobenzene
4-Bromophenyl fluoride
p-Bromofluorobenzene
1-Fluoro-4-bromobenzene
4-Fluorobenzene bromide
4-Fluorobromobenzene
4-Fluoro-1-bromobenzene
p-Fluorobromobenzene
p-Fluorophenyl bromide
4-Fluorophenyl bromide
NSC 10268
NSC 9460

Sources: Registry (2004); RTECS (2004)

Trace BFB (nonspecific) is a volatile organic compound (VOC) that can be analyzed in surface water using gas chromatography with mass spectrometry (GC-MS) (Zhang and Chen, 1992). As a surrogate spike, it was determined in VOCs recovered from soil samples by purge-and-trap GC-MS; 4-BFB was identified as the quantitation reference compound for 1,1,2,2-tetrachloroethane and ethylbenzene in several spiked samples (Schumacher and Ward, 1997). 4-BFB was used as a

calibration check compound for a VOST (volatile organic sampling train) Fractionator and was analyzed by the SW-846 EPA Method 5041, GC-MS technique (St. Germain et al., 1994). [See also Section 5.0.]

2.2 Physical-Chemical Properties

Property	Information	Reference(s)
Physical State	clear, colorless to slightly yellow liquid	Albemarle Corp. (1999)
Odor	odorless	DSBG (2002)
Boiling Point (°C) @760 mm Hg	152-155	Albemarle Corp. (1999); DSBG (2002)
Melting Point (°C)	-16	Albemarle Corp. (1999); DSBG (2002)
Flash Point (°C)	53, 60	Albemarle Corp. (1999); DSBG (2002)
Vapor Pressure at 25 °C (mm Hg)	4.07074	Registry (2004)*
Density at 20 °C (g/cm ³)	1.594	Albemarle Corp. (1999)
Water solubility	insoluble	DSBG (2002)
Molar Solubility	<0.01 M @ pH 1-10	Registry (2004)*
Adsorption Coefficient (K _{OC})	984 @ pH 1-10	Registry (2004)*
log P	2.971±0.386	Registry (2004)*
Bioconcentration Factor (BCF)	107 @ pH 1-10	Registry (2004)*

*calculated properties using Advanced Chemistry Development (ACD/Labs) Software Solaris V4.67 (©1994-2004 ACD/Labs)

4-BFB is stable under normal conditions. When heated to decomposition, it may release hydrogen bromide, hydrogen fluoride, carbon monoxide, and carbon dioxide (DSBG, 2002).

2.3 Commercial Availability

In the 1970s, 4-BFB was manufactured by Kodak Park Division (Rochester, NY) and imported by American Hoechst Corporation (Bridgewater, NJ), Columbia Organic Chemicals Company (Columbia, SC), Henley and Company, Inc. (New York, NY), and Rhone-Poulenc, Inc. (Freeport, TX) (TSCAPP Database, ca. 1977). In 1990, Diaz Chemical Corporation, Hoechst Celanese, and Rhone Poulenc, Inc. were reported as companies producing 4-BFB. In 1998, Diaz Chemical Corporation and Nipa Hardwicke, Inc. were the only companies listed (U.S. EPA, 1998a, 1999). Diaz Chemical Corporation, currently operating as Diaz Intermediates Corporation (West Memphis, AR), produces 99.9% pure 4-BFB (Diaz Intermediates, undated). [Note: Nipa Hardwicke, Inc. (Elgin and Rock Hill, SC) is now called Archimica (Archimica, 1999a,b).]

4-BFB (≥99.0% purity, with ≤0.2% ortho isomer and ≤0.5% total other impurities.) is commercially available from Albemarle Corporation (Baton Rouge, LA) in bulk tanks and 250-kg steel drums (Albemarle Corp., 1999). It is available from Chem Service (West Chester, PA) as a neat chemical standard with ≥98% purity (ChemService, 2004).

Suppliers of 4-BFB include Acros Organics USA, Contract Chemicals, Inc., Honeywell Specialty Chemicals GmbH Seelze, and Spectrum Chemical Manufacturing Corporation (Chemyclopedia, 2004). Numerous other companies, most supplying generally ≤500 g, were listed in the CHEMCATS database: e.g., Bryant Laboratory, Inc. (Berkeley, CA), City Chemical LLC (West Haven, CT), Indofine Chemical Company, Inc. (Hillsborough, NJ), Kessler Chemical, Inc. (Bethlehem, PA), Marshallton Research Laboratories (King, NC), and TCI America (Portland, OR).

3.0 Production Processes

Diaz Intermediates Corporation manufactures 4-BFB by bromination of fluorobenzene in the presence of a catalyst; the reaction mixture contains hydrogen bromide and is quenched in water and/or caustic solution (ADEQ, 2003).

A "greener" commercial process for preparing fluorinated aromatic compounds, developed by scientists at DuPont Central Research and Development, Experimental Station (Wilmington, DE), generated water as the only by-product. In this process (still in testing stage at time of publication), a stream of vaporized benzene in nitrogen gas is passed over cupric fluoride to yield fluorobenzene with 95% selectivity. At 450 °C, 5% of benzene is converted to fluorobenzene, and at 550 °C, cupric fluoride is reduced to copper metal. A stream of hydrogen fluoride and oxygen (2:1) at 350-400 °C regenerates the cupric fluoride and water. This process can be used to make several fluorinated aromatic compounds including difluorobenzenes (Greene and D'Aquino, 2002).

4.0 Production and Import Volumes

4-BFB is an HPV chemical with annual production exceeding one million pounds in the United States (Denison, 2004; U.S. EPA, 1998a, 1999). Under the 1986 Inventory Update Rule (IUR), an aggregate production volume ranging between 10,000 lb (4535.9 kg) and 500,000 lb (226,800 kg) was reported for 4-BFB. In 1990, 1998, and 2002, volumes ranging between >1 million lb (453,600 kg) and 10 million lb (4,536,000 kg) were submitted by companies. In 1994, >500,000 lb (226,800 kg) to 1 million lb (453,600 kg) was reported (U.S. EPA, 2004a). 4-BFB is also an HPV chemical in Europe, where at least one European Union member country annually produces more than 1000 tons (2 million lb) (OECD, 2001).

The Arkansas air quality permit for Diaz Intermediates limits 4-BFB annual production to 6 million pounds (3×10^6 kg) (ADEQ, 2003). In the 1970s, Columbia Organic Chemicals Company reported a production volume under 1000 lb (453.6 kg) (TSCAPP Database, ca. 1977).

5.0 Uses

4-BFB is used as an agrichemical intermediate and in organic syntheses (Albemarle Corp., 1999). Among commercial products identified with certainty is the Grignard reagent prepared from 4-BFB, 4-phenylmagnesium bromide, which is probably prepared more commonly *in situ* during the synthesis, and 4-fluorophenol (Lewis, 1993). 4-BFB is also a suitable internal standard or surrogate spike for GC-MS analysis of VOCs in water and fish, sediment, and soil, and in the analysis of hazardous air pollutants, air quality in car parking areas, and industrial waste leachates (Maeda, 1998; Mehran et al., 1996; Sakamoto and Fukui, 1995; Schumacher and Ward, 1997; Takano et al., 1996; Wong et al., 2002).

