

Chemical Information Review Document

for

N-Butylbenzenesulfonamide [CAS No. 3622-84-2]

Supporting Nomination for Toxicological Evaluation by the
National Toxicology Program

October 2010



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

Abstract

N-Butylbenzenesulfonamide (NBBS) is widely used as a plasticizer. It also possesses antifungal properties. According to the 2006 Inventory Update Reporting database, U.S. production of NBBS was >500,000 pounds since 1986. Environmental studies of NBBS in the United States, Europe, and Japan date back over 30 years. Recent studies in the United States noted the presence of NBBS in the San Francisco Estuary, the Santa Ana River, runoff from agricultural fields in southern California irrigated with treated wastewater or effluent dominated stream water, and water treatment and reclamation plants in southern California; levels ranged from not detected to 16 µg/L. There is high potential for human exposure to NBBS due to its likely occurrence in drinking water and leaching from NBBS-containing products such as cooking utensils. NBBS is a sponsored chemical under the U.S. EPA High Production Volume Challenge Program and is included on the Toxic Substances Control Act inventory. A TC_{Lo} of 3.7 mg/m³ in humans was reported. Of the 42 adipose breast tissue analyzed in one study, NBBS was found in only one sample. Distribution and elimination studies reported that NBBS was taken up rapidly (within 5 minutes) and mostly eliminated within 8 hours. *In vitro* metabolism studies showed that NBBS was metabolized to 2-hydroxy-NBBS but conjugation of the metabolite was not noted. In mice, the oral LD₅₀ was 2900 mg/kg. In rats, oral LD₅₀ values ranged from 1725 to 3560 mg/kg and the inhalation LC₅₀ was 4066 mg/m³. Subchronic studies reported the development of motor dysfunction, altered hematological parameters, and effects on body weight after oral or intraperitoneal (i.p.) administration of NBBS. One study reported a no adverse effect level of 50 mg/kg liver effects and a low incidence of neurodegeneration. Synergistic effects on motor dysfunction were noted when NBBS was co-administered with aluminum chloride. NBBS was cytotoxic to Neuro-2a and C6 glioma cells in a dose-dependent manner. Neuro-2a growth was inhibited at concentrations ranging from 1 to 100 µM, while C6 glioma cell growth was inhibited at concentrations ranging from 10 to 500 µM. NBBS also was cytotoxic to human lymphocytes and dissociated mouse hippocampal neurons. Oral administration of NBBS produced reproductive and developmental effects. Adverse effects (e.g., abnormal gait, tremor, hunched posture, piloerection, and lethargy) were noted in parental animals administered NBBS (400 mg/kg). Significant decreases in body weight also were observed at the same dose. Reproductive performance was impaired in 9 of 12 mating pairs and an increased rate of offspring loss and decreased mean pup weight were reported for female rats that received 400 mg/kg. Pregnant mice administered NBBS at either 500 or 750 mg/kg/day via i.p. injection had significant decreases in the number of live fetuses per dam, average crown-rump lengths, body weight, and placental weight when examined on gestation day 13. NBBS was not genotoxic in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, or TA1538 in the absence or presence of metabolic activation or in human lymphocytes. NBBS is neurotoxic. In rabbits, NBBS produces motor dysfunction and neuronal and dendritic degeneration. NBBS increases microglial activation in various rat brain regions (e.g., hippocampus), suggesting neurotoxicant effects. NBBS was not a dermal irritant in guinea pigs and was slightly irritating to rabbit eyes. Possible targets of interaction for NBBS, based on structural similarity to chemicals in the training set for GeneGo models, included cathepsin B, cathepsin L, cathepsin K, and cathepsin V. Two G-protein coupled receptors, neuropeptide receptor 5R and thromboxane A2 receptor, also were identified as potential targets. Myosin light chain kinase (facilitates myosin interaction with actin filaments to produce contractile activity), protein kinase C, and the γ-secretase complex also were identified as targets.

Executive Summary

Basis for Nomination

N-Butylbenzenesulfonamide (NBBS) was nominated by the National Institute of Environmental Health Sciences for comprehensive toxicological testing based on its extensive use as a plasticizer, lack of adequate toxicological data, and suspicion of toxicity based on the presence of structural alerts which suggest toxic effects. Limited studies in rodents have shown NBBS exposure to cause neurotoxic and adverse developmental and reproductive effects. The benzenesulfonamide substructure present in NBBS is a fairly common building block for industrial chemicals and drugs that have not been widely evaluated. Environmental studies further show that NBBS is a groundwater contaminant and not readily biodegradable.

Nontoxicological Data

NBBS is widely used as a plasticizer in polyacetals, polycarbonates, and polysulfones. It also is used in Nylon 11 and Nylon 12 and in the production of flexible tubing. In addition to its plasticizer properties, NBBS possesses antifungal properties. It is identified in biological and environmental samples by high performance liquid chromatography and gas chromatography. NBBS is available from a variety of suppliers in the United States, China, South Korea, and India. The 2006 Inventory Update Reporting (IUR) database identified Unitex Chemical Corporation as a manufacturer of NBBS and Arkema Inc. and Degussa Corporation as importers. NBBS is produced by reacting *N*-butylamine with benzenesulfonylchloride. According to the IUR database, aggregate U.S. production volume ranged from >500,000 to 1,000,000 pounds (lb) in 1986, >1,000,000 to 10,000,000 lb from 1990 to 2002, and 1,000,000 to <10,000,000 in 2006. Studies that included evaluating NBBS in the environment (e.g., water, soil, and landfill leachate) date back over 30 years. These studies have been conducted in the United States as well as in England, Italy, the Netherlands, Germany, Sweden, and Japan. Recent U.S. studies indicate the presence of NBBS in the San Francisco Estuary, the Santa Ana River, runoff from agricultural fields (in southern California) irrigated with treated wastewater or effluent dominated stream water, and in samples taken from water treatment and reclamation plants in southern California. Levels ranged from not detected to 16 µg/L. NBBS also was isolated from dried roots of *Angelica sinensis*. There is high potential for human exposure to NBBS due to its potential presence in numerous applications. Oral exposure is possible due to its presence in water or leaching from NBBS-containing products such as cooking utensils. One study showed that NBBS leached from polyamide cooking utensils exposed to oil or water. NBBS also was found in drinking water samples that had been enriched with carbon dioxide using five different household carbonation devices. For two occupations in one industry, the National Institute for Occupational Safety and Health (NIOSH) National Occupational Hazards Survey (1981-1983) estimated that 1534 employees were potentially exposed to NBBS. Of those employees, 1169 were females. NBBS is a sponsored chemical under the U.S. EPA High Production Volume Challenge Program and is included on the Toxic Substances Control Act inventory. NBBS was included on the draft Contaminant Candidate List 3 (CCL3) Universe, which was used to develop the final CCL3.

Human Data

A TC_{Lo} of 3.7 mg/m³ in humans was reported. Effects noted included conjunctival irritation and structural or functional changes of the trachea or bronchi. Of 42 adipose breast tissue samples obtained from 21 patients in Spain, NBBS was found in one sample.

Toxicological Data

Chronic exposure, carcinogenicity, initiation/promotion, cogenotoxicity, and immunotoxicity studies were not located for NBBS.

Chemical Disposition, Metabolism, and Toxicokinetics

Distribution studies in rats showed that NBBS is able to enter the brain. Male rats were infused with stable isotope-labeled NBBS and samples of the perfusate, right parietal, right frontal, and right occipital cortexes were evaluated for the presence of NBBS. Brain uptake was rapid; concentrations were equal to or greater than the perfusion solution within 30 seconds. Male rats administered NBBS (1 mg/kg) by intravenous (i.v.) injection showed the presence of NBBS in the brain, blood, and CSF within 1 minute post-injection. Initial brain levels ranged from 1605 to 1830 ng/g. Cerebrospinal fluid (CSF) and blood levels were 202 and 660 ng/mL, respectively. Concentrations in all brain sections, CSF, and blood decreased in a similar manner. Blood NBBS concentrations were 66 ng/mL 60 minutes after administration.

Female rats were administered stable isotope-labeled NBBS (1 mg/kg) by i.v. injection; NBBS was present in blood and all organs and tissues selected for evaluation at various time points up to 24 hours after exposure. In the liver and skeletal muscle, the maximum NBBS concentration occurred two minutes after dosing. The maximum NBBS concentrations in the kidney and fat were observed at one and five minutes post-injection, respectively. Eight hours after dosing, NBBS concentrations in all tissues were <4 ng/g. Pharmacokinetic studies in the female rats showed an initial rapid decline between one and two minutes post-dosing. A more gradual decline in NBBS concentration was observed from two minutes until the end of the study (24 hours). A triexponential decay function was determined to best model the observed data. The calculated half-lives of the three exponential parameters were 0.78, 11, and 1036 minutes.

In vitro metabolism studies showed that NBBS was metabolized to 2-hydroxy-NBBS; conjugation of the metabolite was not noted.

Acute Exposure

One study reported a mouse oral LD₅₀ of 2900 mg/kg. In rats, oral LD₅₀ values ranged from 1725 to 3560 mg/kg, and an inhalation LC₅₀ of 4066 mg/m³ was reported.

Short-Term and Subchronic Exposure

Wistar rats were orally gavage with NBBS (50-1000 mg/kg) for 28 days. Several animals dosed with 1000 mg/kg either died or were killed in extremis. At the high dose, reduced body weight or reduced body weight gain and reduced food consumption were observed in all animals. Lethargy, hunched posture, motor dysfunction, salivation, emaciation, and labored respiration also were noted. Hematological evaluation showed a significant decrease in erythrocyte count in males dosed with 150 mg/kg and a significant decrease in hemoglobin in males dosed with 50 and 150 mg/kg. Absolute and relative kidney (150 mg/kg group) and testes (50 and 150 mg/kg group) weights were increased in males. Males and females had changes in gross liver pathology and histopathology at ≥150 mg/kg. The no observed adverse effect level was 50 mg/kg based on liver effects and low incidence of neurodegeneration.

