NATIONAL TOXICOLOGY PROGRAM

EXECUTIVE SUMMARY OF SAFETY AND TOXICITY INFORMATION

BENZYLTRIMETHYLAMMONIUM CHLORIDE

CAS Number 56-93-9

October 4, 1991

Submitted to:

NATIONAL TOXICOLOGY PROGRAM

Submitted by:

Arthur D. Little, Inc.

Board of Scientific Counselors Draft Report

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OVERVIEW[1]

Nomination History: Benzyltrimethylammonium chloride (BTMAC) was nominated for toxicity and carcinogenicity testing by the National Institute of Environmental Health Sciences in 1987. This nomination was based on high production, worker exposure, and the lack of chronic toxicity data.

Chemical and Physical Properties: BTMAC, a quaternary ammonium compound, is an off-white to yellow powder.

This compound is also available commmercially as a 50-60% by weight aqueous solution. BTMAC has a melting range of 236.0-243.0°C (456.8-469.4°F) with decomposition. This chemical is soluble in water and ethanol. BTMAC is stable at temperatures up to 135°C. This compound is hygroscopic and incompatible with strong oxidizers.

Production/Uses/Exposure: BTMAC is used as a solvent for cellulose, a gel inhibitor in polyester resins, a chemical intermediate, a paint dispersant in the rubber industry, and as an acrylic dyeing assistant. The EPA TSCA inventory reported a production volume of 1,540,000-15,500,000 pounds of BTMAC by 10 manufacturers in 1983. The U.S. International Trade Commission reported a production volume of 4,132,000-3,985,000 pounds for the years 1986-1988, respectively. No production data were available on this compound from SRI's Chemical Economics Handbook. Data from the National Occupational Exposure Survey (NOES), conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983, indicate that 5001 workers, including 2721 female employees, were potentially exposed to BTMAC in the workplace. OSHA has not established a permissible exposure limit (PEL) for BTMAC. NIOSH and ACGIH have not recommended exposure limits for this compound.

Toxicological Effects:

Human: No data were found on the chemical disposition, acute, prechronic, chronic/carcinogenic, reproductive, or teratogenic effects of BTMAC in humans.

Animal: No data were found on the chemical disposition, prechronic, chronic/carcinogenic, reproductive, or teratogenic effects of BTMAC in animals. A rat LD_{50} of 250 mg/kg has been reported for this compound. In mice, the acute oral lethality of BTMAC was reported to be 100% at a concentration of 1600 mg/kg. BTMAC was found to have a muscarine-like (vasodepressor) activity in nonatropinized dogs and nicotine-like (vasopressor) activity in atropinized dogs. This chemical was found to be capable of inducing nicotinic and muscarinic activity in the cat superior ganglion and frog rectus abdominus. It was reported that BTMAC may act at the same ganglionic site as acetylcholine.

Genetic Toxicology: No data were found on the genotoxic effects of BTMAC in eukaryotic systems. BTMAC was found to be nonmutagenic in Salmonella typhimurium strains TA97, TA98, TA100, TA1535, and TA1537 in the presence and absence of metabolic activation.

Structure Activity Considerations: In a study investigating the correlation between lipophilicity or molecular weight, and pharmacokinetic parameters of 14 quaternary ammonium compounds including benzyltrimethylammonium, a correlation was observed between relative lipophilicity and the total plasma clearance, hepatic clearance, and intestinal clearance. However, no correlation was observed between the lipophilicity of the compounds and their elimination rates and renal clearance values.

It was reported that changes in the charge distribution on the aromatic ring as the length of the carbon chain increases may influence the vasopressor and depressor activity of phenylalkyltrimethylammonium compounds. In a study carried out to investigate the nicotinic and muscarinic activity of BTMAC and its alpha-, beta-, and delta-substituted pyridylmethyl-trimethylammonium analogs, a similarity in the muscarinic activity, but not the nicotinic activity, of these compounds was observed.

Quaternary ammonium compounds have been reported to be structurally analogous to decamethonium (a recognized muscular blocking agent) and hexamethonium (an established ganglionic blocking agent).

The quaternary ammonium compound (2-chloroethyl)-trimethylammonium chloride was not carcinogenic to mice or rats following oral (dosed feed) administration.

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[1] The information contained in this executive summary of safety and toxicity information is based on data from current published literature. The summary represents information provided in selected sources and is not claimed to be exhaustive.