4-BFB is used as a tuning, internal, or surrogate standard in several EPA GC methods: 500 series—methods for drinking water; 600 series—methods for wastewater pollutants; 8000 series—methods for monitoring organic pollutants in groundwater, wastewater, and solid waste; air toxic method TO14A; and the Contract Laboratory Program (CLP) method. 4-BFB is also a standard for UST (underground storage tank systems) methods [i.e., releases from these systems containing petroleum or hazardous substances] and the analysis of total petroleum hydrocarbons (ChemService, 2004; U.S. EPA, 2000).

Numerous TOXCENTER records from Chemical Abstracts included patents and patent applications where 4-BFB is apparently used in the preparation of therapeutic drugs containing a 4-fluorophenyl moiety by pharmaceutical companies such as Jansen Pharmaceutica, N.V. Belgium (Kennis and Mertens, 1984); Warner Lambert/Parke-Davis Pharmaceutical Research, USA (Wise et al., 1985); Glaxo Group Limited, UK (Cherry et al., 2004); Bayer A.-G., Germany (Philipps et al., 1990); SmithKline Beecham, USA (Haffner et al., 2003); and Pfizer Products, Inc., USA (Noe and Wolf-Gouveia, 2003).

Some of the analytical methods in which 4-BFB is used for tuning mass spectrometers or as an internal or surrogate standard are listed in **Table 1**.

Table 1. Techniques in Analyzing Environmental Samples

Analytes/Medium	Analytical Methods	Reference(s)
VOCs (unspecified)	Purge-and-trap with capillary column GC/MS compared to U.S. EPA Method 624 (packed column)	Dreisch and Munson (1983)
VOCs in drinking water	U.S. EPA Method 542.2: gas-purge extraction on a three-stage solid-phase trap, thermal desorption into capillary GC	Eichelberger et al. (1990); Munch and Eichelberger (1992)
Boiler fly ash for VOCs	Modified SW-846 Method 8260	Grese and Edwards (1995)
Polar VOCs (non-purgeable) in water	Capillary GC/ion-trap MS using direct aqueous injection. 4-BFB used as tuning standard to calibrate MS.	Pyle et al. (1995)
Soils ¹	Purge-and-trap GC/MS. Quantitation of reference compound compared with surrogate spikes and internal standard	Schumacher and Ward (1997)
Incinerator flue gas ¹	Volatile organic sampling train (VOST) Fractionator tested	St. Germain et al. (1994)
VOCs in ground water, soil, and sediment ¹	U.S. EPA Contract Laboratory Program (CLP) GC/MS	Sun (1993)
VOCs in surface water ¹	U.S. EPA Method (unspecified) GC/MC	Zhang and Chen (1992)

¹bromofluorobenzene (nonspecific)

Abbreviations: GC = gas chromatography; MS = mass spectrometry; VOC = volatile organic compound

6.0 Environmental Occurrence and Persistence

The Defense Depot—Memphis, Tennessee (DDMT), a secured military supply, storage, and maintenance facility in operation from 1942 to 1997, National Priorities List (NPL) site was found to be of "no apparent public health hazard" to nearby residents from 1989 to 1999. 4-BFB was among the parameters tested in four sampling programs (Screening Sites program, Remedial Investigation program, Base Realignment and Closure [BRAC] program, and background sampling) and was not detected in surface and subsurface soil, surface water, or sediment (ATSDR, 1999).

4-BFB was listed as a product of incomplete combustion (PIC) from a turbulent flame laboratory reactor burning principal organic hazardous constituents under conditions of a simulated atomization failure (ATSDR, 2002; Chang et al., 1988; Finaldi, 1991). However, it was not included in the EPA list of PICs as a target analyte. Instead, it was used for spiking Tenax-only

sampling tubes as part of quality assurance for the analytical procedure VOST SW-846 Method 0030 (U.S. EPA, 1998b).

The ability of a mixture of microorganisms to degrade specific compounds can enhance the performance of waste-treatment systems. A microbial mixture (consisting of five pseudomonads, one klebsiella, four rhodococci, and two fungal strains) was found capable of degrading a range of methyl and halogen-substituted benzenes, phenols, and benzoic acids. 4-BFB was completely removed in 72 hours (Goulding et al., 1988). For the biodegradation of hazardous waste, rhodococci, widely distributed in soil and sludge, was tested. *Rhodococcus opacus* GM-14, however, failed to grow on 4-BFB after 14 days of incubation (Zaitsev et al., 1995).

7.0 Human Exposure

No data for specific human exposures were found. Potential exposure to 4-BFB may occur for workers involved in the production of pharmaceuticals, pesticides, and other organics from 4-BFB.

8.0 Regulatory Status

As a chemical in commerce, 4-BFB is listed on the TSCA Inventory (U.S. EPA, 2004b). It is an HPV chemical in the United States and Europe (OECD, 2001; U.S. EPA, 1998a, 1999). Under the HPV Challenge Program, it appears to still be an orphan chemical (i.e., without sponsorship) (Denison, 2004).

9.0 Toxicological Data

9.1 General Toxicology

9.1.1 Human Data

4-BFB is irritating to the eyes, skin, and mucous membranes. Overexposure via ingestion can cause nausea, vomiting, abdominal pain, and diarrhea (DSBG, 2002).

9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

In male Wistar rats orally administered 4-BFB (87.5 mg/kg [500 μ mol/kg] body weight), 67% of the dose was recovered in the urine after 24 hours. Aromatic ring hydroxylation was a main pathway for urine excretion; phenolic metabolites were 75% of the total metabolites. The regioselectivity of aromatic ring hydroxylation (C2/6:C3/5) was 74:26. Hydroxylation at the positions ortho to the bromine was only 40% of that predicted by molecular orbital theory, presumably due to steric hindrance. Pretreatment of rats with various cytochrome P450 inducers (acetone, β -naphthoflavone, and phenobarbital) showed very little influence of the P450 enzyme on the regioselectivity of the aromatic hydroxylation (Koerts et al., 1997).

9.1.3 Acute Exposure

Acute toxicity values for 4-BFB are presented in **Table 2**.

Table 2. Acute Toxicity Values for 4-BFB

Route	Species (sex and strain)	LD ₅₀ /LC ₅₀	Reference(s)
oral	Rat (sex and strain n.p.)	LD ₅₀ = 2700 mg/kg (15.43 mmol/kg)	RTECS (1999)
		LD ₅₀ = 2248 mg/kg (12.84 mmol/kg)	Anonymous (1993)
		LD ₅₀ = 3788 mg/kg (21.64 mmol/kg)	
inh	Rat (sex and strain n.p.)	LC ₅₀ (4-h) = 18 g/m ³ (2500 ppm)	DSBG (2002); RTECS (1999)

Abbreviations: h = hour(s); inh = inhalation; LC₅₀ = concentration lethal to 50% of test animals; LD₅₀ = lethal dose for 50% of test animals; n.p. = not provided

Tremor, change in motor activity, and ataxia were observed in the oral study. Tremor, dyspnea, and change in motor activity were observed in the inhalation study (RTECS, 1999). 4-BFB (doses not provided [n.p.]) was irritating to rabbit eyes and skin (DSBG, 2002). In albino rabbits, application of 0.5 mL to the semi-occluded intact skin for four hours produced a primary irritation index of 0.33 (Bagley et al., 1996). [Note: 4-BFB was reported to not be an irritant by Anonymous (1993).]