In male Wistar rats administered NBBS (300 mg/kg) by intraperitoneal (i.p.) injection seven times at six-hour intervals, altered gait with and without hind limb paresis was observed. In preliminary studies, deaths occurred after at least four doses were administered. Reduced vertical movement or standing, self paw biting, teeth grinding, and circling movements also were noted. Necropsy findings included hemorrhagic and ulcerative forestomachs. Concurrent studies were conducted in male Wistar rats administered NBBS (300 mg/kg) by i.p. injection four times at six-hour intervals. Significant decreases in the time of stereotypic movements, bursts of stereotypic movement, number of horizontal movements, and total ambulatory counts were observed 20 minutes after administration of the initial dose. In addition to the decreased time of stereotypic and horizontal movements, a decrease in the number of vertical

movements was observed two hours after administration of the initial dose. These effects were not seen at any of the other administered doses and time points.

Additional oral and inhalation studies in rats with dosing regimens ranging from 30 days and 30 to 122 days, respectively, yielded a TD_{Lo} of 15 mg/kg and TC_{Lo} values of 1.5 to 3 mg/m³.

Synergistic/Antagonistic Effects

New Zealand White rabbits were administered 100µg NBBS, aluminum chloride (AlCl₃), or NBBS and AlCl₃ every four weeks for eight months via intracisternal (i.c.) injection. When NBBS and AlCl₃ were co-administered, the observed motor dysfunction was similar to that of animals that only received AlCl₃. However, onset of effects occurred more rapidly. Rabbits co-administered NBBS and AlCl₃ also were aggressive, which was not observed in other treatment groups.

NBBS was negative in the *in vitro* (at 50 µM) and *in vivo* (up to 400 mg/kg) National Cancer Institute Anticancer Drug Screening assays.

Cytotoxicity

NBBS was cytotoxic to Neuro-2a and C6 glioma cells in a dose-dependent manner. Neuro-2a growth was inhibited at concentrations ranging from 1 to 100 µM, while C6 glioma cell growth was inhibited at concentrations ranging from 10 to 500 µM. A dose-dependent increase in lactate dehydrogenase concentration and a dose-dependent decrease in [³H]-thymidine incorporation were observed at the same concentrations that produced cell death. NBBS (35-2000 µg/mL) also was cytotoxic to human lymphocytes and dissociated mouse hippocampal neurons.

Reproductive/Toxicological Effects

Male and female Wistar rats were administered NBBS (100, 200, or 400 mg/kg) by oral gavage beginning two weeks prior to mating and continuing during the mating period. Males were dosed for a minimum of 28 days, while females were dosed until post-partum day 3. Adverse effects (e.g., abnormal gait, tremor, hunched posture, piloerection, and lethargy) were noted in parental animals administered 400 mg/kg NBBS. Significant decreases in body weight were noted in high-dose males and females. Comparatively, a significant increase in body weight was noted in low-dose females during the pre-mating period. Reproductive performance was impaired in 9 of 12 high-dose mating pairs. A significant decrease in absolute testis and epididymides weight was observed in males at the 400 mg/kg dose. Histopathology of the testes and epididymides revealed several effects (e.g., spermatid retention and oligospermia). An increased rate of offspring-loss (pre- and post-implantation and post-partum) and decreased mean pup weight were noted for female rats administered the high dose.

Pregnant mice were administered NBBS (500 or 750 mg/kg/day) via i.p. injection and examined on gestation day 13. The number of live fetuses per dam, average crown-rump lengths, body weight, and placental weight were significantly decreased compared to control dams in both treatment groups.

Genotoxicity

NBBS (up to 5000 µg/plate) was not genotoxic in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, or TA1538 in the absence or presence of metabolic activation or in human lymphocytes.

Other Data

NBBS is a demonstrated neurotoxicant in experimental animals. Intracisternal administration to female New Zealand White rabbits produced a dose-dependent effect on motor dysfunction. Intraperitoneal administration of NBBS failed to produce the severity of effects observed after i.c. administration. Histopathological evaluation showed neuronal and dendritic degeneration. Combined administration of

NBBS, AlCl₃, and calcitrol for three and six months to Wistar rats decreased microtubule associated protein 2 reactivity in the frontal cortex and increased choline acetyltransferase immunoreactivity in the ventral horn of the lumbar spinal cord and glial fibrillary acidic protein (GFAP) in the hippocampus. Increased GFAP immunoreactivity in various brain regions (e.g., hippocampus) was also noted in Wistar rats after acute NBBS administration.

NBBS was not a dermal irritant on guinea pigs and was defined as slightly irritating in rabbit eyes.

Structure-Activity Relationships

N-sec-Butylbenzenesulfonamide

A single oral acute toxicity study for *N-sec-butylbenzene* from 1953 cited an LD₅₀ of >500 mg/kg.

Benzenesulfonamide

Benzenesulfonamide is used in the synthesis of dyes, photochemicals, and disinfectants; in electroplating; and in polyamide production. The NIOSH National Occupational Exposure Survey (1981-1983) estimated that 2957 employees, 1600 of which were females, had been exposed to benzenesulfonamide. The oral LD₅₀ values for mice and rats were 740 and 991 mg/kg, respectively. Subchronic and short-term studies have lasted between 30 days and 30 weeks. Oral TD_{Lo} values ranged from 636 mg/kg to 12.18 g/kg.

N,N-Diethylbenzenesulfonamide

N,N-Diethylbenzenesulfonamide was identified as an insect repellent. The rat oral LD₅₀ was 890 mg/kg. Adverse reproductive (e.g., increased post-implantation mortality) and teratological effects also were noted.

GeneGo Analysis

Nine metabolites, five major and four minor, were predicted after first-pass metabolism. Two minor metabolites were proposed to be epoxides. The CYP450 models predicted that NBBS would have some affinity for many of the evaluated isozymes; the highest affinity noted was for CYP2C19. However, the Tanimoto (structural) similarity percentages (TP) were below 50%. Similar results were determined in models of the Phase 2 metabolism. The model of serum protein binding percentage predicted some affinity 70.33% (TP = 60.98). The brain-blood barrier model indicated some penetration (0.36, TP = 52.75).

One protein binding model where the TP was 52% indicated that NBBS was predicted to inhibit transport through the human P-glycoprotein transporter. Of the 25 models evaluated, five predicted that NBBS would be active (calculated value >0.5) and the TP value was >50%. These models evaluated effects for antiangina activity (0.5, TP = 52.94), antibacterial activity (0.83, TP = 60.00), antidiabetic activity (0.60, TP = 53.93), antimigraine activity (0.51, TP = 52.75), and anticancer activity (0.72, 52.75).

Numerous toxic effects were predicted for NBBS. For example, NBBS was predicted to cause anemia (0.92, TP = 60.98), be neurotoxic (0.97, TP = 51.02), carcinogenic in rats and mice *in vivo* (0.58-0.83, TP ~60), and genotoxic (0.64, TP = 60.00). Comparatively, NBBS was not predicted to be mutagenic in the AMES mutagenicity binary model and was minimally cytotoxic.

Based on structural similarity ($\geq 75\%$), several proteins and receptors were identified as potential targets. Several members of the cathepsin protein family were identified, including cathepsin B (amyloid precursor protein secretase; involved in the proteolytic processing of amyloid precursor protein), cathepsin L (plays a major role in intracellular protein catabolism), cathepsin K (involved in bone remodeling and resorption and could contribute to tumor invasiveness), and cathepsin V (plays an important role in corneal physiology). Two G-protein coupled receptors, neuropeptide receptor 5R and

thromboxane A2 receptor, also were identified as potential targets. Myosin light chain kinase (facilitates myosin interaction with actin filaments to produce contractile activity), protein kinase C, and the γ -secretase complex (cleaves β -amyloid precursor protein to produce amyloid β -peptide) also were identified as targets. Based on the model which predicted inhibition of the human P-glycoprotein transporter, inhibition of the multi-drug resistance protein 1 also was proposed.

Leadscope Analysis

Genetic Toxicity

The 29 genetic toxicity models in Leadscope encompass predictions for mutagenicity (13), DNA damage (3), *in vivo* clastogenicity (5), and *in vitro* clastogenicity (8). Sensitivity and specificity of the models range from 6.67% to 96% and 38.7% to 96.8%, respectively. NBBS was predicted as positive in two models, negative in 14 models, and not in domain in 13 models. The 2 positive models were for inducing sister chromatid exchange (SCE) in CHO cells (sensitivity: 87.7%, specificity: 42.4%) and SCE in other cells (sensitivity: 96%, specificity: 38.7%); the positive prediction probabilities were 0.594 and 0.91, respectively. For both models, there were four structural features present in NBBS that also were present in the prediction model and one chemical that was at least 30% structurally similar.

Neurotoxicity

The neurotoxicity models in Leadscope encompass predictions for newborn rat, rodent, and mouse behavior; sub-models represent optimized active/inactive chemicals. Sensitivity and specificity of the models range from 43.2% to 78.4% and 86.4% to 91.4%, respectively. NBBS was predicted as negative in two models (which were composed of two submodels each) and not in domain in one model. The negative models were for rodent pup behavior and rat pup behavior; the overall positive prediction probabilities were 0.0698 and 0.157, respectively. For all four sub-models, there were six to seven features that were present in the prediction model and one chemical that was at least 30% structurally similar. Compared to the predicted results, previous experimental data have shown that NBBS is a neurotoxicant in rodent models. Additionally, *in utero* exposure to NBBS produces developmental effects on fetuses and pups.