I. NOMINATION HISTORY AND REVIEW

1. Nomination History

    1. Source: National Institute of Environmental Health Sciences (NIEHS) [NTP, 1989; NIEHS, 1987]

    2. Date: December, 1987

    3. Recommendations:
        - Toxicity
        - Carcinogenicity

    4. Priority: --

    5. Rationale/Remarks:
        - High production volume
        - Worker exposure
        - Lack of chronic toxicity data
        - Originally nominated by NIOSH for Salmonella testing

2. Chemical Evaluation Committee Review

    1. Date of Review: August 8, 1991

    2. Recommendation:
        - Toxicity (including neurotoxicity)
        - Carcinogenicity
        - Teratogenicity

    3. Priority: Moderate

    4. NTP Chemical Selection Principles: 3, 8

    5. Rationale/Remarks:
        - High production
        - Potential for exposure
        - Lack of toxicity data
        - Structural interest in quaternary ammonium compounds

3. Board of Scientific Counselors Review

    1. Date of Review:

    2. Recommendations:

    3. Priority:

    4. Rationale/Remarks:

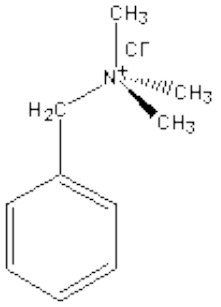
4. Executive Committee Review

    1. Date of Review:

    2. Decision:

II. CHEMICAL AND PHYSICAL DATA

1. Chemical Identifiers



BENZYLTRIMETHYLAMMONIUM CHLORIDE

Molecular formula: $C_{10}H_{16}NCl$ **Molecular weight:** 185.70

CAS No. 56-93-9

RTECS No. B08400000

2. Synonyms and Trade Names

Synonyms: benzenemethanaminium, N,N,N-trimethyl-, chloride (9CI); ammonium, benzyltrimethyl-, chloride (8CI); BTM; trimethylbenzylammonium chloride; N,N,N,-trimethyl-benzenemethanaminium chloride; BTMAC; TMBAC

Trade Names: No data were found

3. Chemical and Physical Properties

Description: Off-white to yellow powder [Lenga, 1988].

Melting Point: 236.0-239.0°C (456.8-462.2°F) [Karsai et al., 1986];
239.0°C (462.2°F) {decomposes} [Aldrich, 1990; Lenga, 1988];
241.0-243.0°C (465.8-469.4°F) {decomposes} [Hume and Holland, 1965];
243.0°C (469.4°F) [Weast, 1989].

Boiling Point: No data were found.

Specific Gravity: No data were found.

Refractive Index: No data were found.

Solubility in Water: Soluble in water [Sax and Lewis, 1987; Weast, 1989].

Solubility in other Solvents: Soluble in ethanol, and butanol; slightly soluble in butyl phthalate and tributyl phosphate [Sax and Lewis, 1987].

Log Octanol/Water Partition Coefficient: No data were found.

Reactive Chemical Hazards: Stable up to 135°C, above which benzyl chloride and trimethylamine are formed [Sax and Lewis, 1987]. Both solid and liquid forms are incompatible with strong oxidizers. Upon decomposition, both forms emit toxic fumes of carbon monoxide, carbon dioxide [Lenga, 1988], nitrogen oxides, hydrochloride gas [Lenga, 1988; Sax and Lewis, 1989] and ammonia [Sax and Lewis, 1989]; hygroscopic [Lenga, 1988; Aldrich, 1990].

Flammability Hazards: No data were found.

III. PRODUCTION/USE

1. Production

    1. Manufacturing Process

Benzyltrimethylammonium chloride is prepared by heating, to boiling, benzyl chloride and trimethyl amine in absolute ethanol. In addition, a reaction involving benzyl dimethyl amine and methyl chloride with or without solvent may also be used to manufacture this compound [Karsai et al., 1986]. In a study conducted by Hume and Holland, benzyltrimethylammonium chloride was prepared by dissolving phenylmethyl chloride in ether and adding an excess of trimethylamine (25% in methanol). The product was collected and recrystallized from alcohol and ether [Hume and Holland, 1965].

2. Producers and Importers

Producers	**Reference**
U.S. Producers:	
Aldrich Chemical Company, Incorporated Milwaukee, Wisconsin	USEPA, 1990; Chemical Week Buyers' Guide, 1990; OPD, 1990
ARS Chemical Corporation Providence, Rhode Island	USEPA, 1990
Ashland Chemical Company Janesville, Wisconsin	USEPA, 1990; OPD, 1990
Brin-Mont Chemicals, Incorporated Greensboro, North Caroline	USEPA, 1990
Chemos Corporation Newark, New Jersey	USITC, 1989
C.H. Patrick & Company, Incorporated Greenville, South Carolina	USEPA, 1990
Hexcel Corporation Specialty Chemicals Division Zeeland, Michigan	USEPA, 1990; USITC, 1987
High Point Chemical Corporation High Point, North Carolina	USEPA, 1990; USITC, 1989
Janssen Chimica, Beerse Belgium Spectrum Chemical MFG Corporation, Gardena, California	Chemical Week Buyers' Guide, 1990; OPD, 1990
Lindau Chemicals Incorporated Columbia, South Carolina	USEPA, 1990; Chemical Week Buyers' Guide, 1990; OPD, 1990
Miles Laboratories, Incorporated Sumner Division Zeeland, Michigan	USEPA, 1990
Piedmont Chemical Industries, Incorporated High Point, North Carolina	USEPA, 1990; Chemical Week Buyers' Guide, 1990; USITC, 1989; OPD, 1990
Proctor Chemical Company, Incorporated Salisbury, North Carolina	USEPA, 1990
R.S.A. Corporation Arsley, New York	USEPA, 1990; Chemical Week Buyers' Guide, 1990; USITC, 1989; OPD, 1990
Sherex Chemical Company, Incorporated Dublin, Ohio	Chemical Week Buyers' Guide, 1990; USITC, 1989
Southern U.S. Chemical Company Rock Hill, South Carolina	USEPA, 1990
Southwestern Analytical Chemicals, Incorporated Austin, Texas	USEPA, 1990
Sybron Chemicals Incorporated Wellford, South Carolina Birmingham, New Jersey	USEPA, 1990; SRI, 1990a; Chemical Week Buyers' Guide, 1990 USITC, 1989; OPD, 1990
Unitex Chemical Corporation Greensboro, North Carolina	USEPA, 1990; SRI, 1990a; USITC, 1989
U.S. Oil Company East Providence, Rhode Island	USEPA, 1990
Yorkshire Nachem, Incorporated Braintree, MA	OPD, 1990