9.1.4 Short-term and Subchronic Exposure

No data were available.

9.1.5 Chronic Exposure

No data were available.

9.1.6 Synergistic/Antagonistic Effects

No data were available.

9.1.7 Cytotoxicity

No data were available.

9.2 Reproductive and Teratological Effects

No data were available.

9.3 Carcinogenicity

No data were available.

9.4 Initiation/Promotion Studies

No data were available.

9.5 Anticarcinogenicity

No data were available.

9.6 Genotoxicity

4-BFB was reported to be not mutagenic in the Ames test and chromosome aberration tests *in vitro*; however, no study details were provided in the MSDS (DSBG, 2002) or the German publication (Anonymous, 1993).]

9.7 Cogenotoxicity

No data were available.

9.8 Antigenotoxicity

No data were available.

9.9 Immunotoxicity

In the Magnusson and Kligman guinea pig maximization test, 4-BFB (dose n.p.) was a mild sensitizer; it produced a 20% sensitization rate (DSBG, 2002). [Note: 4-BFB was reported to not be a sensitizer in Anonymous (1993).]

9.10 Other Data

No data were available.

10.0 Structure-Activity Relationships

The results from NTP studies conducted for two structurally related analogues to 4-BFB, *p*-dichlorobenzene and bromobenzene, are presented below.

1,4-Dichlorobenzene [CAS No. 106-46-7]

1,4-Dichlorobenzene is used as an insecticidal fumigant, germicide, chemical intermediate, and space deodorant for restrooms and garbage; in dyes and pharmaceuticals; and for moth control (NTP, 1987, 2004b).

Short-Term or Subchronic Studies: In Fischer 344 rats receiving 1,4-dichlorobenzene (300-1500 mg/kg) via gavage for 13 weeks, a decrease in survival and weight gain and an increase in liver weight-to-brain weight ratio, serum cholesterol levels, and urinary porphyrins were seen. Degeneration and necrosis of hepatocytes, hypoplasia of the bone marrow, lymphoid depletion of the spleen and thymus, and epithelial necrosis of the nasal turbinates were reported for both males and females. In males only, renal tubular cell degeneration and increases in the kidney weight-to-brain weight ratio and blood urea nitrogen level were observed. Additionally, there were reductions in serum triglycerides, hematocrit, red blood cell count, and hemoglobin level (NTP, 1987).

In B6C3F₁ mice, 1,4-dichlorobenzene (85-1800 mg/kg) reduced survival, body weight gain, white blood cell count and increased the liver weight-to-brain weight ratio. Hepatocellular degeneration and hepatocellular cytomegaly were also observed in the animals. In males only, serum cholesterol levels and serum protein and triglycerides were increased (NTP, 1987).

Carcinogenicity: In two-year gavage studies, there was clear evidence of carcinogenicity with 1,4-dichlorobenzene (150, 300, or 600 mg/kg) in male Fischer 344 rats and in male and female B6C3F₁ mice (NTP, 1987, 2004b).

Male rats showed an increased severity in nephropathy, epithelial hyperplasia of the renal pelvis, mineralization of the tubules in the renal medulla, and focal hyperplasia of renal tubular epithelium. There was an increase in the incidence of tubular cell adenocarcinomas of the kidneys and mononuclear cell leukemia. Female rats only exhibited increased incidences of nephropathy (NTP, 1987).

In male and female mice, 1,4-dichlorobenzene increased the incidences of nonneoplastic liver lesions and hepatocellular carcinomas and adenomas. Males only had an increased incidence of nephropathy, thyroid gland follicular cell hyperplasia, adrenal gland medullary hyperplasia, focal hyperplasia of the adrenal gland capsule. They also had hepatoblastomas and pheochromocytomas of the adrenal gland. In females, renal tubular regeneration and follicular cell adenomas of the thyroid gland were reported (NTP, 1987).

Genotoxicity: 1,4-Dichlorobenzene (up to 100 µg/plate) was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 in the presence or absence of metabolic activation. It failed to induce chromosome aberrations or sister chromatid exchanges (SCEs) in Chinese hamster ovary cells. Negative results were reported in the micronucleus test, while inconclusive results were reported in the mouse lymphoma assay (NTP, 1987, 2004b).

Bromobenzene [CAS No. 108-86-1]

Bromobenzene is used as a chemical intermediate, solvent, and motor oil additive. Short-term toxicity studies (i.e., 13-week inhalation and gavage studies) with bromobenzene have been conducted in Fischer 344 rats and B6C3F₁ mice; no results were available. It was negative for mutagenicity in the *Salmonella* test. It was also negative for the induction of chromosome aberration but weakly positive for induction of SCEs (NTP, 2004a).

Bromobenzene is a classic hepatotoxicant (Locke and Brauer, 1991). Its hepatotoxicity is strongly correlated with covalent binding of reactive metabolites, generated during its oxidative biotransformation, to cellular proteins; bromobenzene 3,4-oxide has been suggested the "most significant toxicologically" (Koen and Hanzlik, 2002; Rombach and Hanzlik, 1999). In mice and rats, a decrease in glutathione (GSH) levels was observed (Heijne et al. 2003; Szymanska, 1998; Wang et al., 2001). In mice, increases in ALT activity, γ -glutamyltransferase activity in serum, and malondialdehyde concentration in liver were also seen (Szymanska, 1998). In rat liver, bromobenzene caused a statistically significant decrease in hepatic adenosine triphosphate (ATP) and phosphodiester levels and an increase in phosphomonoester levels (Locke and Brauer, 1991). At the transcriptome level, bromobenzene affected differentially expressed genes involved in many processes, including drug metabolism, oxidative stress, GSH depletion, and intracellular signaling (Heijne et al., 2004).

11.0 Online Databases and Secondary References

11.1 Online Databases

STN International Files

AGRICOLA	CHEMCATS	NIOSHTIC
BIOSIS	EMBASE	NTIS
BIOTECHNO	ESBIOBASE	Registry
CABA	IPA	RTECS
CANCERLIT	MEDLINE	TOXCENTER

National Archives and Records Administration
Code of Federal Regulations (CFR)

In-House DatabasesCurrent Contents on Diskette[®]

The Merck Index, 1996, on CD-ROM

Other Databases

TSCAPP (TSCA Plant and Production—TSCA Inventory Reporting, 1975-1977)

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Acknowledgements

Support to the National Toxicology Program for the preparation of 4-Bromofluorobenzene [460-00-4]—Review of Toxicological Literature was provided by Integrated Laboratory Systems, Inc., through NIEHS Contract Number N01-ES-35515. Contributors included: Raymond R. Tice, Ph.D. (Principal Investigator); Marcus A. Jackson, B.A. (Project Coordinator); Bonnie L. Carson, M.S. (Senior Chemical Information Scientist); Claudine A. Gregorio, M.A.; Yvonne H. Straley, B.S.; Nathanael P. Kibler, B.A.; and Barbara A. Henning.