Reproductive and Developmental Toxicity

The developmental toxicity models in Leadscope encompass predictions for structural dysmorphogenesis, visceral dysmorphogenesis, fetal survival, and fetal growth. The reproductive toxicity models encompass predictions for toxicity in male and female rats, mice, and rodents. Sub-models in the reproductive and developmental toxicity evaluations represent optimized active/inactive chemical ratios. Sensitivity and specificity of the reproductive models range from 36.3% to 63.8% and 83.9% to 96.5%, respectively. Sensitivity and specificity of the developmental toxicity models range from 22.1% to 57.4% and 84.4% to 95.3%. NBBS was classified as negative in all the evaluated models (26), except for one where it was defined as not in domain. The positive predictive probability values ranged from 0.0665 to 0.289 for the reproductive models and 0.283 to 0.487 in the developmental models. Compared to the predicted results, previous experimental data has shown that NBBS is a female and male rat reproductive toxicant.

Carcinogenicity

NBBS was evaluated in two sets of carcinogenicity endpoint models; seven are rodent models based on the 2-year rodent bioassays and four are cell transformation *in vitro* assay models. The sensitivity and specificity of the rodent models range from 32.5% to 44.7% and 90.2% to 95.1%, respectively. The sensitivity and specificity of the *in vitro* models range from 87.8% to 93.9% and 22.5% to 55.8%. NBBS was classified as negative in all of the *in vivo* rodent models; positive prediction values ranged from 0.187 to 0.283. Comparatively, NBBS was classified as positive in all of the *in vitro* models of cell transformation; positive prediction values ranged from 0.545 to 0.765. The *in vitro* models were identified as (1) cell transformation, (2) C3H10T1-2, (3) SHE, and (4) BALBc-3T3.

Human Adverse Effects

Thirteen models predicted cardiac endpoints, including: conduction disorders, coronary artery disorders, myocardial infarct disorders, palpitations, and rate rhythm disorders. The sensitivity and specificity of the models range from 32.1% to 65.7% and 85.8% to 93.6%, respectively. NBBS was classified as negative in all the models; positive prediction values ranged from 0.0574 to 0.431.

Five models predicted hepatobiliary endpoints, including: bile duct, gall bladder, liver jaundice, liver acute damage, and liver enzyme release. The sensitivity and specificity of the models range from 23.9% to 51.7% and 91.4% to 97.9%, respectively. NBBS was classified as negative in one model (prediction probability = 0.171) and not in domain for four models.

Six models predicted urinary endpoints, including: bladder, blood in urine, kidney, kidney function tests, nephropathy, and urolithiasis. The sensitivity and specificity of the models range from 34.5% to 55.8% and 89.2% to 96.5%, respectively. NBBS was classified as negative in four models and not in domain in two models; positive prediction values ranged from 0.235 to 0.333.

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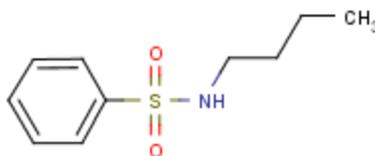
1.0 Basis for Nomination

N-Butylbenzenesulfonamide (NBBS) was nominated by the National Institute of Environmental Health Sciences for comprehensive toxicological testing based on its extensive use as a plasticizer, lack of adequate toxicological data, and suspicion of toxicity based on the presence of structural alerts which suggest toxic effects. Limited studies in rodents have shown NBBS exposure to cause neurotoxic and adverse developmental and reproductive effects. The benzenesulfonamide substructure present in NBBS is a fairly common building block for industrial chemicals and drugs that have not been widely evaluated. Environmental studies further show that NBBS is a groundwater contaminant and not readily biodegradable.

2.0 Introduction

NBBS is widely used as a plasticizer in polyacetals, polycarbonates, and polysulfones. It also is used in Nylon 11 and Nylon 12 and in the production of flexible tubing. NBBS allows for easier machining and removal of plastics from molds, produces a better finish, and imparts heat stability ([Proviron Fine Chemicals, 2003](#)). In addition to its plasticizer properties, NBBS possesses antifungal properties (Kim et al., 2000 [PMID:10805572]).

N-Butylbenzenesulfonamide
[3622-84-2]



2.1 Chemical Identification and Analysis

N-Butylbenzenesulfonamide (C₁₀H₁₅NO₂S; mol. wt. = 213.30) is also called:

- Benzenesulfonic acid butyl amide
- Benzenesulfonamide, *N*-butyl-
- N*-Butylbenzene sulfonamide
- N*-Butylbenzenesulfonamide
- N*-Butylbenzenesulphonamide

PubChem CID: [19241](#)

InChI: 1S/C10H15NO2S/c1-2-3-9-11-14(12,13)10-7-5-4-6-8-10/h4-8,11H,2-3,9H2,1H3

SMILES: CCCCNS(=O)(=O)C1=CC=CC=C1

Sources: ChemIDplus (undated-a), PubChem (undated)

NBBS was detected in 1 of 42 human breast adipose tissue samples obtained from volunteer patients during biopsy. The samples were extracted with hexane and concentrated under a nitrogen stream, then cleaned up using high performance liquid chromatography with a silica column and a mobile phase consisting of *n*-hexane and ethyl acetate (95:5 v/v) at a flow rate of 1 mL/min. A pulse of ethyl acetate (4 mL) was introduced 16 minutes after sample injection. The fraction that eluted between 4 and 17 minutes was collected and concentrated before being

injected into a gas chromatography-time-of-flight mass spectrometer to measure (GC-TOF MS) NBBS (Hernandez et al., 2009 [PMID:19097043]).

Samples of Australian domestic solid waste landfill leachate and bottled and cask wines were extracted with dichloromethane and then analyzed for NBBS using GC with accurate mass selected ion recording. Radiolabeled NBBS was used as an internal standard. Using this method, NBBS was detected in leachate at <0.3 to 94.6 ng/mL and in the wines at concentrations up to 2.17 ng/mL (Duffield et al., 1994 [PMID:7861748]).

2.2 Physical-Chemical Properties

Property	Information	Reference
Physical State	Clear oily liquid	ChemicalLand21.com (undated-a)
Odor	Almost odorless	Proviron Fine Chemicals (2003)
Boiling Point (°C)	326.7 ± 25.0 @ 760 Torr*	Registry (2010)
Melting Point (°C)	-30	ChemicalLand21.com (undated-a)
Flash Point (°C)	151.4 ± 23.2*	Registry (2010)
Vapor Pressure (Torr)	2.12 × 10 ⁻⁴ *	Registry (2010)
Specific Gravity	1.148	ChemicalLand21.com (undated-a)
Water Solubility	insoluble	ChemicalLand21.com (undated-a)
Octanol-water partition coefficient (log K _{ow})	2.1	Proviron Fine Chemicals (2003)
Log P	2.566 ± 0.299*	Registry (2010)
Bioconcentration Factor	52.50 (pH 1-7), 52.49 (pH 8), 52.38 (pH 9), 51.28 (pH 10) @ 25 °C*	Registry (2010)

*calculated properties using Advanced Chemistry Development (ACD/Labs) Software V8.14 (©1994-2010 ACD/Labs).

2.3 Commercial Availability

NBBS, sold under the name Proviplast 024, is produced by Proviron Fine Chemicals (Belgium) ([Proviron, 2006](#)). Kum Yang Co., Ltd. (South Korea), Simagchem Corporation (China), and Volant-Chem Corp. (China) also are producers of NBBS ([BuyersGuideChem, 2009](#)).

U.S. suppliers of NBBS include AK Scientific Inc., Frinton Laboratories, Rit-Chem Co., Inc., GNC Group, Inc., TCI America, Sigma-Aldrich, HallStar Company, and Interchem Corporation ([BuyersGuideChem, 2009](#); [ChemicalRegister, 2010](#); [HallStar, 2007](#); [Sigma-Aldrich, 2010](#); [TCI America, 2010](#)). Global suppliers include Jinan Haohua Industry Co., Ltd., Volant-Chem Corp., Kinbester Co., Ltd., and Hangzhou Dayangchem Co. Ltd., all from China, Chemos GmbH from Germany, and Aarti Drugs Limited from India ([BuyersGuideChem, 2009](#); [ChemicalRegister, 2010](#)).

The 2006 Inventory Update Reporting (IUR) database identified Arkema Inc. (Philadelphia, PA) and Degussa Corporation (Parsippany, NJ) as importers of NBBS. Unitex Chemical Corporation (Greensboro, NC) was identified as a manufacturer of NBBS (U.S. EPA, 2010a). [Note: "IUR regulation requires manufacturers and importers of certain chemical substances included on the Toxic Substances Control Act (TSCA) Chemical Substance Inventory to report site and manufacturing information for chemicals manufactured (including imported) in amounts of 25,000 pounds or greater at a single site. Additional information on domestic processing and use must be reported for chemicals manufactured in amounts of 300,000 pounds or more at a single site" (U.S. EPA, 2010b).]

3.0 Production Processes

NBBS is produced by reacting *N*-butylamine (CAS No. 109-73-9) with benzenesulfonylchloride (CAS No. 98-09-9) ([Proviron Fine Chemicals, 2003](#)).

4.0 Production and Import Volumes

According to the IUR database, the aggregate U.S. production volume of NBBS ranged from >500,000 to 1,000,000 pounds (lb) in 1986, >1,000,000 to 10,000,000 lb from 1990 to 2002, and 1,000,000 to <10,000,000 in 2006 (U.S. EPA, 2010a, 2010c).

5.0 Uses

NBBS is used widely as a plasticizer in polyacetals, polycarbonates, and polysulfones. It also is used in Nylon 11 and Nylon 12 ([Proviron Fine Chemicals, 2003](#)). Additionally, it is used in the production of films, transparent coatings, and plastic resins ([Kumar et al., 2007](#); Strong et al., 1991 [PMID:2058361]). It was previously described as a starting reagent for the synthesis of a proposed sulfonyl carbamate herbicide ([Stephens, 1976 pat.](#)).