European Producers	
Chemische Fabriek Zaltbommel "CFZ" BV Zaltbommel, (Gelderland), The Netherlands	SRI, 1990b
Pentagon Chemicals Limited Workington, (Cumbria), United Kingdom	SRI, 1990b
Importers:	
Carroll Products, Inc. Wood River Junction, Rhode Island	USEPA, 1990

3. Volume

   The production volume of benzyltrimethylammonium chloride is reported in the public file of the EPA TSCA Inventory. In 1983, 16 companies were listed as manufacturers of this compound. Ten of the manufacturers reported a total production volume ranging from 1,540,000 to 15,500,000 pounds. Five manufacturers did not report production volumes, and one reported no production of benzyltrimethylammonium chloride. No data on import volume were provided in the TSCA Inventory [USEPA, 1990].

   The U.S. International Trade Commission reported an annual production volume for benzyltrimethylammonium chloride of 4,132,000-3,985,000 pounds for the years 1986-1988, respectively [USITC, 1986-1989].

   No production data were available from SRI's Chemical Economics Handbook [SRI, 1991].

4. Technical Product Composition

   Benzyltrimethylammonium chloride is available as a 50-60% [Aldrich, 1990; U.S. Coast Guard, 1985] and 60-62% [Sax and Lewis, 1987] by weight aqueous solution. In addition, this compound is supplied as a solid at a purity of 97-98% [Aldrich, 1990; Chemical Marketing Reporter, 1983].

2. Use

   Solvent for cellulose [Sax and Lewis, 1987]

   Gelling inhibitor in polyester resins [Sax and Lewis, 1987]

   Chemical intermediate [Sax and Lewis, 1987]

   Paint dispersant for the rubber industry [Chemical Marketing Reporter, 1983]

   Acrylic dyeing assistant used extensively in the textile industry [Moore et al., 1987]

   Patented for use in plant growth regulation compositions and processes for regulating plant growth [Karsai et al., 1986]

IV. EXPOSURE/REGULATORY STATUS

1. Consumer Exposure

   No data were found on consumer exposure to benzyltrimethylammonium chloride.

2. Occupational Exposure

   Data from the National Occupational Exposure Survey (NOES), conducted by the National Institute for Occupational Safety and Health (NIOSH) during the years 1981 to 1983, estimated that 5001 workers, including 2721 female employees, were potentially exposed to benzyltrimethylammonium chloride. The NOES database does not contain information on the frequency, level or duration of exposure to workers of any chemicals listed therein [NIOSH, 1990].

Occupational exposure may result from the use of this compound in the chemical [Sax and Lewis, 1987], rubber [Chemical Marketing Reporter, 1983] and textile industries [Moore et al., 1987].

3. Environmental Occurrence

   No data were found on environmental occurrence of benzyltrimethylammonium chloride.

4. Regulatory Status

   OSHA has not established a permissible exposure limit (PEL) for benzyltrimethylammonium chloride.

5. Exposure Recommendations

   ACGIH has not recommended a threshold limit value (TLV) for benzyltrimethylammonium chloride.

   NIOSH has not recommended an exposure limit (REL) for benzyltrimethylammonium chloride.

V. TOXICOLOGICAL EFFECTS

A. Chemical Disposition

   1. Human Data

      No data were found on the chemical disposition of benzyltrimethylammonium chloride in humans.

   2. Animal Data

      No data were found on the chemical disposition of benzyltrimethylammonium chloride in animals.

B. Acute

   1. Human Data

      No data were found on the acute toxicity of benzyltrimethylammonium chloride in humans.

   2. Animal Data

      oral, rat An acute oral LD_{50} of 250 mg/kg has been reported for rats of unspecified strain [Dewitt et al., 1953]. No other data were provided.

      oral, mice The acute oral lethality of benzyltrimethylammonium chloride in an unspecified number of TAC:SWfBr male mice was reported to be 100% at 1600 mg/kg. In this study, benzyltrimethylammonium chloride was administered orally as a 2% concentration suspended in 0.5% methylcellulose [Ellis et al., 1980]. No other data were reported.

      aquatic, water flea A 48-hour LC_{50} for benzyltrimethylammonium chloride in water fleas (Daphnia pulex) was determined to be 11.94 ppm in an aquatic static bioassay [Moore et al., 1987].