Appendix A: Units and Abbreviations

°C = degrees Celsius

µg/L = microgram(s) per liter

µg/m³ = microgram(s) per cubic meter

µg/mL = microgram(s) per milliliter

µM = micromolar

bw = body weight

EPA = Environmental Protection Agency

F = female(s)

g = gram(s)

g/mL = gram(s) per milliliter

GC = gas chromatography

h = hour(s)

HPV = high production volume

i.g. = intragastric

i.p. = intraperitoneal(ly)

kg = kilogram(s)

L = liter(s)

lb = pound(s)

LC = liquid chromatography

LC₅₀ = lethal concentration for 50% of test animals

LD₅₀ = lethal dose for 50% of test animals

LD = low dose

M = male(s)

MD = mid dose

mg/kg = milligram(s) per kilogram

mg/m³ = milligram(s) per cubic meter

mg/mL = milligram(s) per milliliter

min = minute(s)

mL/kg = milliliter(s) per kilogram

mm = millimeter(s)

mM = millimolar

mmol = millimole(s)

mmol/kg = millimoles per kilogram

mo = month(s)

mol = mole(s)

mol. wt. = molecular weight

MS = mass spectrometry

n.p. = not provided

NTP = National Toxicology Program

ppb = parts per billion

ppm = parts per million

SCE = sister chromatid exchange

TSCA = Toxic Substances Control Act

VOC = volatile organic compound

Appendix B: Description of Search Strategy and Results

1-Bromo-4-fluorobenzene; 4-Bromofluorobenzene (CAS RN 460-00-4; ILS CODE X0100) Description of Search Strategy and Results (Search Package)

Filename: X0100 Srch Pkg Sum.070204.doc

Nomination

1-Bromo-4-fluorobenzene (BFB) is a high-production-volume (HPV) chemical, listed in the initial Toxic Substances Control Act (TSCA) Inventory that has not found a sponsor in the U.S. Environmental Protection Agency (U.S. EPA) HPV Challenge Program. It is structurally analogous to certain halogenated benzenes, bromobenzene, and *p*-dichlorobenzene, the latter of which NTP has found to be a rodent carcinogen. It is used as a chemical intermediate in the production of certain pharmaceuticals, agricultural chemicals, and, possibly, photographic chemicals.

Search Strategy

The keywords and search strategy used in the simultaneous search of several biomedical databases and NTIS are shown in Attachment A.

STN Database Results

	<u>L20 (4-BFB)</u>	<u>L23 (Nonspecific BFB)</u>	<u>Total</u>
MEDLINE	0	1	1
CANCERLIT	0	0	0
AGRICOLA	0	0	0
NIOSH TIC	1	0	1
EMBASE	2	3	5
CABA	0	0	0
ESBIOBASE	0	0	0
BIOTECHNO	0	0	0
BIOSIS	2	1	3
IPA	0	0	0
TOXCENTER	95	21	116
NTIS	2	0	2

Most of the TOXCENTER records were from CA, and these were primarily patents for pharmaceuticals and pesticides in which BFB was used as a starting material and the products contained 4-fluorophenyl moieties. The STN Registry file was searched May 12, 2004 and there were 1473 records for 460-00-4 in CAPLUS. The STN CHEMLIST record was retrieved on June 23 to check for regulations. The databases PROMT (57 hits), CEN (Chemical and Engineering News) (8 hits), and CIN (Chemical Industry Notes) (5 hits) were searched on June 23 to retrieve business-related information. CAPLUS was searched on July 1, 2004; the CAS RN was combined with the role pollutant to retrieve only two references. Another 18 records were retrieved combining the CAS RN with the CA sections 59, 60, and 61 that would include air, water, and soil pollution records. Twenty records were found in the Chemical Information System databases on May 18:

BIOLOG database (biodegradation references)	1
DATALOG database (environmental fate references)	2
ISHOW database (physical properties)	4
RISKLINE	1
RTECS	1
SANSS	1
TSCA Inventory	1
TSCAPP database (TSCA plant and production data, 1975-1977)	5
TSCATS database (TSCA test submissions)	4

Other information was sought in May and June 2004 in trade and government agency literature available on the Internet. Google was the major search engine used. Specific web sites searched included the U.S. EPA OPPT Inventory Update Rule database, other EPA web sites, the NTP web site (for toxicity studies of structural analogs), the Code of Federal Regulations online via <http://www.access.gpo.gov>, Chemyclopedia Online, and the ChemService Inc. catalog of environmental analytical standards for U.S. EPA methods.

Search Results

The search results are organized into groups in the order of their subject codes. Subgroups are in the order in which they are discussed in this summary. Within the groups, the records are ordered by the first author's surname or the publication title.

Authoritative and Other Reviews (Subject Codes 05 and 11)

A 9-page German toxicology review is available (Anonymous, 1993). The DSBG MSDS contains similar information. BFB was included in a set of drinking water toxicity profiles sponsored by the Army Medical R&D Command (Daugherty et al., 1992).

Chemical Identification (Subject Code 13a)

Registry and SANSS database records for BFB comprise this small group. Several synonyms were listed in the search strategy above.

Chemical-Physical Properties (Subject Code 13b)

BFB, C₆H₄BrF, mol. wt. 175.00, is a clear colorless to slightly yellow flammable liquid of b.p. 152 °C and m.p. -16 °C. Its density at 20 °C is 1.594 g/cm³ or 13.3 lb/gal. Its flash point is 60 °C (Albemarle Corp., 1999). Calculated properties are available in the Registry record. They include bioconcentration factor 107 at pH 1-10, K_{oc} 984 at pH 1-10, log P 2.97±0.386, molar solubility <0.01 mol/L, and vapor pressure 4.07074 at 25.0 °C. Leo (1978; cited by ISHOW) calculated a log P value of 3.13. An experimental value for log P may be available in Dun et al. (1983). Piazza et al. (1995) developed multivariate QSAR models for BFB and other halogenated benzenes based on comparisons of physical-chemical properties with molecular topology. Vizi et al. (1977) calculated thermodynamic functions of BFB and other dihalobenzenes from spectroscopic and structural data.

Analytical Methods (13c)

BFB is used as an analytical, tuning, and surrogate standard in many U.S. EPA methods. The variety of environmental media for which these methods are suitable is illustrated in the following table.

Analytes/Medium	U.S. EPA Method	Reference
VOCs in drinking water; water	524.2 (capillary GC/MS)	Eichelberger et al. (1990); Munch and Eichelberger (1992)
?	Purge and trap with capillary GC/MS compared with Method 624 (packed column)	Dreisch and Munson (1983)
Boiler fly ash	Modification of 8260 (capillary GC/MS)	Grese and Edwards (1995)

Analytes/Medium	U.S. EPA Method	Reference
Polar VOCs (nonpurgeable) in water	Capillary GC/ion-trap MS. BFB used as a tuning standard to calibrate mass spectrometer.	Pyle et al. (1995)
Soil	Purge and trap GC/MS. Quantitation of reference compound compared with surrogate spikes and internal standard (usual roles of BFB)	Schumacher and Ward (1997)
Incinerator flue gas	Test of the volatile organic sampling train (VOST) fractionator	St. Germain et al. (1994)
VOCs in groundwater, soil, and sediment	Contract Laboratory Program (CLP) GC/MS	Sun (1993) (Chinese)
VOCs in surface water	Unspecified EPA method	Zhang and Chen (1992)

Commercial Availability

Producers (01a)

A 1998 list of companies producing compounds in the Inventory Update Rule database included Diaz Chemical Corporation and Nipa Hardwicke, Inc., as BFB producers (U.S. EPA, IUR 1998). Diaz Chemical Corporation is currently operating as Diaz Intermediates Corporation, West Memphis, Arkansas. It produces 99.9%-pure BFB (Diaz Intermediates, undated). Nipa Hardwicke, located in Elgin, SC, and Rockhill, SC, is part of BTP plc, and its name along with other BTP plc facilities that provide key intermediates to pharmaceutical and agricultural companies was changed to Archimica in 1999 (Archimica, 1999 a,b). [Clariant merged with BTP plc in 2000 (Archimica, 2000)]. The Elgin, SC, facility specializes in bromination (Archimica, undated a,b). An Archimica fluorination plant is in Puerto Rico and the bulk pharmaceuticals plant in Springfield, Missouri (formerly the Roche Syntex agribusiness plant), produces brominated chemicals for Hoffmann LaRoche AG pharmaceuticals (Archimica, 1999c).