6.0 Environmental Occurrence and Persistence

Studies of the presence of NBBS in environmental media (e.g., water, soil, and landfill leachate) date back over 30 years. For example, NBBS was identified as a contaminant of ground and drinking water in Italy in 1991 (Brambilla et al., 1991). Additionally, NBBS was detected in the Delaware River in 1977; concentrations ranged from trace amounts to 0.6 ppb (Sheldon and Hites, 1979). Studies have been conducted in the United States as well as in England, Italy, the Netherlands, Germany, Sweden, and Japan. The following information summarizes recent evaluations of environmental contamination at various locations throughout the world, with emphasis on the United States.

Sampling of water systems around New Jersey from 1997 to 2000 indicated the presence of NBBS; the amount was not quantified. All but one water system used ground water as their supply source and most of the systems had treatment systems in place for removal of contaminants (e.g., granulated activated charcoal) ([New Jersey Department of Environmental Protection, 2007](#)).

NBBS was present in combined samples taken in 1999 and 2000 from different locations within the San Francisco Estuary and in samples collected in 2002 from the Santa Ana River in California. NBBS was present in the Delta (Sacramento River and San Joaquin River), North Bay (Petaluma River, San Pablo Bay, Napa River, and Grizzly Bay), and South Bay (Coyote Creek, Dumbarton Bridge, Redwood Creek, and Alameda) regions of the estuary. Concentrations ranged from 111 to 454 ng/L (detection limit 250 pg/L) (Oros et al., 2003 [PMID:12932491]). Although NBBS was not present in samples taken from sampling sites along the Santa Ana River, NBBS concentrations ranged from 0 to 94 ng/L in samples of effluent from four waste water treatment plants that contributed ~73% of the effluent discharged into the Santa Ana River (Gross et al., 2004 [PMID:15378981]).

Pre- and post-tertiary treatment water samples taken at a water treatment plant and two water reclamation plants in southern California were evaluated for the presence of a variety of organic

chemicals, including NBBS. A sample of surface water at two drinking water reservoirs and a sample of treated water used to recharge groundwater also were evaluated. NBBS was found in all pre-tertiary treatment water samples and was present at the highest concentration (~1 to 16.3 µg/L) compared to the other substances detected. It also was present in most of the post-tertiary treatment samples; however, concentrations depended on the treatment method used. Lime coagulation or microfiltration combined with reverse osmosis was more effective in removing NBBS than was granular media filtration. NBBS also was present in groundwater and surface water samples but below the method detection level (Soliman et al., 2007 [PMID:17370841]).

Runoff from agricultural fields irrigated with treated wastewater and/or effluent-dominated stream water (streams with flows composed of treated wastewater) revealed the presence of NBBS (0.35 to 2 µg/L). Runoff samples were taken from fields in Ventura County, CA, during two growing seasons (July 1999 to April 2000) (Pedersen et al., 2003 [PMID:12590482], 2005 [PMID:15740050]).

NBBS also was detected in samples taken from eight locations in the Rhine River in Germany in 2001. Levels ranged from 92 to 190 ng/L (Schwarzbauer and Heim, 2005 [PMID:16280149]). Leachate samples obtained in 1994 from three sites in Sweden had concentrations of NBBS that ranged from 709 to 5300 ng/L (Welander, 1997).

Studies have shown that NBBS leaching from equipment parts or tubing can be misconstrued as groundwater contamination. For example, NBBS (concentrations from 800 to 531,000 µg/L) identified as a groundwater contaminant in wells at Lawrence Livermore National Laboratory Site 300 was later found to be leaching from nylon tubing used in the well pumps and not a groundwater contaminant (Gregory et al, 2007).

NBBS was isolated from the methanolic extract of dried roots of *Angelica sinensis*. Pooled petroleum and chloroform partitions of the methanolic extract were subjected to flash column chromatography. Thirteen fractions were collected; fraction F5 (7.0 g) was identified as containing 1.9 mg NBBS (Deng et al., 2006).

Biodegradation studies using the Modified Sturm Test indicated that the average degradation value for NBBS was 18% (Proviron Fine Chemicals, 2003).

7.0 Human Exposure

There is high potential for human exposure to NBBS due to its widespread use as a plasticizer in polyacetals, polycarbonates, and polysulfones as well as in Nylon 11 and Nylon 12. Oral exposure is likely due to its presence in water or leaching from NBBS-containing products such as cooking utensils. Polyamide cooking utensils (17, PAA6 and PA6, according to labels) were exposed to oil at 175 °C for 30 minutes or 4 hours and water at 100 °C for 30 minutes or 4 hours. In oil and water, NBBS migrated from the cooking utensils at a concentration >10 µg/L (Skjevrak et al., 2005 [PMID:16227185]). NBBS also was found in 20 of 33 drinking water samples that had been enriched with carbon dioxide using five different household carbonation devices (Jahr and Roscher, 2001).

Over 20 years ago, the National Institute for Occupational Safety and Health (NIOSH) National Occupational Hazards Survey (1981-1983) estimated that 1534 employees in two occupations at the rubber and miscellaneous plastics products industry were potentially exposed to NBBS. Of those employees, 1169 were females (NIOSH, undated-a). Nationwide, 24 facilities were thought to have NBBS present (RTECS, 2008). According to the 2006 IUR database, 100 to 999 industrial manufacturing, processing, and use workers were exposed to NBBS and there was a total of between 1 and 99 manufacturing, processing, and use sites within the United States (U.S. EPA, 2010a).

8.0 Regulatory Status

NBBS is a sponsored chemical under the U.S. Environmental Protection Agency's High Production Volume Challenge Program and is included on the TSCA inventory; requirements for testing under TSCA expired on February 17, 2010 (U.S. EPA, 2010d, 2010e). NBBS was included on the draft Contaminant Candidate List 3 (CCL3) Universe, which was used to develop the final CCL3 (U.S. EPA, 2009).

Internationally, NBBS is specified on the public portion of the Domestic Substances List of Canada (Environment Canada, 2010). It also is listed on the European Inventory of Existing Chemical Substances, the Existing Chemicals List inventory of Korea, and the Existing and New Chemical Substances inventory of Japan (The HallStar Co., 2007).

9.0 Toxicological Data

9.1 General Toxicology

9.1.1 Human Data

A TC_{Lo} of 3.7 mg/m³ was reported in humans. Effects noted included conjunctival irritation and structural or functional changes of the trachea or bronchi (RTECS, 2008).

Adipose breast tissue samples were obtained from 21 volunteers in Spain. Samples were screened for a variety of organic contaminants (e.g., polychlorinated biphenyls) using GC-TOF MS. Of the 42 samples evaluated, NBBS was found to be present in one sample. [Note: Based on the information provided, it is unclear whether the NBBS was from an adipose breast tissue or cancer sample] (Hernandez et al., 2009 [PMID:19097043]).

9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

Male Sprague-Dawley rats were infused for 15 to 30 seconds into the external carotid artery with stable isotope-labeled NBBS. The perfusion was terminated by decapitation and samples of the perfusate, right parietal, right frontal, and right occipital cortexes were evaluated for presence of NBBS. Results showed that brain uptake was rapid. Concentrations were equal to or greater than that of the perfusion solution within 15-30 seconds. Studies with different perfusion media (saline versus serum) showed that NBBS highly binds to plasma proteins (Kumar et al., 2007).

Male Sprague-Dawley rats were administered NBBS (1 mg/kg) by intravenous (i.v.) injection. At 1, 5, 15, 30, and 60 minutes post-injection, arterial blood was collected before three animals were killed. Select brain sections (right parietal cortex, cerebellum, and spinal cord) and cerebrospinal fluid (CSF) from the cistern magna were collected. The time-course study showed that NBBS levels in the brain, blood, and CSF were the highest one minute after

injection. Initial brain levels ranged from 1605 to 1830 ng/g. CSF and blood levels were 202 and 660 ng/mL, respectively. Levels in all brain sections, CSF, and blood decreased in a similar manner. Blood NBBS concentrations were 66 ng/mL 60 minutes after administration (Kumar et al., 2007).

Female Wistar rats were administered stable isotope-labeled NBBS (1 mg/kg) by i.v. injection. Blood was collected through a previously implanted catheter in the right external jugular vein at select time points. Animals were then killed and the liver, kidney, peripheral fat, and skeletal muscle were evaluated for NBBS, which was present in all sampled tissues. In the liver and skeletal muscle, the maximum NBBS concentration was achieved two minutes after dosing. The maximum NBBS concentration in the kidney and the fat was achieved one and five minutes, respectively, after dosing. NBBS levels in all tissues were <4 ng/g at eight hours after dosing (Kumar et al., 2007).

Pharmacokinetic studies were conducted using the blood collected from the female Wistar rats described above. Plasma NBBS concentrations decreased from 603 ng/mL, observed one minute after administration, to 9.5 ng/mL at 24 hours. The time course showed an initial rapid decline between one and two minutes post-dosing. A more gradual decline in NBBS concentrations was observed from two minutes until the end of the study (24 hours). A triexponential decay function was determined to best model the observed data. The calculated half-lives of the three exponential parameters were 0.78, 11, and 1036 minutes (Kumar et al., 2007).

Female Wistar rats were orally administered NBBS (1 mg/kg) in condensed milk followed by administration of radiolabeled NBBS (1 mg/kg) via the lateral tail vein. In another set of animals, only radiolabeled NBBS was administered via the tail vein. For both studies, blood was collected for the following 24 hours. For the first study, oral bioavailability ranged from 52% to 79%. Plasma-concentrations were triphasic; calculated half-lives were 0.32, 27, and 500 minutes. Blood and plasma clearance rates were 13 and 7 mL/min, respectively. Similar results were obtained in the second study. The calculated half-lives were 0.34, 29, and 480 minutes. Blood and plasma clearance rates were 11 and 5.5 mL/min, respectively (U.S. EPA, 2010f).