C. Prechronic

   1. Human Data

      No data were found on the prechronic effects of benzyltrimethylammonium chloride in humans.

   2. Animal Data

      No data were found on the prechronic effects of benzyltrimethylammonium chloride in animals.

D. Chronic/Carcinogenicity

1. Human Data

No data were found on the chronic/carcinogenic effects of benzyltrimethylammonium chloride in humans.

2. Animal Data

No data were found on the chronic/carcinogenic effects of benzyltrimethylammonium chloride in animals.

E. Reproductive Effects and Teratogenicity

1. Human Data

No data were found on the reproductive and teratogenic effects of benzyltrimethylammonium chloride in humans.

2. Animal Data

No data were found on the reproductive and teratogenic effects of benzyltrimethylammonium chloride in animals.

F. Genetic Toxicology

1. Prokaryotic Data

Salmonella typhimurium Benzyltrimethylammonium chloride was tested in a preincubation modification of the Salmonella/microsome assay in the absence of metabolic activation and in the presence of liver S-9 from Arochlor-induced male Sprague-Dawley rats and Syrian hamsters. The assay was conducted in Salmonella strains TA97, TA98, TA100, TA1535, and TA1537 at doses of benzyltrimethylammonium chloride ranging from 0.0 (solvent control {water}) to 10,000 mg/plate. Benzyltrimethylammonium chloride was found to be nonmutagenic in all strains tested at all concentrations [Zeiger et al., 1988].

2. Eukaryotic Data

No data were found on the genotoxic effects of benzyltrimethylammonium chloride in eukaryotic systems.

G. Other Toxicological Effects

1. Immunotoxicity

No data were found on the immunotoxic effects of benzyltrimethylammonium chloride in animals or humans.

2. Neurotoxicity

intravenous, rat The gastrocnemius muscle twitch response of quaternary ammonium salts, including benzyltrimethylammonium chloride, was evaluated in TAC:SD/NfBr rats of unspecified sex and number. In this study, an intravenous injection of 25 mg/kg of benzyltrimethylammonium chloride dissolved in tetrahydrofurfuryl alcohol induced a gastrocnemius muscle twitch response of +10.1 ± 1.5 (maximum % change). The authors reported that because benzyltrimethylammonium chloride induced cholinergic effects, it was not evaluated further in this study, as only compounds without cholinergic properties were investigated [Ellis et al., 1980]. No other data were provided.

cannulated right femoral vein, dogs The vasopressor and depressor activities of phenylalkyl-

trimethylammonium compounds, including benzyltrimethylammonium chloride, were investigated using mongrel dogs (n=11) of both sexes. The animals were anesthetized and benzyltrimethylammonium chloride dissolved in physiological saline was injected into the cannulated right femoral vein of nonatropinized dogs at a concentration of 40 mg/kg. In addition, benzyltrimethylammonium chloride was administered at concentrations of 40 mg/kg and 400 mg/kg following the intravenous administration of 0.5 mg/kg atropine sulfate.

When administered to nonatropinized animals at a concentration of 40 mg/kg, benzyltrimethylammonium chloride was found to exhibit vasodepressor (i.e., muscarine-like) activity based on the decreased blood pressure observed. A ten-fold increase in the dose (400 mg/kg) was found to induce a vasopressor (i.e., nicotine-like) response in atropinized animals as determined by the increased blood pressure observed. However, a vasopressor response was not induced when benzyltrimethylammonium chloride was administered to atropinized animals at a concentration of 4 mg/kg. The vasopressor activity of benzyltrimethylammonium chloride on a molar basis relative to the other phenylalkyltrimethylammonium compounds tested was found to be 1.0 [Hume and Holland, 1965]. The specific blood pressure changes observed in this study were not reported.

external carotid artery, cat; intravenous, cat; in vitro, frog rectus abdominous The nicotinic and muscarinic activities of benzyltrimethylammonium chloride and its alpha-, beta-, and gamma-substituted pyridylmethyltrimethylammonium analogs (See section VI, Structure Activity Relationships) on the cat (unspecified strain) superior cervical ganglion were studied by Hamilton and Rubinstein, 1967. (Preliminary, nonquantitative studies were also conducted, the descriptions/results of which have not been included in this summary.) The effects of these compounds on ganglion stimulation were compared to those of nicotine, acetylcholine (a known cholinergic agonist having both nicotinic and muscarinic receptors), and pilocarpine (exhibits muscarine-like activity). In the first part of the study, nicotine-like activity was assessed in the presence of atropine, and muscarine-like activity was determined during nicotine administration. Benzyltrimethylammonium chloride and the other compounds studied were dissolved in 0.9% saline and administered in a constant volume of 0.1 ml retrogradely into the external carotid artery, with the lingual artery tied off, in the absence of antagonist (16 animals), during intravenous nicotine (1.2 mg/kg) infusion (4 animals), and after 2 mg/kg intravenous adminstration with atropine (3 animals). Contractures of the nictitating membrane resulting from drug or preganglionic nerve stimulation were recorded semi-isometrically using a force-displacement transducer. At the beginning of each experiment, an initial tension of 5 grams was applied to the membrane, and the preganglionic nerve was then stimulated maximally in order to adjust the sensitivity of the preamplifier to record, on scale, the maximal contracture. The authors stated that in some [unspecified] experiments, preganglionic electrical stimulation was employed periodically in order to determine the maximal possible response and to indicate possible blockade. In other [unspecified] experiments, a single 10-second burst of stimulation (25 shocks/sec) was given at the beginning and end of testing. In experiments with atropine, the contractural response was expressed as a percentage of the maximal response to preganglionic nerve stimulation at supramaximal voltage (0.7-msec duration and 25 shocks/sec). In studies with nicotine, the response was measured as deflection of the pen (in mm) over the linear part of the tracing, because the maximal tracing obtained was only about 50% of the normal contracture due to preganglionic nerve stimulation. The equipotent molar ratios (EPMR) were determined for the three test conditions using acetylcholine as the standard for comparison.