Albemarle Corp. (1999) sells BFB ($\geq 99.0\%$ pure) in bulk tanks and in 250-kg HDPE-lined steel drums, four drums per pallet (1 metric ton) (retrieved from Albemarle web site on June 25, 2004). The concentration of the ortho isomer is $\leq 0.2\%$ and that of total other impurities is $\leq 0.5\%$.

In the 1970s, BFB was manufactured by the Kodak Park Division [Eastman Kodak], Rochester, NY, and imported to plants of Columbia Organic Chemicals in Columbia, SC; American Hoechst Corp., Bridgewater, NJ; and Rhone-Poulenc, Freeport, TX (TSCAPP database, ca. 1977).

Suppliers (01b)

Chemycyclopedia 2004 listed four suppliers: Acros Organics USA, Contract Chemicals, Inc., Honeywell Specialty Chemicals GmbH Seelze, and Spectrum Chemical Manufacturing Corporation. A search of the database CHEMCATS found several other suppliers: Container amounts, when listed, were generally 500 g or less. Matrix Scientific (2003) listed quantities of 250 g, 1 kg, and 5 kg. Quantities sold as analytical standards are generally low. For example, ChemService (2004) offers 5-g quantities of BFB and one-milliliter containers of solutions in methanol or acetone containing 2000 or 10,000 ppm BFB. Suppliers of the BFB Grignard reagent, $\text{FC}_6\text{H}_4\text{MgBr}$ [352-13-6], include Boulder Scientific Co. (undated) and Sigma-Aldrich (2004). Both

sell it as 2.0 M solutions in diethyl ether. Boulder sells the solution in 5-gal. pails, 55-gal. drums, and variously sized cylinders.

Production Processes (01d)

Industrial-scale production of fluorinated aromatics is done by diazotization of substituted anilines with sodium nitrite in anhydrous hydrogen fluoride. The resulting aryldiazonium fluoride decomposes *in situ*, releasing nitrogen (Boudakian, 1986). Fluorobenzene is produced by diazotization of aniline (benzenamine) with sodium nitrite and sulfuric acid in the presence of fluoboric acid (HBF₄) (Balz-Schiemann reaction). The diazotization is done at -5 °C and the fluorination proceeds when the reaction mixture is warmed (Daley and Daley, 2001). [This may be a laboratory preparation since the reference is an organic chemistry text book.] Electrophilic substitutions [such as bromination] on fluorobenzene strongly favor the para over the ortho position (Rosenthal and Schuster, 2003). At Diaz Intermediates Corporation, BFB is produced by bromination of fluorobenzene with bromine in the presence of a catalyst; the reaction mixture containing HBr is quenched in water and/or caustic solution. The organic phase is purified by fractionation (ADEQ, 2003).

In the late 1980s, Zeneca, DuPont, and Mallinckrodt had large-volume, continuous process facilities for producing fluorobenzene derivatives using hydrogen fluoride-diazotization technology. Due to overcapacity, Mallinckrodt bowed out in 1993. Batch makers traditionally use the Balz-Schiemann reaction or halogen exchange with potassium fluoride. Asahi Chemical, Japan developed a synthetic method starting from cyclohexanone. DuPont and Zeneca had major captive uses for fluoroaromatics as intermediates in syntheses of agricultural chemicals and pharmaceuticals. Rhone-Poulenc produced fluoroaromatics in the UK and France by the HF and KF processes.

Sodium tetrafluoroborate and sodium chloride are generated as waste in the Balz-Schiemann process. DuPont has developed a “greener” process in which water is the only by-product. In this process (still at the laboratory stage at the time of this article), a stream of benzene in nitrogen is passed over cupric fluoride at 450-550 °C to give fluorobenzene, hydrogen fluoride, and copper metal. Cupric fluoride is regenerated by a hot stream of hydrogen fluoride and oxygen (Green and D’Aquino, 2002). Other synthetic methods reported in the literature started from 4-bromophenylammonium cation (Gail and Coenen, 1994); used a catalyst of zinc bromide on montmorillonite (a clay) or silica for selective para bromination of fluorobenzene (Ross et al., 1998); and brominated fluorobenzene in the presence of iron filings (Suter and Weston, 1941).

Production and Import Volumes (01c)

A search of the U.S. EPA 2002 Inventory Update Rule web page for “460004” found the following range of production volumes:

YEAR	RANGE, MILLION POUNDS
1986	0.010 - 0.500
1990	>1 - 10
1994	>0.500 - 1
1998	>1 - 10
2002	>1 - 10

The Arkansas air quality permit for Diaz Intermediates limits 4-BFB annual production to 6 million pounds per year. The limit for 3-BFB, the meta-isomer, is about 800,000 pounds (or is it about 1.6 million pounds?) (ADEQ, 2003).

In 1994, U.S. production of fluoroaromatics was 1.2 million pounds (600 short tons). Fluorobenzene was the major compound and “the major source for fluorophenyl groups in organic synthesis” (Chem. Mark. Rep., April 29, 1996).

Other Processes (01e)

At Diaz Intermediates Corp. (undated b,d), brominated isomers of fluorobenzene are processed further into bromo- and fluoroanisoles, bromo- and fluorophenols, fluorobenzaldehydes, and bromo- and fluorophenyl ethers. Frim (2001 abstr.) stated that BFB is used to prepare “several high value pharma intermediates via Pd/C catalysis...”; derivatives shown in a diagram included fluorobenzene, 4-fluorobenzoic acid, isopropyl *p*-fluorobenzoate, 4,4'-difluorobiphenyl, and 4,4'-difluorobenzophenone. Suter and Weston (1941) reported reactions of the Grignard reagent, 4-fluorophenylmagnesium bromide, to give 4-fluoro- derivatives of phenylethylamines. In other synthetic methods found in the STN International search results, BFB was used to prepare 4-fluorophenol (Adda, 2002 pat. [assignee Bromine Compounds, Limited]); compounds prepared by electroreductive and other coupling reactions (e.g., Courtois et al., 1997); herbicides (Hagen et al., 1993a,b pat. appl. [assignee BASF A.-G.]); rodenticides (Prieto et al., 2000 [Almirall Prodesfarma]); and organic photosensitive materials and hole-transport agents for organic electroluminescent devices (Watanabe et al., 2001 pat. appl. [Tosoh Corp.]).