In vitro metabolism studies were conducted using liver homogenates from Aroclor-1254-induced and non-induced male Fisher rats, non-induced New Zealand White female rabbits, and donor human liver. NBBS (1 mM or 200 µg) was incubated with homogenates for four hours and samples were analyzed for the metabolites using GC/MS. NBBS was metabolized to 2-hydroxy-NBBS in all samples. It was proposed that metabolism occurred through a cytochrome P450 (CYP450) mechanism. Conjugation of the metabolite *in vitro* was not noted (U.S. EPA, 2010f).

Female rats were orally administered NBBS (1 mg/kg) in condensed milk followed by administration of radiolabeled NBBS (1 mg/kg) via the lateral tail vein. Urine was collected for 24 hours. A hydroxylated metabolite of NBBS was identified in the urine. Urinary excretion was 1.09-1.69 ng/mL. [Note: The data provided indicated that urinary excretion from control animals was 1.32-3.13 ng/mL] The total fraction of radiolabeled NBBS excreted was 0.007-0.034% (U.S. EPA, 2010f).

9.1.3 Acute Exposure

Acute toxicity values for NBBS are presented in the table below.

Table 1. Acute Toxicity Values for NBBS

Route	Species (sex and strain)	LD ₅₀ /LC ₅₀	Reference
Oral	Mouse (sex and strain n.p.)	2900 mg/kg	RTECS (2008)
Oral	Rat (M&F and Sprague Dawley)	2070 mg/kg	U.S. EPA (2010f)
Oral	Rat (sex and strain n.p.)	3560 mg/kg	RTECS (2008)
Oral	Rat (sex and strain n.p.)	2170 mg/kg	RTECS (2008)
Oral	Rat (sex and strain n.p.)	1725-2050 mg/kg	IUCLID (2000)
Oral	Rat (sex and strain n.p.)	1725 mg/kg	IUCLID (2000)
inh.	Rat (M&F and Wistar)	4066 mg/m ³	U.S. EPA (2010f)
Dermal	Rat (M&F and Sprague-Dawley)	>2000 mg/kg	U.S. EPA (2010f)
Dermal	Rabbit (sex and strain n.p.)	>1150 mg/kg	IUCLID (2000)

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

Inhalation studies in mice and rats yielded TC_{Lo} values of 3-5.2 mg/m³/2 hours and 0.8-5.2 mg/mg³/4 hours, respectively. Observed effects included structural or functional changes to the trachea or bronchi, somnolence, ataxia, respiratory depression, and changes in lung, liver, and adrenal weight. A separate inhalation study in rats yielded an LC_{Lo} value of 385 mg/m³/4 hours; lacrimation and dyspnea were noted (RTECS, 2008).

9.1.4 Short-Term and Subchronic Exposure

Male and female Wistar rats were orally gavaged with NBBS (50, 150, or 1000 mg/kg) for 28 days. At the high dose, one female rat died spontaneously on day 15. Additional males and females were killed in extremis between days 8 and 18. At the high dose, reduced body weight or body weight gain was observed in all animals. A reduction in food consumption, lethargy, hunched posture, uncoordinated movements, abnormal gait, salivation, emaciation, and labored respiration also were observed. Hematological evaluation showed a significant decrease in erythrocyte count in males dosed with 150 mg/kg and a significant decrease in hemoglobin in males dosed with 50 and 150 mg/kg. Absolute and relative kidney (150 mg/kg group) and testes (50 and 150 mg/kg group) weights were increased in males. Adverse effects were noted from gross pathology and histopathology of the liver in males and females at ≥150 mg/kg. Thymus, sciatic nerve, and cervical cord effects also were noted. The no observed adverse effect level was 50 mg/kg based on liver effects and low incidence of neurodegeneration ([U.S. EPA, 2010f](#)).

Male Wistar rats were administered NBBS (300 mg/kg) by i.p. injection seven times at six-hour intervals. Within 10 to 20 minutes after the initial dosing, altered gait with and without hind limb paresis was noted. In preliminary studies, deaths occurred after at least four doses were administered. Additional altered effects included reduced vertical movement or standing, self paw biting, teeth grinding, and circling movements. Bladders filled with bloody urine and hemorrhagic and ulcerative forestomachs were seen during necropsy. Further evaluation of the stomachs showed the presence of high leukocyte infiltrations in the epithelial portions and dilated blood vessels in subserosal layers of the stomach. In the interstitial spaces of the

medullary part of the kidney, slight infiltration of erythrocytes was also reported (Lee et al., 1995 [PMID:8588290]).

In a study run concurrently with the above study, the spontaneous motor activity of male Wistar rats was evaluated after administration of NBBS (300 mg/kg) by i.p. injection four times at 6-hour intervals. Evaluations occurred 20 minutes and two hours after each dose. Significant decreases in the time of stereotypic movements, bursts of stereotypic movement, number of horizontal movements, and total ambulatory counts were observed 20 minutes after administration of the initial dose. Significant decreases in the time of stereotypic movements, number of horizontal movements, and number of vertical movements were observed two hours after administration of the initial dose. However, effects on the same parameters were not noted after any of the other administered doses at either time point (Lee et al., 1995 [PMID:8588290]).

Results from additional short-term and subchronic studies are presented in the table below.

Table 2. Short-Term and Subchronic Studies for NBBS¹

Route	Species	Dosing Regimen	TD _{Lo} /TC _{Lo}	Effects
Oral	Rat	30 days/intermittent ²	15 mg/kg	Changes in serum composition, and leukocyte and erythrocyte counts
inh.	Rat	30 days/intermittent	3 mg/m ³	Blood changes and structural changes in vessels
inh.	Rat	91 days/intermittent	1.5 mg/m ³	Structural changes in vessels
inh.	Rat	122 days/intermittent	1.5 mg/m ³	Changes in cell counts (unspecified), emphysema, and male reproductive effects
inh.	Guinea pig	30 days/intermittent	1.5 mg/m ³	Leukopenia and other blood changes
inh.	Guinea pig	91 days/intermittent	3 mg/m ³	Changes in cell counts (unspecified)

Abbreviations: inh. = inhalation; TC_{Lo} = lowest concentration to produce any toxic effect in test animals; TD_{Lo} = lowest dose reported to produce any toxic effect in test animals

¹ Source: RTECS (2008)

² Intermittent = dosing occurred during discrete periods (Symyx Technologies, Inc., 2007)

9.1.5 Chronic Exposure

No data were located.

9.1.6 Synergistic/Antagonistic Effects

New Zealand White rabbits were administered 100 µg NBBS, aluminum chloride (AlCl₃), NBBS and AlCl₃ (100 µL of a 1 mg/mL NBBS solution prepared in 1 mg/mL AlCl₃), or saline every four weeks for eight months via intracisternal (i.c.) injection. Rabbits were evaluated for clinical signs of toxicity (e.g., abnormalities in spontaneous behaviors and altered posture). Immunohistochemical evaluation of neurotoxicity also was evaluated. When NBBS and AlCl₃ were co-administered, the observed motor dysfunction was similar to that observed in animals that only received AlCl₃; however, the onset of effects occurred more rapidly. Rabbits co-administered NBBS and AlCl₃ were aggressive, which was not observed in either of the single-agent treatment groups. Calculation of the coneurotoxicity coefficient (CNC), where a value >1 suggests potentiation of toxicity, yielded values between 1.1 and 1.6 for the initial 15 weeks

of treatment. The CNC value was ≤ 1 for the remaining course of the study. A mean score for the severity of neuropathological changes was 1.36 for animals treated with both toxicants (Strong and Garruto, 1991 [PMID:1745433]).

Anti-Carcinogenicity

NBBS was negative in the *in vitro* (50 μM) and *in vivo* (≤ 400 mg/kg) National Cancer Institute Anticancer Drug Screening assays (PubChem, undated).

9.1.7 Cytotoxicity

NBBS was cytotoxic to Neuro-2a and C6 glioma cells in a dose-dependent manner after a 72-hour exposure period. Neuro-2a growth was inhibited at concentrations ranging from 1 to 100 μM , while C6 glioma cell growth was inhibited at concentrations ranging from 10 to 500 μM . Cell growth IC_{50} values (inhibitory concentration for 50% of samples) were 10 and 100 μM in Neuro-2a and C6 glioma cells, respectively. A dose-dependent increase in lactate dehydrogenase concentration and decrease in [^3H]-thymidine incorporation were observed at the same concentrations that produced cell death. Decreases in glial fibrillary acidic protein (GFAP) also were noted in both cell types (Nerurkar et al., 1991 abstr., 1993). NBBS (35-2000 $\mu\text{g}/\text{mL}$) also was cytotoxic to human lymphocytes; cytotoxicity was observed at 1000 and 2000 $\mu\text{g}/\text{mL}$ (IUCLID, 2007).

NBBS was cytotoxic to dissociated mouse hippocampal neurons. Exposure of neurons 10 days after plating to concentrations ranging from 10 to 50 μM NBBS for 2 to 4 days led to reductions in neurofilament and α -tubulin staining in distal neurites. Comparatively, staining in the perikarya and proximal neurites was preserved. Additionally, neurite outgrowth was inhibited (Wakayama et al., 1992 abstr.).