The muscarinic activity of the test compounds was also studied by determining the ability of the compound to induce salivation from the decentralized submaxillary glands of 7 cats. For this procedure, a saline-filled cannula was inserted into the submaxillary duct and the effluent was directed so as to displace saline over a drop-recorder. Displaced saline which touched the contacts closed an electrical circuit and was recorded as a vertical stroke on the recording paper. The chorda tympani was sectioned and benzyltrimethylammonium chloride (in saline) and the other test compounds were administered at a volume of 0.5-1.0 ml via a cannula in the femoral vein of each cat. The response measured was the total number of drops of saline displaced after each dose. Again, EPMR values were determined using acetylcholine as the standard.

To further examine the acetylcholine-like agonist activity of benzyltrimethylammonium chloride and

the other test compounds, the rectus abdominous muscle was excised from 4 pithed frogs and mounted in an organ bath. The compounds were prepared in appropriate concentrations by diluting 0.01 M stock solutions with aerated Clark's modified ringer's solution. The test employed a 4-minute cycle of dosing consisting of 90 seconds of test compound contact, 90 seconds of stretching, and a 1-minute baseline recording. EPMRs were determined relative to acetylcholine to evaluate the contracture of the abdominous muscle.

The EPMRs for benzyltrimethylammonium chloride relative to acetylcholine following its administration via the external carotid artery of the cat (with the lingual artery tied off) in the absence of antagonist, during nicotine administration, and following atropine injection are presented in Table 1. (Nicotine and pilocarpine have also been included for comparison.)

Table 1. Contracture of the Nictitating Membrane Following Administration Via the External Carotid Artery of the Cat

	EPMR Values[a]		
	Administration conditions		
Compound	No Antagonist	After Atropine[b]	During Nictoine[c]
Acetylcholine	1.00	1.00	1.00
Nicotine	0.05± 0.008	0.03 ±0.005	no response
Pilocarpine	2.33 ±0.312	no response	0.05 ±0.077
Benzyltrimethyl ammonium chloride	0.25± 0.036	0.45± 0.078	0.17 ±'0.033

[a] Equipotent molar ratio with acetylcholine as the standard

[b] Atropine used assess nicotinic activity

[c] Nicotine used to assess muscarinic activity

The above results suggest that benzyltrimethylammonium chloride can stimulate both nicotinic and muscarinic acetylcholine receptors in the ganglion. In the absence of antagonist, benzyltrimethylammonium chloride was more active than acetylcholine and less active than nicotine. Following the addition of atropine, the EPMR of benzyltrimethylammonium chloride decreased significantly (P=0.05) while this value increased in the presence of nicotine (P=0.05).

Results concerning the contracture of the frog rectus abdominous in vitro and the salivary response of the acutely decentralized submaxillary gland of the cat in vivo as determined by the EPMR values are presented below. (Nicotine and pilocarpine have also been included for comparison.)

Table 2. Contracture of Frog Rectus Abdominus and Salivary Response of Decentralized Submaxillary Gland of the Cat

	EPMR Values [a]	
Compound	Frog Rectus	Cat Salivation
Acetylcholine	1.00	1.00
Nicotine	1.28 ± 0.459	1.03 ± 0.204
Pilocarpine	8.55 ± 3.840 x 104	0.15 ± 0.043
Benzyltimethyl-ammonium chloride	24.70 ± 2.897	0.74 ± 0.138

[a] Equipotent molar ratio with acetylcholine as the standard

Benzyltrimethylammonium chloride was found to be a more active agonist than acetylcholine in the isolated frog rectus. The authors report that the nicotine-like activity of benzyltrimethylammonium

chloride on the frog rectus paralleled that of the cat ganglion after atropine administration. The authors further stated that despite the limitations of the use of saliva induction as an indicator of muscarinic activity, and if the values obtained in this investigation are considered to reflect the stimulation of atropine-sensitive muscarinic receptors, then there is a remarkable similarity in the activity of pilocarpine, acetylcholine, and benzyltrimethylammonium chloride.