Uses (01f)

BFB is a chemical intermediate or starting material in organic syntheses. Among commercial products identified with certainty are the Grignard reagent prepared from BFB, 4-phenylmagnesium bromide, which is probably prepared more commonly *in situ* during the synthesis, and 4-fluorophenol. The latter is used as a fungicide and an intermediate for pharmaceuticals (Lewis, 1993 [*Hawley's Condensed Chemical Dictionary*, 12th ed.]). Although the BFB Grignard reagent conceivably may be the starting material for numerous derivatives (confirmed in some of the patent abstracts examined), an ILS check of some relatively simple, apparent derivatives quickly identified other routes to their preparation. When the Grignard reagent is used, the MgBr is replaced by other groups. Several sources were examined to identify compounds with 4-fluorophenyl moieties (4-FC₆H₄-).

Numerous 4-fluorophenyl derivatives were found in *Chemyclopedia 2004* (CAS RNs were not given for some compounds):

4-Fluorophenol [371-41-5]	2-(4-Fluorophenyl)indole [782-17-2]
(4-Fluorophenoxy)methylbutyrolactone	4-Fluorophenyl isocyanate [1195-45-5]
3-(4-Fluorophenoxy)benzyl bromide [65295-58-1]	4-Fluorophenylmagnesium bromide [352-13-6]
4-Fluorophenylacetic acid [405-50-5]	(<i>p</i> -Fluorophenyl)phenylphosphine oxide [54300-32-2]
4-Fluorophenylacetonitrile [459-22-3]	1-(4-Fluorophenyl)piperazine [2252-63-3]
3-(4-Fluorophenyl)alanine [19883-77-3]	1-(4-Fluorophenyl)piperazine dihydrochloride [64090-19-3]
3-(4-Fluorophenyl)alanine [18125-46-7] (Optical isomer?)	1-(4-Fluorophenyl)-4-piperidone
4-Fluorophenylboronic acid [1765-93-1]	4-Fluorophenyl sulfone [383-29-9]
4-[4-Fluorophenyl]ethynylphenol [197770-48-2] (Fuji Photo Film Co., Ltd.)	4-Fluorophenyl 2-thienyl ketone [579-49-7]
4-Fluorophenylhydrazine hydrochloride [823-85-8]	1-(4-Fluorophenyl)-2-(1 <i>H</i> -1,2,4-triazol)-1-ylethanone [58905-21-8]

Numerous TOXCENTER records from Chemical Abstracts represented patents and patent applications by pharmaceutical companies. BFB was included in the indexing but seldom in the

abstracts. The Grignard derivative was also indexed in a few database records. Apparently BFB is used as one of the reactants in preparing therapeutic drug [candidates] containing a 4-fluorophenyl moiety. Patent assignees in the subset of well-known pharmaceutical manufacturers included:

- Abbot Laboratories, USA (Black et al., 2000 pat. appl.),
- AstraZeneca, Sweden (Malmstrom and Swahn, 2003 pat. appl.),
- Aventis Pharma S.A, France (Nemecek et al., 2003 pat. appl.),
- Bayer A.-G., Germany (Philipps et al., 1990 pat. appl.), and
- Bristol Myers Squibb, USA (Nicolai and Teulon, 2001 pat.),
- E.I. du Pont de Nemours and Company, USA (Cain et al., 1991),
- Eisai Company, Limited, Japan (e.g., Bridges et al., 1993 pat. appl.),
- Eli Lilly and Company, USA (Dodge et al., 2003 pat.),
- Glaxo Group Limited, UK (Cherry et al., 1994 pat. appl.),
- Hoffman-La Roche AG (Switzerland) (e.g., Ackermann et al., 2002 pat. appl.),
- Janssen Pharmaceutica, N.V., Belgium (e.g., Kennis and Mertens, 1984 pat.),
- Merck and Company, Inc. (Ali et al., 2003 pat. appl.),
- Pfizer Products, Inc., USA (Noe and Wolf-Gouveia, 2003 pat. appl.),
- Pharmacia and Upjohn Company, USA (Nieman et al., 2002 pat. appl.),
- Pharmacia Corporation, USA (e.g., Barta et al., 2003 pat. appl.),
- Rhone-Poulenc Rorer S.A. (Bourzat et al., 1998 pat. appl.),
- SmithKline Beecham USA (Haffner et al., 2003 pat. appl.),
- Warner Lambert/Parke-Davis Pharmaceutical Research, USA (Wise et al., 1985).

A separate subset of TOXCENTER/CA abstracts on pharmaceuticals prepared using BFB include the following organizations:

- Ligand Pharmaceuticals, Inc., USA (Fensome et al., 2000 pat. appl.; Grubb et al., 2000 pat. appl.; Jones et al., 1997a,b,c,d,e patents; Zhang et al., 2000 pat. appl.),
- National Institutes of Health (Rogowski et al., 1990 pat. appl.), and
- Research Triangle Institute (Rothman et al., 1995 pat.).

One subgroup in this package includes monographs of 4-fluorophenyl derivatives from the CD-ROM of *The Merck Index*, 12th ed. (Budavari, 1996). Many are pharmaceuticals. Older Janssen patents and publications were frequently cited. Unfortunately, the results from the TOXCENTER database do not include many of the older patents and patent applications, so we were unable to match known drugs with preparation methods known to start with BFB. U.S. EPA specifies use of BFB for tuning mass spectrometers used for analytical methods of the 500, 600, and 8000 series (Chemical Engineering News, March 18, 1991). Specific methods for which ChemService supplies BFB as a tuning standard are 502/524, 624/1624, 5041, 8240B, CLP Volatiles, CLP Semivolatiles, CLP Quick Turnaround Method-Volatiles, and T014A (air). BFB is also used as an internal standard for 524.2 (in a high-concentration mixture) and 551.1. BFB is used as a surrogate standard alone or in mixtures for methods 502/524, 624/1624, 5035A, 5041, 8010B, 8020B, 8240B, and CLP volatiles (ChemService, 2004). Method 8261, a GC/MS method for VOCs in liquid, solid, oily waste, and animal tissues, requires BFB for a tuning standard. Mass intensity criteria are given for m/z 50, 75, 95 (base peak, 100% relative abundance), 96, 173-177. The criteria are for relative abundance with respect to m/z 95 or m/z 174, the primary characteristic ion. Secondary characteristic ions are m/z 95 and 176.

A supplemental discussion of known or probable uses of BFB is in Attachment B.

Environmental Releases, Occurrence, and Fate (04)

An accidental collision of a tanker truck with a passenger van released 10 gallons of BFB on March 16, 2001, in Erie, Pennsylvania (www.action.pa).

Greenpeace International (Finaldi, 1991) and ATSDR listed bromofluorobenzene as a product of incomplete combustion (PIC) of hazardous waste incineration. Practically all information linking BFB to environmental pollution can be attributed to its use as an analytical standard or surrogate in U.S. EPA methods for the examination of hazardous wastes, emissions, ambient air, surface and drinking water, and contaminated soils. However, when brominated or fluorinated compounds are present in hazardous wastes, brominated and fluorinated benzenes have been identified among the PICs in the emissions from waste incineration (Trenholm, personal communication, June 30, 2004). U.S. EPA NRMRL (1998) [Development of a Hazardous Waste Incinerator Target Analyte List of Products of Incomplete Combustion] did not include BFB as a target analyte. BFB was mentioned in the document as being used for spiking Tenax-only sampling tubes as part of the quality assurance procedure for the analytical method.