9.2 Reproductive and Teratological Effects

Male and female Wistar rats were administered NBBS (100, 200, or 400 mg/kg) by oral gavage. Dosing was initiated two weeks prior to mating. Males were dosed for a minimum of 28 days, while females were dosed until post-partum day three. Detailed clinical observations (e.g., body weight and sperm parameters) and histopathological examinations were conducted. No deaths or toxic effects were reported in animals treated with 100 or 200 mg/kg NBBS. Two females treated with the high dose were found dead during the mating period. At the high dose, adverse effects were noted in parental animals; effects included abnormal gait, tremor, hunched posture, piloerection, and lethargy. High-dose males and females had significant decreases in body weight. Comparatively, low-dose females showed significant increases in body weight during the pre-mating period. Decreased feed consumption by both sexes recovered later in the observation and dosing periods. Reproductive performance was impaired in 9 of 12 high-dose mating pairs. A significant decrease in absolute testis and epididymides weight was observed in high-dose males. Histopathological evaluation of the testes and epididymides noted several effects including Sertoli cell vacuolation, spermatid retention, multinucleated giant cells, desquamation of germ cells, absence of spermatids, atrophy of testis, and oligospermia. An increase rate of offspring loss (pre- and post-implantation, and post-partum) was noted for high-dose female rats. Mean pup weight also was decreased in pups from the females. Adverse effects [not described] also were noted (IUCLID, 2007).

Pregnant mice (Jcl:ICR) were administered NBBS (500 or 750 mg/kg/day) via i.p. injection then examined on gestation day 13. The number of live fetuses per dam, average crown-rump lengths, body weight, and placental weight in both treatment groups were significantly decreased compared to control dams. The chorionic villi were less ramified in the treated groups when compared to control placenta (Hashimoto et al., 1991 abstr.).

9.3 Carcinogenicity

No data were located.

9.4 Initiation/Promotion Studies

No data were located.

9.5 Genotoxicity

NBBS (up to 5000 µg/plate) was not genotoxic in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, or TA1538 in the absence or presence of metabolic activation (IUCLID, 2000; U.S. EPA, 2010f). NBBS (35-2000 µg/mL) also was not mutagenic in human lymphocytes; observed polyploidy formation was within historical control levels (IUCLID, 2007).

9.6 Cogenotoxicity

No data were located.

9.7 Immunotoxicity

No data were located.

9.8 Other Data

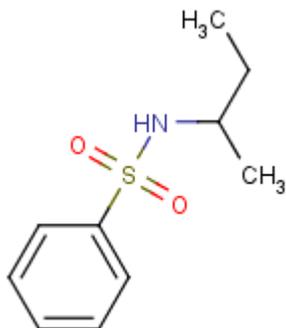
Intracisternal administration of NBBS (10-100 µg) to female New Zealand White rabbits once a month for a year produced a dose-dependent effect on motor dysfunction. Observed effects included hyperreflexia, impaired backpedaling, splaying of limbs, decreased forelimb tone, and exaggerated hind limb extensor tremors. The rate of weight gain in treated animals was decreased 25% compared to control animals. Hematological parameters were not affected by NBBS administration. When administered by i.p. injection, NBBS failed to produce the severity of effects observed after i.c. administration. Histopathological evaluation showed neuronal and dendritic degeneration (Strong et al., 1990 abstr., 1990, 1991 [PMID:2058361]). Intraperitoneal administration of NBBS to male Wistar rats over a 24- to 42-hour period also produced motor dysfunction. Immunohistological staining with anti-acetylcholinesterase antibodies was decreased in alpha-motor neurons in lamina IX of the lumbar spinal cord (Lee et al., 1995 [PMID:8588290]; U.S. EPA, 2010f). Combined administration of NBBS, AlCl₃, and calcitrol to Wistar rats for three and six months increased choline acetyltransferase immunoreactivity in the ventral horn of the lumbar spinal cord and GFAP in the hippocampus and decreased microtubule-associated protein 2 reactivity in the frontal cortex (Cho et al., 1994 abstr.). Acute administration of NBBS to Wistar rats increased GFAP immunoreactivity in the substantia nigra, hippocampus, medial septal nucleus, nucleus accumbens, cerebrum, and brainstem (Cho et al., 1995).

NBBS was not a dermal irritant on guinea pigs and was defined as slightly irritating in rabbit eyes (IUCLID, 2000).

10.0 Structure-Activity Relationships

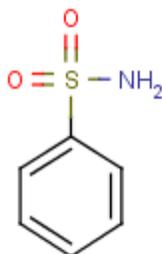
10.1 Structurally Similar Chemicals

N-sec-Butylbenzenesulfonamide [CAS No. 23705-41-1; PubChem CID: 211877]



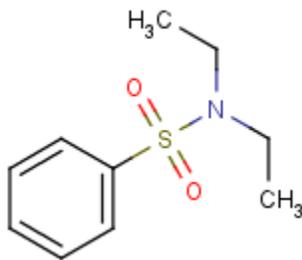
A single oral acute toxicity study from 1953 cited an LD₅₀ of >500 mg/kg bw (ChemIDplus, undated-b; RTECS, 1996a).

Benzenesulfonamide [CAS No.98-10-2; PubChem CID: 7370]



Benzenesulfonamide is used in the synthesis of dyes, photochemicals, and disinfectants; in electroplating; and in polyamide production (ChemicalLand21.com, undated-b). Benzenesulfonamide is included on the TSCA Inventory List. The NIOSH National Occupational Exposure Survey (1981-1983) estimated that 2957 employees, 1600 of which were females, were exposed to benzenesulfonamide (NIOSH, undated-b). Oral LD₅₀ values for mice and rats were 740 and 991 mg/kg bw, respectively. The i.p. LD₅₀ in mice was 1000 mg/kg bw (ChemIDplus, undated-c; RTECS, 1997). Subchronic and short-term studies in rats treated orally with benzenesulfonamide for 30 days up to 30 weeks reported numerous adverse effects. Impaired liver function, changes in leukocyte counts, and weight loss or decreased weight gain were reported after treatment for 30 days; the TD_{L0} was 5280 mg/kg bw. Treatment with benzenesulfonamide for 9 weeks caused impaired liver function, unspecified changes in erythrocyte counts, and death; the TD_{L0} was 12.18 g/kg bw. Rats given benzenesulfonamide for 30 weeks exhibited unspecified changes in serum composition; the TD_{L0} was 636 mg/kg bw (RTECS, 1997; Symyx Technologies, Inc., 2007).

N,N-Diethylbenzenesulfonamide [CAS No. 1709-50-8; PubChem CID: [74367](#)]



N,N-Diethylbenzenesulfonamide was identified as an insect repellent ([ChemicalLand21.com, undated-c](#)). An oral rat acute toxicity study reported an LD₅₀ of 890 mg/kg bw. Adverse reproductive (e.g., increased post-implantation mortality) and teratological effects were associated with administration of the chemical (RTECS, 1996b).

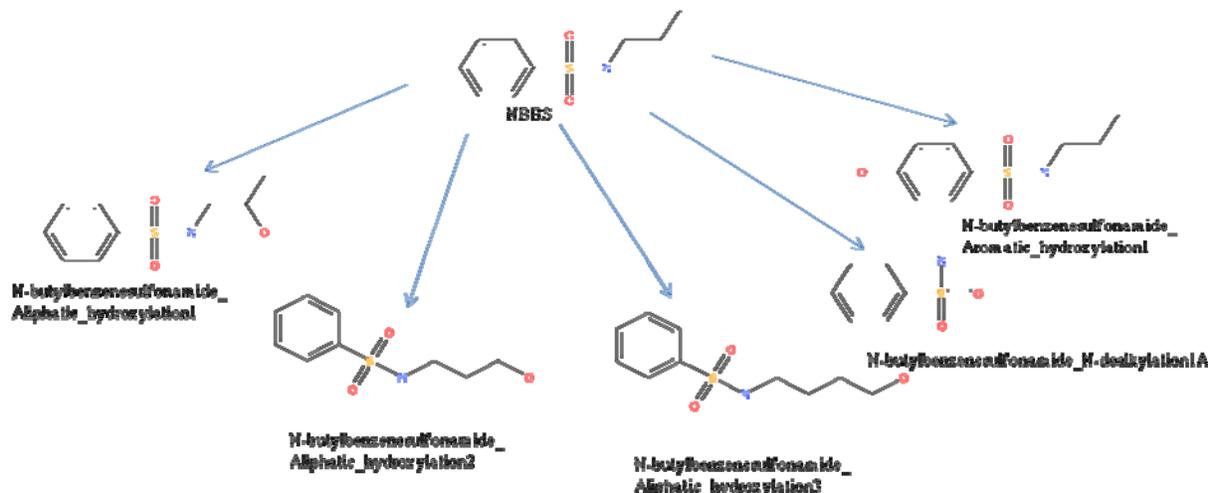
10.2 GeneGo Analysis

For each GeneGo quantitative-structure activity relationship (QSAR) model, a QSAR value was calculated. For non-binary models, the calculated values ranged between two threshold values to be classified as active in the model. These threshold values corresponded to the negative logarithm of the activity for the most active compound in the training set and the negative logarithm of 50 μ M (-1.7). For binary models (e.g., AMES mutagenicity binary model), the definition of an active chemical is model dependent. In addition to the QSAR value, a Tanimoto similarity percentage (TP) was calculated which indicates the percentage similarity of NBBS to the most-similar compound in the training set.

Overall, the evaluated QSAR models predicted neurological, carcinogenic, and genotoxic effects. Additionally, NBBS was predicted to produce anemia. Based on the predicted targets, NBBS is proposed to affect proteolysis and apoptosis, muscle contraction, platelet aggregation, and fetal development.

ADME QSARs

Nine metabolites, five major and four minor, were predicted after first-pass metabolism. Of the major metabolites, four were hydroxylated (three on the aliphatic chain and one on at the para-position of the aromatic ring) and one was dealkylated (see Figure below). Two minor metabolites were proposed to be epoxides while the remaining two were hydrolyzed epoxides. The first-pass conjugated metabolites consisted of *N*-acetyl or *N*-sulfate substituted NBBS. *In vitro* and *in vivo* studies support the presence of hydroxylated NBBS metabolites, specifically the presence of an aliphatic-hydroxylated metabolite. However, conjugation of the metabolite was not observed.