It was concluded that benzyltrimethylammonium chloride is capable of stimulating both nicotinic and muscarinic receptors. The authors report that it is extremely likely that this cholinergic compound acts at the same ganglionic site as acetylcholine [Hamilton and Rubinstein, 1967].

3. Biochemical Toxicology

in vitro, human sickle hemoglobin Tetrasubstituted ammonium salts including benzyltrimethylammonium chloride were investigated for their effects on the solubility of human deoxygenated sickle hemoglobin. Gelled samples consisting of benzyltrimethylammonium chloride and deoxygenated sickle hemoglobin at a total volume of 240 ml were centrifuged for 1 hour at 30°C. The antigelling potency of the test compound was determined from the slope of the solubility profile (concentration of sickle hemoglobin versus concentration of additive), which is directly proportional to molar effectiveness in inhibiting gelation. The slope for benzyltrimethylammonium chloride was found to be 48 g/dlM, indicating that this compound is a moderately effective inhibitor of gelation [Mazhani et al., 1984].

VI. STRUCTURE ACTIVITY RELATIONSHIPS

Although the toxicity of aryl/alkyl quaternary ammonium compounds is not well established, several human fatalities resulting from overexposure to these compounds have been reported. All common aryl/alkyl quaternary ammonium derivatives reportedly may produce similar toxic reactions. In reviewing 10 human fatalities in which this type of quaternary ammonium compound was implicated, it was found that the nature of the human toxic response varied widely with the specific dose and concentration of the compound, as well as with the route of administration and survival time of the victim. For example, intravenous, intramuscular, or intrauterine administration of 5-15 mg/kg of body weight of quaternary ammonium compounds having alkyl groups ranging from 15-18 carbons caused death in 5 patients. Three of these patients receiving one of the compounds (Zephirol® {benzalkonium chloride}) suffered complete cardiovascular collapse. The same compound administered orally at 100 to 400 mg/kg caused death in 5 patients within three hours. A common symptom observed in these cases was curariform paralysis. Intramuscular injection reportedly resulted in liver and kidney necrosis. Detailed clinical descriptions of each poisoning by the respective aryl/alkyl quaternary ammonium compound were not available. It has been also been reported that concentrated aqueous solutions (10-20%) of these quaternary ammonium compounds commonly produce superficial necrosis of mucous membranes with which they come in contact [Gosselin et al., 1984].

The correlation between lipophilicity, or molecular weight, and certain pharmacokinetic parameters has been determined for a series of structurally related quaternary cations including benzyltrimethylammonium. The structure-pharmacokinetic relations were fitted using a computer program (NONLIN) and were represented by linear, parabolic, or S-shaped curves. In this study, a positive correlation was observed between relative lipophilicity and the total plasma clearance, hepatic clearance, and intestinal clearance of the compounds. However, no correlation was observed between the lipophilicity of the compounds and their elimination rates and renal clearance values. The only structural requirement for the occurrence of renal secretion of these compounds appeared to be the positive charge. The authors also concluded that in addition to ring structure, aliphatic groups rendering the compound sufficiently lipophilic will tend to increase the extent of biliary excretion. They also reported that the intrinsic clearance values determined in this study indicate that membrane transport in the liver and intestine, but not in the kidneys, will tend to increase with the lipophilicity of the organic cation [Neef and Meijer, 1984].

In a study described in section VG.2, the vasopressor and depressor activities of 4 phenylalkyltrimethylammonium compounds were investigated in mongrel dogs. Phenyltrimethylammonium iodide (see figure 1, below) and benzyltrimethylammonium chloride were found to be depressors, having

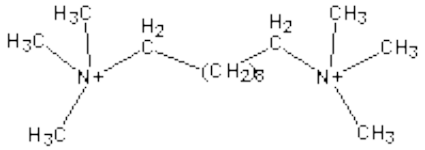
muscarinic-like activity. 2-Phenylethyltrimethylammonium iodide and 3-phenylpropyltrimethylammonium bromide (see figure 1, below) were found to have nicotinic-like activity (vasopressor). The authors suggest that this difference may result from the changes in the charge distribution on the aromatic ring as the length of the carbon chain increases [Hume and Holland, 1965].

In a study described in section VG.2 in which the nicotinic and muscarinic activities of benzyltrimethylammonium chloride and its alpha-, beta-, and delta-substituted pyridylmethyltrimethylammonium analogs (see figure 1, below) were assessed, a similarity in the muscarinic activity of the 3 pyridyl compounds and benzyltrimethylammonium chloride was observed. However, a marked difference in nicotinic activity of these compounds was noted. The authors state that these results suggest that, in molecules having a six-membered ring with a methyltrimethylammonium attached, there is no profound variation in muscarinic activity or parasympathomimetic activity when the position of attachment of the methyltrimethylammonium to the ring is altered. In fact, it has been suggested that compounds with a "methylene neck" might be expected to have distinct muscarinic activity. Also, it is believed that muscarinic activity is inherent in molecules that have no more than the equivalent of five large atoms attached to the cationic head [Hamilton and Rubinstein, 1967].