If the database search record does not specify that BFB is used as an analytical standard or at least identify an analytical method known to require BFB as a standard, one would have to examine original articles to determine if BFB was a pollutant or present only as an analytical standard in studies such as the following. [Note that the TOXCENTER/CA record indexing is not as specific as that for its CA/CAPLUS record. For example, the indexing for Gorshteyn and Robban. (2000) in the CA record specifies that BFB was used as a surrogate, but the TOXCENTER/CA record indexing lists it among the analytes.] Was BFB a pollutant in the emissions of a calciner burning hazardous waste (Boardman et al., 2000), a pollutant in the “proposed cellulose triacetate film base machine on methylene chloride” (TSCA test submission by Eastman Kodak, 1988)? Was it leached from fabrics used for collapsible potable water storage tanks (Hao et al., 1992)? Was it present in environmental samples containing humic substances [it interacted with them] (Mishima and Nakagawa, 2004)? Was BFB an impurity in hydrogen chloride produced as a product or by-product (Nyman, 1996)? Was it present in soils (Roy and Griffin, 1991), sewage sludges (Webber et al., 1996), and ambient air (Yin, 1994)? U.S. EPA methods might have been used in all of these environmental studies, so BFB use as an analytical standard is probable. More analytical studies of environmental samples are included in Analytical Methods (13c).

Diaz Chemical at its Holley, New York, facility, accidentally released *m*-BFB in 1995 and 1997 through reaction vessel rupture disks. This facility has long history of releases of hazardous chemicals and numerous residents of surrounding homes brought a lawsuit against Diaz in 2002 (Democrat and Chronicle, May 15, 2002). Diaz filed for bankruptcy and the facility was abandoned in June 2003, leaving behind intact drums and tanks of many brominated and other chemicals, including fluorobenzene and crude *m*-BFB. No mention was made of BFB at this site (Cloyd et al., 2004). The West Memphis, AK, facility of Diaz Intermediates operates under Arkansas Department of Environmental Quality minor source air permit #1743-AR-4 (ADEQ, 2003 [Original permit #1743-A was issued in 1997]). The permit was modified in 2003 to allow for *m*-BFB production at this site.

Zaitsev et al. (1995) reported on the biodegradation of halogenated benzenes (including BFB) by a strain of *Rhodococcus opacus*. Goulding et al. (1988) studied the bacterial biodegradation of substituted benzenes (including BFB).

Exposure Potential (02)

Inhalation and dermal exposures are the most likely routes for workers involved in production of pharmaceuticals, pesticides, and other organics from BFB and for persons environmentally exposed from accidental releases. No specific human exposure information was found.

Regulations (24)

BFB is regulated in the USA under TSCA. U.S. EPA has received TSCA test submissions under sections 2.0, 8(d), and 8(e) (U.S. EPA, 2004). It is an HPV chemical in the USA and Europe, where at least one EU member country produces more than 1000 tons (> 2 million pounds) BFB annually. It remains a candidate for sponsorship under the U.S. EPA HPV Challenge Program (CHEMLIST, 2004). The continued orphan status was confirmed in a June 2004 report published by Environmental Defense (Denison, 2004). Diaz Intermediates did not respond to their letter. Among companies declining to be a sponsor for other chemicals, several custom manufacturers replied that they felt that their clients should shoulder the responsibility.

Human Data (18)

No studies were found in this category.

ADME (12)

The pattern of 4-chlorofluorobenzene ring hydroxylation by P450 in male Wistar rats was similar to that predicted by molecular orbital theory, but hydroxylation at the positions ortho to the bromo- or iodo-substituents in BFB or 4-iodofluorobenzene was reduced by 40% and 60%, respectively, compared to the extent of hydroxylation of 4-chlorofluorobenzene, presumably due to steric hindrance (Koerts et al., 1997).

Acute Toxicity (03)

BFB was included in a compilation of *in vivo* rabbit skin irritation data (Bagley et al., 1996). QSAR relationships were developed for corrosivity and skin irritation potential of several chemicals including BFB (Barratt, 1996a). Properties considered included log P, molecular volume, and dipole moment. E.I. DuPont de Nemours and Company (1985a,b) determined inhalation and oral LD₅₀s in rats in a TSCA test submission to U.S. EPA. The RTECS record gives the values as 18 g/m³ (= 18 mg/L) (4-hour exposure) and 2700 mg/kg bw, respectively. The German review (Anonymous, 1993) stated that rat oral LD₅₀s were 2248 and 3788 mg/kg bw. Tremor, change in motor activity, and ataxia were observed in the oral study. Tremor, dyspnea, and change in motor activity were observed in the inhalation study (RTECS). Rhone-Poulenc, Inc. (1987) also reported a 4-hour inhalation study in rats to U.S. EPA.

No studies were found in the following categories:

- Short-Term and Subchronic Toxicity (06a)
- Chronic Toxicity (06b)
- Antagonisms and Synergisms (22)
- Reproductive / Developmental Toxicity (10)
- Carcinogenicity (07a)
- Other Biological Activities (14)

Immunotoxicity (08)

In the Magnusson and Kligman guinea pig maximization test, BFB produced a 20% sensitization rate (DSBG [Deep Sea Bromine Group, Bromine Compounds Ltd.], 2002) [in Reviews Group 05/11].

Genotoxicity (09)

The DSBG (2002) MSDS stated that BFB is not mutagenic by the Ames test (no details). The TOXCENTER/RISKLINE abstract of the German review (Anonymous, 1993) stated “There have been no indications of point-mutagenic or clastogenic activity in Salmonella/microsome and chromosome aberration tests *in vitro*.” No original genotoxicity studies were identified in the literature search.

Structure-Activity Relationships (25)

Some QSAR studies were mentioned under acute toxicity (Group 03). SAR studies including BFB and its structural analogs were published by Warne et al. (1999), Cronin and Schultz (1997), and Six and Altschul (1996) (acute Microtox test with *Vibrio fischeri*). Kaiser and Gough (1988) compared acute toxicity to *Photobacterium phosphorem* to octanol-water coefficients. CAS RNs of structural analogs identified from the indexing of TOXCENTER/CA abstracts are included in this group.

NTP has conducted 4-day and 13-week inhalation studies and 13-week gavage studies in F344 rats and B6C3F1 mice. Bromobenzene was negative in *Salmonella* and negative in an *in vitro* chromosome aberration assay. It was weakly positive in induction of sister chromatid exchange *in vitro* (NTP Status Report for bromobenzene, 2004).

NTP conducted 14-day, 13-week, and 2-year gavage studies in F344 and B6C3F1 mice with *p*-dichlorobenzene. It showed clear evidence of carcinogenicity in male and female mice and male rats. It was negative in *Salmonella*, *in vivo* and *in vitro* chromosome aberration and SCE assays and was equivocal in the mouse lymphoma assay (NTP Status Report for *p*-dichlorobenzene, 2004; NTP TR-319, 1987).