Six of the seven second-pass major metabolites predicted were hydroxylated metabolites of the predicted major first-pass hydroxylated metabolites; three were hydroxylated on the aromatic ring while the remaining three were hydroxylated on the aliphatic chain. *N*-dealkylation of the aromatic hydroxylated metabolite also was predicted. The minor second-pass metabolites were either aliphatic or aromatic hydroxylated or *N*-dealkylated.

The CYP450 models, overall, predicted that NBBS would have some affinity for many of the evaluated isozymes (CYP1A2, CYP2B6, CYP2C19, CYP2D6, and CYP3A4). The highest affinity was noted for CYP2C19 (pKm = 1.33). However, the TP values were <50% for all the models. Models that evaluated the inhibitory activity of NBBS and its metabolites yielded similar results; compounds were identified as potential inhibitors of CYP2C9, CYP2D6, and CYP3A4 however, TP values were <50%. The one exception was the model for inhibition of human soluble epoxide hydrolase which predicted low inhibition activity by NBBS. Models of the Phase 2 metabolism enzymes sulfotransferases and UDP-glycosyltransferases predicted that NBBS would have affinity for the human sulfotransferase 1A1. However, as mentioned for the CYP models, the TP value was low (19.18). While *in vitro* and *in vivo* studies suggest that NBBS is metabolized by CYP450, the isoform(s) responsible have not been discussed.

Additional ADME models evaluated blood-brain barrier penetration, binding affinity to human serum albumin, serum protein binding, water solubility, and the octanol-water distribution coefficient of NBBS. The models predicted that NBBS could enter the brain and moderately binds serum proteins. Overall, the first-pass metabolites (major, minor, and conjugated) had brain penetration ability similar to NBBS while the second-pass metabolites were predicted to have decreased brain-penetrating ability. The prediction that NBBS could enter the brain is supported by *in vivo* studies indicating rapid brain uptake after perfusion and i.v. administration.

Protein Binding QSAR for NBBS

While many of the protein binding QSAR models indicated that NBBS was considered active in the model, the TP values were typically <40%. One model where the TP was 52% indicated that NBBS was predicted to inhibit transport through the human P-glycoprotein transporter (pIC₅₀ = -

1.06). The aliphatic-hydroxylated metabolites of NBBS also were predicted to inhibit transport through the human P-glycoprotein transporter.

Therapeutic Activity QSARs for NBBS

Of the 25 models evaluated, five predicted that NBBS would be active (calculated value > 0.5) and the TP value was >50%. Predicted therapeutic effects were antiangina activity (0.5, TP = 52.94), antibacterial activity (0.83, TP = 60.00), antidiabetic activity (0.60, TP = 53.93), antimigraine activity (0.51, TP = 52.75), and anticancer activity (0.72, 52.75). Compared to the prediction, the National Cancer Institute Anticancer Drug Screening assays indicated that NBBS did not possess anticancer activity *in vitro* or *in vivo*.

Toxic Effects QSARs for NBBS

Numerous toxic effects (calculated value >0.5 and TP value >50%) were predicted for NBBS. NBBS was predicted to cause anemia (0.92, TP = 60.98); be neurotoxic (0.97, TP = 51.02), hepatotoxic (0.57, 66.67), and nephrotoxic (0.53, 60.98) in rats, mice, and humans; and be carcinogenic (0.58-0.83, TP ~60) and genotoxic in rats and mice (0.64, TP = 60.00). NBBS was predicted to be negative in the AMES mutagenicity binary model (0.04 [0 defined as nonmutagenic], TP = 66.67). In the general cytotoxicity model for log growth inhibition in MCF7 model, where log GI₅₀ from 6 to 8 is defined as toxic and values less than 3 are less toxic, a predicted value of 4.62 was determined (TP = 59.26). The model for general toxicity, based on log Maximum Recommended Therapeutic dose (mg/kg bw/day), yielded a value of 0.69 (TP = 59.49); chemicals above the 0.5 cutoff value are classified as less toxic.

Literature studies support the prediction that NBBS has neurotoxic activity. Short-term studies also support the prediction that NBBS produces liver and kidney effects. Previous cytotoxicity studies, while not in MCF7 cells, indicate that NBBS has cytotoxic activity in different cell types. Previous AMES studies were negative, which supports the model prediction.

Possible Targets for NBBS and Metabolites

Based on structural similarity ($\geq 75\%$), NBBS was identified as a potential inhibitor of several proteins and receptors. Several members of the cathepsin protein family were identified as proposed targets, including cathepsin B (amyloid precursor protein secretase; involved in the proteolytic processing of amyloid precursor protein), cathepsin L (plays a major role in intracellular protein catabolism), cathepsin K (involved in bone remodeling and resorption and could contribute to tumor invasiveness), and cathepsin V (plays an important role in corneal physiology). Two G-protein coupled receptors, neuropeptide receptor 5R and thromboxane A2 receptor, also were identified as potential targets. Myosin light chain kinase (facilitates myosin interaction with actin filaments to produce contractile activity), protein kinase C, and the γ -secretase complex (cleaves β -amyloid precursor protein to produce amyloid β -peptide) also were identified as targets. Based on the model which predicted inhibition of the human P-glycoprotein transporter, inhibition of the multi-drug resistance protein 1 also was proposed.

For the predicted metabolites, the majority of the inhibitory effects identified were associated with the second-pass, conjugated metabolites: N-butylbenzenesulfonamide_N-dealkylation1A_N-acetyl_transfer1, N-butylbenzenesulfonamide_Aromatic_hydroxylation1_N-sulfate_transfer1, N-butylbenzenesulfonamide_Aliphatic_hydroxylation1_N-acetyl_transfer1,

and *N*-butylbenzenesulfonamide_Aromatic_hydroxylation1_N-acetyl_transfer1. Targets included members of the carbonic anhydrase enzyme (I, II, IV, XIV, XII, VB, IX, XIII, VII, VA, and VI) and metalloprotease families; ALOX5; and ALDX. Additionally, the first pass major metabolite *N*-butylbenzenesulfonamide_Aliphatic_hydroxylation3 was predicted to be a caspase-1, γ -secretase complex, and protein kinase C inhibitor, a neuropeptide receptor 5R antagonist, and a glutamate receptor agonist.

10.3 Leadscope Analysis

For each Leadscope model suite evaluated, a positive prediction probability (ranging from 0-1) was calculated. Values >0.5 were defined as positive. If the test compound was not at least 30% similar to one in the training set and at least one model feature was not in the test compounds, the chemical was defined as "not in the domain" and prediction probability was not determined.

A summary of the models where positive prediction values were obtained is provided in the table below. Models where a negative prediction value was obtained, but contradictory literature studies are available, also are presented.

Model	Positive Prediction Value ¹	Model Features ²	Training Set Chemicals with $\geq 30\%$ Similarity	Literature Results
<i>Genotoxicity</i>				
Sister Chromatid Exchange in CHO cells	0.594	4 (1,2,3,4)	1	No experimental data
Sister Chromatid Exchange in CHO cells	0.91	4 (3,4,5,6)	1	No experimental data
<i>Carcinogenicity</i>				
BALBc-3T3	0.578	4 (2,3,4,7)	1	No experimental data
C3H10T1-2	0.765	2 (3,4)	1	No experimental data
SHE	0.61	2 (2,3)	1	No experimental data
Cell transformation	0.545	2 (2,3)	1	No experimental data
<i>Neurotoxicity</i>				
Pup behavior – Rat	0.157			NBBS is a neurotoxicant [see Other Data section] and <i>in utero</i> NBBS exposure produces developmental effects [see Reproductive and Toxicological Data section]. While direct evidence is not available, the literature suggests that NBBS would likely effect newborn rodent behavior.
Pup behavior – Rodent	0.0698			
<i>Reproductive Toxicity</i>				
Repro Mouse Male	0.487			NBBS is a female and male rat reproductive

Model	Positive Probability Prediction Value ¹	Model Features ²	Training Set Chemicals with $\geq 30\%$ Similarity	Literature Results
Repro Rat Male	0.3			toxicant [see Reproductive and Developmental Data section].
Repro Rodent Male	0.354			
Repro Rat Female	0.283			
Repro Rodent Female	0.314			

¹Values >0.5 were defined as positive by the Leadscope Analysis.

²Numbers in parentheses identify the NBBS structural features that were predicted to be positively associated with the evaluated toxicity or toxic endpoint; 1 = monosaturated benzene moiety, 2 = butane moiety, 3 = propane moiety, 4 = rotatable bonds, 5 = aryl-sulfonamide moiety, 6 = sulfonamide moiety, 7 = benzene moiety

Genetic Toxicity

The 29 genetic toxicity models in Leadscope encompass predictions for mutagenicity (13), DNA damage (3), *in vivo* clastogenicity (5), and *in vitro* clastogenicity (8). Sensitivity and specificity of the models range from 6.67% to 96% and 38.7% to 96.8%, respectively. NBBS was predicted as positive in two models, negative in 14 models, and not in domain in 13 models. The 2 positive models were for inducing sister chromatid exchange (SCE) in CHO cells (sensitivity: 87.7%, specificity: 42.4%) and SCE in other cells (sensitivity: 96%, specificity: 38.7%); the positive prediction probabilities were 0.594 and 0.91, respectively. For both models, there were four structural features present in NBBS that also were present in the prediction model and one chemical that was at least 30% structurally similar.

For the SCE in CHO cells model, the monosaturated benzene ring, unbranched aliphatic chain (butane, propane moieties), the presence of rotatable bonds were classified as positive features that contributed to the evaluated activity. The presence of a benzene ring and specific physical properties (e.g., polar surface area, presence of hydrogen bond donors and acceptors) were classified as features that negatively contributed to the activity.