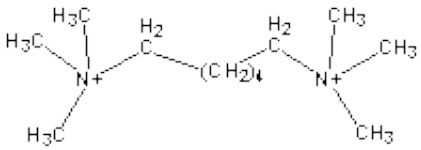
Quaternary ammonium compounds have been reported to be structurally analogous to decamethonium (a recognized muscular blocking agent) and hexamethonium (an established ganglionic blocking agent) (see figure 1, below) [Gosselin et al., 1984].

The NCI/NTP tested the quaternary ammonium compound, (2-chloroethyl)trimethylammonium chloride, for possible carcinogenicity by administering the chemical in feed to male and female F344 rats and male and female B6C3F1 mice for 108 and 102 weeks, respectively. Groups of 50 rats were administered wither 1,500 or 3,000 ppm, and groups of 50 mice were administered 500 or 2,000 ppm for the duration of the study. No tumors occurred in the rats or mice of either sex at incidences that could be associated with the administration of the test chemical. The study concluded that under the conditions of this bioassay, (2-chloroethyl)-trimethylammonium chloride was not carcinogenic for F344 rats or B6C3F1 mice [NCI, 1979].

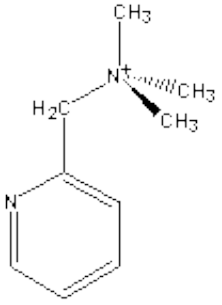
Figure 1:



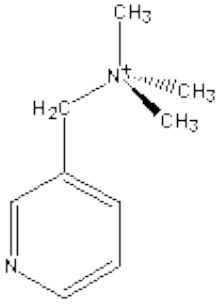
Decamethonium



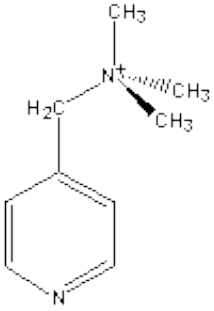
Hexamethonium



Alpha-pyridylmethyl-trimethylammonium



Beta-pyridylmethyl-trimethylammonium



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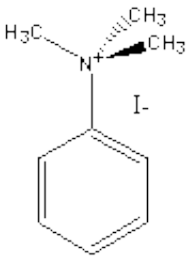
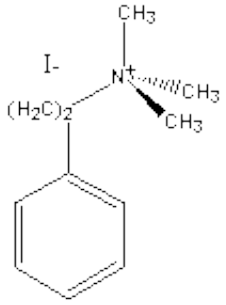
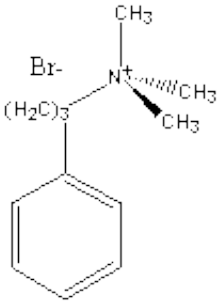


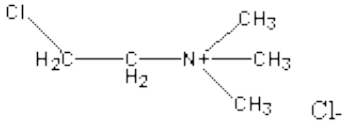
Phenyltrimethyl-ammonium iodide



2-phenylethyltrimethyl-ammonium iodide



3-phenylpropyltrimethyl-ammonium bromide



(2-chloroethyl) trimethyl-ammonium chloride

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APPENDIX I. ON-LINE DATABASES SEARCHED

	DATE OF SEARCH	TIME PERIOD
BRS:		
HZDB	December, 1990	
DIALOG:		
Agricola	December, 1990	1970-1990
Agris International	December, 1990	1974-1990
Aquatic Sciences Abstracts	December, 1990	1974-1990
Biosis Previews	December, 1990	1969-1990
CAB Abstracts	December, 1990	1972-1990
Cancerlit	December, 1990	1963-1990
Compendex Plus	December, 1990	1970-1990
CRIS USDA	December, 1990	
Embase	December, 1990	1974-1990
Enviroline	December, 1990	1970-1990
Environmental Bibliography	December, 1990	1974-1990
Energy Sci & Technology	December, 1990	1983-1990

Federal Register	December, 1990	1977-1990
Foods Adlibra	December, 1990	1974-1990
FSTA	December, 1990	1969-1990
Life Sciences Collection	December, 1990	1978-1990
Medline	December, 1990	1966-1990
NTIS	December, 1990	1964-1990
Occupational Safety and Health	December, 1990	1973-1990
PTS Newsletter	December, 1990	1987-1990
PTS Prompt	December, 1990	1972-1990
Pollution Abstracts	December, 1990	1970-1990
Trade and Industry ASAP	December, 1990	1983-1990
MEAD:		
Nexis/Lexis-BNA ENV	November, 1990	
NLM:		
Chemline	December, 1990	
HSDB	December, 1990	
RTECS	December, 1990	
Toxline 65	December, 1990	1965-1980
Toxline	December, 1990	1981-1980
Toxlit	December, 1990	1981-1990
Toxlit 65	December, 1990	1965-1980
STN:		
CA	December, 1990	1967-1990
Chemlist	December, 1990	

APPENDIX II. SAFETY INFORMATION

HANDLING AND STORAGE

Benzyltrimethylammonium chloride is hygroscopic and should be stored in a tightly closed container in a cool, dry place. [Aldrich, 1990]. This compound is stable at temperatures up to 135°C. Above this temperature, benzyl chloride and trimethylamine are formed [Sax and Lewis, 1987]. This compound is a corrosive and reacts with oxidizing agents [Lenga, 1988].