Attachment A
History of Search Session on STN International May 28, 2004

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FILE 'MEDLINE, CANCERLIT, NIOSHTIC, AGRICOLA, CABA, BIOTECHNO, EMBASE,
ESBIOBASE, IPA, BIOSIS, TOXCENTER, NTIS' ENTERED AT 13:12:08 ON 28 MAY 2004
L1          95 S 460-00-4
L2          33 S 1 (W) BROMO (W) 4 (W) FLUOROBENZENE
L3          1 S 1 (W) FLURO (W) 4 (W) BROMOBENZENE
L4          4 S 4 (W) BROMO (W) 1 (W) FLUROBENZENE
L5          26 S 4 (W) BROMOFLUROBENZENE
L6          26 S 4 (W) BROMOFLUROBENZENE
L7          0 S 4 (W) BROMOPHENYL (W) FLUROIDE
L8          0 S 4 (W) FLURO (W) 1 (W) BROMOBENZENE
L9          0 S 4 (W) FLUROBENZENE BROMIDE
L10         9 S 4 (W) FLUROBROMOBENZENE
L11         1 S 4 (W) FLUROPHENYL (W) BROMIDE
L12         0 S NSC (W) (10268 OR 9460)
L13         7 S P (W) (BROMOFLUROBENZENE OR FLUROBROMOBENZENE OR
              FLUROPHENYL (W) BROMIDE)
L14         96 S L1 OR L2
L15         48 S L3 OR L4 OR L5 OR L10 OR L11 OR L13
L16         105 S L14 OR L15
L17         51 S BROMOFLUROBENZENE OR BROMOPHENYL (W) FLUROIDE OR FLUROBENZENE (W) BROMIDE
              OR FLUROPHENYL (W) BROMIDE
L18         70 S FLUROBROMOBENZENE OR L17
L19         26 S L18 NOT L16
              SET DUPORDER FILE
L20         102 DUP REM L16 (3 DUPLICATES REMOVED)
              ANSWER '1' FROM FILE NIOSHTIC
              ANSWERS '2-3' FROM FILE EMBASE
              ANSWERS '4-5' FROM FILE BIOSIS
              ANSWERS '6-100' FROM FILE TOXCENTER
              ANSWERS '101-102' FROM FILE NTIS
L21         102 SORT L20 1-102 TI
              SAVE L21 X100SPECIFIC/A
L22         26 DUP REM L19 (0 DUPLICATES REMOVED)
              ANSWER '1' FROM FILE MEDLINE
              ANSWERS '2-4' FROM FILE EMBASE
              ANSWER '5' FROM FILE BIOSIS
              ANSWERS '6-26' FROM FILE TOXCENTER
L23         26 SORT L22 1-26 TI
              SAVE L23 X100NONSPEC/A
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Attachment B Extended Discussion of Known and Probable Uses of BFB

Recently, Merck/Schering Plough Pharmaceuticals filed a New Drug Application for a cholesterol-lowering combination of simvastatin (Zocor[®]) and ezetimibe (ezetrol; Zetia[™]), which contains two 4-fluorophenyl groups per molecule (Business Wire, Nov. 17, 2003). Aventis has conducted preclinical studies of 4-fluorophenylpiperazine as a potential topical antibacterial agent (R&D Focus Drug News, Oct. 9, 2000). FDA has approved Merck & Co.'s drug Emend[®] (aprepitant), which contains a 4-fluorophenyl moiety, for use in combination with other anti-vomiting medicines in cancer patients undergoing highly emetogenic cancer chemotherapy (Business Wire, March 26, 2003). Aventis Pharmaceuticals has a patent application for use of a compound with a 4-fluorophenyl moiety as a "prodrug" for treatment of dementia and dopamine-induced psychosis (Manufacture Chemical, Sept. 2003).

Compounds in which BFB has been used to add 4-fluorophenyl moieties commonly contain heterocyclic rings such as tropane, imidazole, quinoline, piperazine, piperidine, and pyridine. Less commonly, the rings are substituted pyrroles, pyrazoles, triazoles, thiazoles, triazines, and indoles. Other 4-fluorophenyl derivatives include platinum complexes and amino acids (from examination of 100 of the June 2004 PubMed records with fluorophenyl* in the title). The activities of biologically active compounds are changed subtly when fluorine replaces hydrogen in the molecule, e.g., binding interactions. Titanocene(IV) complexes that show antitumor activity have been produced from *d,l*-p-fluorophenylalanine (*d,l*-Fphe) as a ligand. *d,l*-Fphe can replace phenylalanine in normal biosynthesis, and *d,l*-Fphe and its titanocene complexes have been shown to disrupt cell division and DNA replication (Ritter, 1995). *d,l*-Fphe and other fluorinated amino acids might prove useful in producing genetically engineered proteins and tissues synthesized in biological systems (Tirrell et al., 1994).

BFB is a precursor for the agricultural fungicides flusilazole (fluzilazol) and flutriafol (Ioffe and Kampf, 2002). See *The Merck Index* group. Flusilazol is bis(4-fluorophenyl)methyl(1*H*-1,2,4-triazol-1-ylmethyl)silane. DuPont trade names for flusilazole, which was patented in 1983 and 1985, are Nustar, Olymp, and Punch. ICI patented a similar fungicide in which the methylsilane moiety is replaced by a carbinol and one of the fluorophenyl groups has an ortho fluoride. Another similar fungicide is BASF's Opus. One phenyl group has an ortho chlorine and the central group is an oxirane ring. Known insecticides with 4-fluorophenyl moieties are DDT analogs DFDD and DFDT (Budavari, 1996; Farm Chemicals Handbook, 2004).

BFB may also be used to synthesize monomers for polymerization reactions. Bayer Corp. produced a polyether sulfone and polyphenylene ketone ketone [*sic*] sulfones using bis(4-fluorophenyl) sulfone as a monomer (Stinson, 1993, 1996). Polymerized fluorophenylthiophenes have been shown to be capable of serving as polymer electrode materials in all-plastic batteries with a polymer gel film as electrolyte (no military or commercial applications known at the time of this article) (Plastics News, March 17, 1997). Los Alamos National Laboratory used electrically conducting poly-3-(4-fluorophenyl)thiophene (PFPT) in highly efficient electrochemical capacitors (Anonymous, 1994). Novel flame retardant poly(arylene ether phosphine oxide)s synthesized from 4,4'-bis(fluorophenyl)methylphosphine oxide and bisphenols were reported by Riley et al. (1997). Zheng et al. (2001) and Zhang and Bell (1999) studied coatings for aluminum and steel, some of which used *N*-(4-fluorophenyl)maleimide as one of the monomers. The monomer was prepared from 4-fluoroaniline and maleic anhydride (so BFB may not have been used).

Attachment C
URLs for X0100 Internet Searches: 1-Bromo-4-fluorobenzene (460-00-4)

May 12, 2004

DSGB (2002) MSDS

[http://www.dsb.com/brome/brome.nsf/viewAllByUNID/D2C4DB809BA7FB3B42256C6D002C9FDE/\\$file/9510_enbromofluorobenzene.pdf](http://www.dsb.com/brome/brome.nsf/viewAllByUNID/D2C4DB809BA7FB3B42256C6D002C9FDE/$file/9510_enbromofluorobenzene.pdf)

Standards for EPA Methods

[http://www.accustandard.com/asi/pdfs/06_Indiv\(91-96\).pdf](http://www.accustandard.com/asi/pdfs/06_Indiv(91-96).pdf)
[http://www.accustandard.com/asi/pdfs/06_Indiv\(91-96\).pdf](http://www.accustandard.com/asi/pdfs/06_Indiv(91-96).pdf)