For the SCE in other cells model, the sulfonamide moiety, propane moiety, the presence of rotatable bonds were classified as features that positively contributed to the evaluated activity. The presence of a benzene ring and specific physical properties (e.g., polar surface area, presence of hydrogen bond donors and acceptors) were classified as features that negatively contributed to the activity.

Neurotoxicity

The neurotoxicity models in Leadscope encompass predictions for newborn rat, rodent, and mouse behavior; sub-models represent optimized active/inactive chemicals. Sensitivity and specificity of the models range from 43.2% to 78.4% and 86.4% to 91.4%, respectively. NBBS was predicted as negative in two models (which were composed of two submodels each) and not in domain in one model. The negative models were for rodent pup behavior and rat pup behavior; the overall positive prediction probabilities were 0.0698 and 0.157, respectively. For all four sub-models, there were six to seven features that were present in the prediction model and one chemical that was at least 30% structurally similar.

Compared to the predicted results, previous experimental data have shown that NBBS is a neurotoxicant in rodent models [see Other Data section]. Additionally, *in utero* exposure to NBBS produces developmental effects on fetuses and pups [see Reproductive and Toxicological Data section]. While direct evidence is currently not available, the literature suggests that NBBS would likely have an effect in newborn rodent behavior.

Reproductive and Developmental Toxicity

The developmental toxicity models in Leadscope encompass predictions for structural dysmorphogenesis, visceral dysmorphogenesis, fetal survival, and fetal growth. The reproductive toxicity models encompass predictions for toxicity in male and female rats, mice, and rodents. Sub-models in the reproductive and developmental toxicity evaluations represent optimized active/inactive chemical ratios. Sensitivity and specificity of the reproductive models range from 36.3% to 63.8% and 83.9% to 96.5%, respectively. Sensitivity and specificity of the developmental toxicity models range from 22.1% to 57.4% and 84.4% to 95.3%. NBBS was classified as negative in all the evaluated models (26), except for one where it was defined as not in domain. The positive predictive probability values ranged from 0.0665 to 0.289 for the reproductive models and 0.283 to 0.487 in the developmental models.

In the reproductive male mouse model (concordance: 75.9%, sensitivity: 63.8%, specificity: 83.9%), where the positive predictive probability was 0.487, there were five features that were present in the prediction model and one chemical that was at least 30% structurally similar. Evaluation of the training set chemicals indicated that the most structurally similar chemical in the database was identified as saccharin (LS-1805-copy-1).

Compared to the predicted results, previous experimental data has shown that NBBS is a female and male rat reproductive toxicant. Exposure impaired reproductive performance, produced a significant decrease in absolute testis and epididymides weights, and produced histopathological alterations in both sexes [see Reproductive and Developmental Data section].

Carcinogenicity

NBBS was evaluated in two sets of carcinogenicity endpoint models; seven are rodent models based on the 2-year rodent bioassays and four are cell transformation *in vitro* assay models. The sensitivity and specificity of the rodent models range from 32.5% to 44.7% and 90.2% to 95.1%, respectively. The sensitivity and specificity of the *in vitro* models range from 87.8% to 93.9% and 22.5% to 55.8%.

NBBS was classified as negative in all of the *in vivo* rodent models; positive prediction values ranged from 0.187 to 0.283. Comparatively, NBBS was classified as positive in all of the *in vitro* models of cell transformation; positive prediction values ranged from 0.545 to 0.765. The *in vitro* models were identified as (1) cell transformation, (2) C3H10T1-2, (3) SHE, and (4) BALBc-3T3. For the first three models, there were two structural features present in NBBS that also were present in the prediction model and there was one chemical that was at least 30% structurally similar to NBBS present in the training set. For the BALBc-3T3 model, there were four structural features present in NBBS that also were present in the prediction model and there was one chemical that was at least 30% structurally similar to NBBS present in the training set.

For the BALBc-3T3, cell transformation, and SHE models, the presence of an aliphatic chain (propane and butane moieties encompassed by the chain) positively contributed to the carcinogenic activity. The presence of a propane moiety also positively contributed to the cell transformation activity in C3H10T1-2 cells while the butane moiety was negatively associated with toxicity. For all models, evaluation of the training set chemicals indicated that the most structurally similar chemical in the database was identified as saccharin (LS-1805-copy-1).

Human Adverse Effects

Adverse cardiological, hepatobiliary, and urinary tract effects were evaluated in 24 models.

Thirteen models predicted cardiac endpoints, including: conduction disorders, coronary artery disorders, myocardial infarct disorders, palpitations, and rate rhythm disorders. The sensitivity and specificity of the models range from 32.1% to 65.7% and 85.8% to 93.6%, respectively. NBBS was classified as negative in all the models; positive prediction values ranged from 0.0574 to 0.431.

Five models predicted hepatobiliary endpoints, including: bile duct, gall bladder, liver jaundice, liver acute damage, and liver enzyme release. The sensitivity and specificity of the models range from 23.9% to 51.7% and 91.4% to 97.9%, respectively. NBBS was classified as negative in one model (prediction probability = 0.171) and not in domain for four models.

Six models predicted urinary endpoints, including: bladder, blood in urine, kidney, kidney function tests, nephropathy and urolithiasis. The sensitivity and specificity of the models range from 34.5% to 55.8% and 89.2% to 96.5%, respectively. NBBS was classified as negative in four models and not in domain in two models; positive prediction values ranged from 0.235 to 0.333.

11.0 Online Databases and Secondary References Searched

11.1 Online Databases

National Library of Medicine Databases

PubMed

ChemIDplus – chemical information database that provides links to other databases such as CCRIS, DART, GENE-TOX, HSDB, IRIS, and TRI. A full list of databases and resources searched are available at <http://www.nlm.nih.gov/databases/>.

STN International Files

AGRICOLA	IPA
BIOSIS	MEDLINE
BIOTECHNO	PASCAL
CABA	Registry
EMBASE	TOXCENTER
ESBIOBASE	

Information on the content, sources, file data, and producer of each of the searched STN International Files is available at <http://www.cas.org/support/stngen/dbss/index.html>.

Government Printing Office
Code of Federal Regulations (CFR)

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None used

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- Benzenesulfonamide: <http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=7370>
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Appendix A: Units and Abbreviations

°C = degrees Celsius

µg/L = microgram(s) per liter

AlCl₃ = aluminum chloride

CAS = Chemical Abstracts Service

CCL3 = Contaminant Candidate List 3

CNC = coneurotoxicity coefficient

CSF = cerebrospinal fluid

EPA = Environmental Protection Agency

F = female(s)

g = gram(s)

GC = gas chromatography

GC-TOF MS = gas chromatography-time-of-flight mass spectrometry

GFAP = glial fibrillary acidic protein

i.c. = intracisternal(ly)

IC₅₀ = inhibitory concentration for 50% of samples

inh. = inhalation

i.p. = intraperitoneal(ly)

IUR = Inventory Update Reporting

i.v. = intravenous(ly)

lb = pound(s)

LC₅₀ = lethal concentration for 50% of test animals

LC_{LO} = lowest concentration low

LD₅₀ = lethal dose for 50% of test animals

M = male(s)

mg = milligram(s)

mg/kg = milligram(s) per kilogram

mg/m³ = milligram(s) per cubic meter

mL = milliliter(s)

mL/min = milliliter(s) per minute

mol. wt. = molecular weight

NBBS = *N*-butylbenzenesulfonamide

ng/g = nanogram(s) per gram

ng/L = nanogram(s) per liter

ng/mL = nanogram(s) per milliliter

NIOSH = National Institute for Occupational Safety and Health

n.p. = not provided

pg/L = pictogram(s) per liter

PMID = PubMed identification

ppb = parts per billion

TC_{LO} = lowest concentration to produce any toxic effect in test animals

TD_{LO} = lowest dose to produce any toxic effect in test animals

TSCA = Toxic Substances Control Act

U.S. = United States

v/v = volume to volume basis

Appendix B: Description of Search Strategy and Results

Preliminary searches of PubMed and the Internet (via Google) helped shape the search strategy. STN International Registry and RTECS searches were conducted on February 10, 2010, with CAS Registry Number 3622-84-2. Files MEDLINE, AGRICOLA, CABA, EMBASE, IPA, BIOSIS, TOXCENTER, FSTA, FROSTI, ESBIODBASE, and BIOTECHNO were searched simultaneously on February 11, 2010. The history of the online session is reproduced below.

```
FILE 'MEDLINE, AGRICOLA, CABA, IPA, BIOSIS, TOXCENTER, FSTA, FROSTI,
EMBASE, ESBIODBASE, BIOTECHNO' ENTERED AT 09:27:12 ON 11 FEB 2010

L1          0 S DUPORDER FILE
            SET DUPORDER FILE
L2          0 S (BENZENESULFONIC OR BENZENESULPHONIC)(W) ACID(W) BUTYL(W)
            AMIDE
L3          149 S 3622-84-2
L4          14 S BUTYL(W)BENZENE(W)(SULFONAMIDE OR SULPHONAMIDE)
L5          223 S UNIPLEX
L6          197 S BUTYLBENZENESULFONAMIDE OR BUTYLBENZENESULPHONAMIDE
L7          0 S BENZENE(W)(SULFONIC OR SULPHONIC)(W)ACID(W)BUTYL(W)AMIDE
L8          87 S BUTYL(2W)(BENZENESULFONAMIDE OR BENZENESULPHONAMIDE)
L9          127 S BUTYL(4A)(BENZENESULFONAMIDE OR BENZENESULPHONAMIDE)
L10         570 S L2-L9
L11         294 DUP REMOVE L10 (276 DUPLICATES REMOVED)
L12         294 SORT L11 1-294 TI
            SAVE L12 X0700BBSA/A
```

Of the 294 records saved, 93 (2 from CABA, 12 from BIOSIS, 77 from TOXCENTER, 2 from EMBASE) were retrieved and saved. Additional records were obtained from PubMed searches and through reference reviews.