EMERGENCY FIRST AID PROCEDURES

Eye: First check the victim for contact lenses and remove if present. Flush victim's eyes with water or normal saline solution for 20 to 30 minutes while simultaneously calling a hospital or poison control center. Do not put any ointments, oils, or medication in the victim's eyes without specific instructions from a physician. Immediately transport the victim to a hospital even if no symptoms (such as redness or irritation) develop.

Skin: IMMEDIATELY flood affected skin with water while removing and isolating all contaminated clothing. Gently was affected skin areas thoroughly with soap and water. If symptoms such as inflammation or irritation develop, IMMEDIATELY call a physician or go to a hospital for treatment.

Inhalation: IMMEDIATELY leave the contaminated area and take deep breaths of fresh air. If symptoms (such as wheezing, coughing, shortness of breath, or burning in the mouth, throat, or chest) develop, call a physician and be prepared to transport the victim to a hospital.

Provide proper respiratory protection to rescuers entering an unknown atmosphere. Whenever possible, Self-Contained Breathing Apparatus (SCBA) should be used.

Ingestion: DO NOT INDUCE VOMITING. Corrosive chemicals will destroy the membranes of the mouth, throat and esophagus and, in addition, have a high risk of being aspirated into the victim's lungs during vomiting which increases the medical problems.

If the victim is conscious and not convulsing, give 1 or 2 glasses of water to dilute the chemical and IMMEDIATELY call a hospital or poison control center. Be prepared to transport the victim to a hospital if advised by a physician.

If the victim is convulsing or unconscious, do not give anything by mouth, ensure that the victim's airway is open and lay the victim on his/her side with the head lower than the body. DO NOT INDUCE VOMITING. IMMEDIATELY TRANSPORT THE VICTIM TO A HOSPITAL.

PROTECTIVE EQUIPMENT

Eye:	Safety goggles.
Gloves:	Two pairs of dissimilar protective gloves shall be worn when handling the neat chemical, otherwise one pair. When contact with this chemical has been known to occur, change gloves immediately.
Clothing:	Minimally, a disposable laboratory suit (e.g. Tyvek ®) shall be worn, as specified in the most current NTP Statement of Work or the NTP Health and Safety Minimum Requirements.
Respiratory Protection:	A NIOSH-approved chemical cartridge respirator with an organic vapor and high-efficiency particulate filter cartridge shall be used when handling the powder form of this chemical. When handling the liquid, a NIOSH-approved chemical cartridge respirator with an organic vapor cartridge shall be used.

EXTINGUISHANT

Dry chemical, carbon dioxide or halon extinguisher

MONITORING PROCEDURES

There is no NIOSH analytical method reported in the NIOSH Manual of Analytical Methods for benzyltrimethylammonium chloride.

SPILLS AND LEAKAGE

Persons not wearing the appropriate protective equipment and clothing shall be restricted from areas of spills until cleanup has been completed. When exposure to unknown concentrations may occur, air-purifying respirators may not be used. Chemical cartridge respirators with organic vapor cartridges may not be used when airborne concentrations exceed 1000 ppm.

If benzyltrimethylammonium chloride is spilled the following steps shall be taken:

1. In order to prevent dust formation, use moistened paper towels to clean up a solid spill. Avoid dry sweeping.

2. If a liquid solution is spilled, use vermiculite, sodium bicarbonate, sand, or paper towels to contain and absorb the spill.

3. Clean the spill area with dilute alcohol (approximately 60-70%) followed by a strong soap and warm water washing.

4. Dispose of all absorbed material as hazardous waste.

DECONTAMINATION OF LABORATORY EQUIPMENT

TDMS Terminal:	Whenever feasible, a protective covering (e.g.,plastic wrap) shall be placed over the keyboard when in use.
General Equipment:	Before removing general laboratory equipment (i.e., lab carts, portable hoods and balances) from animal dosing rooms and/or chemical preparation areas, a decontamination process shall be conducted in addition to routine housekeeping procedures.

WASTE MANAGEMENT AND DISPOSAL PROCEDURES

Waste Management:	If an inhalation study is to be conducted, all exhaust air from the inhalation chamber must be cleaned with appropriate air cleaning devices unless the laboratory has informed local and state air pollution regulatory agencies of both the laboratory's operating practices and the potential hazards of the chemicals in use. Compliance with all federal, state and local air pollution laws and regulations is required. A specific air cleaning system design must consider the specific conditions of the laboratory (eg., air flow rates and volumes, mixing of exhaust streams, size of inhalation chamber, etc.) and the dosing regimen selected. Air cleaning systems designs must be described by the laboratory and approved by the NTP Office of Laboratory Health and Safety.
Waste Disposal:	Securely package and label, in double bags, all waste material. All potentially contaminated material (i.e., carcasses, bedding, disposable cages, labware) shall be disposed of by incineration in a manner consistent with federal (EPA), state, and local regulations or disposed of in a licensed hazardous waste landfill.