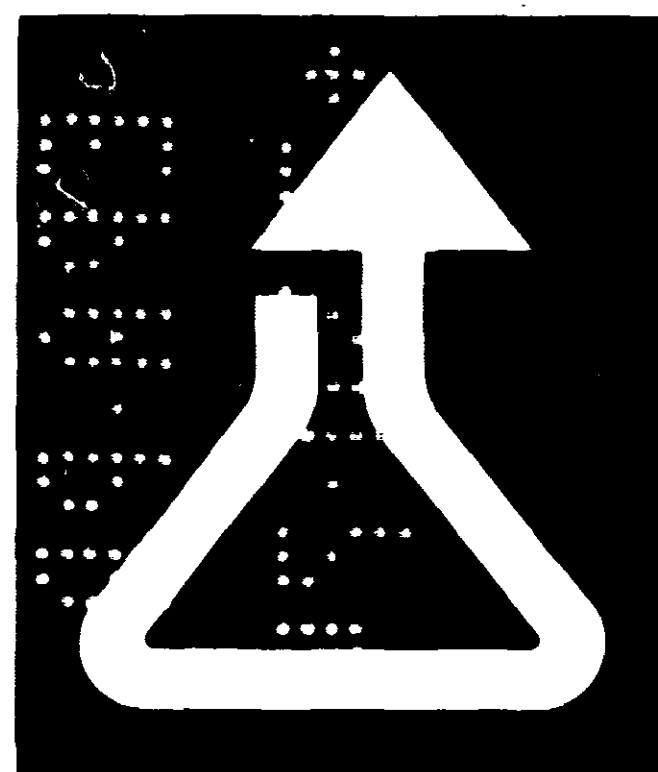


BENZETHONIUM CHLORIDE NF GERMICIDE CONCENTRATE



**ROHM
AND
HAAS**

PHILADELPHIA, PA. 19105

DANGER

KEEP OUT OF REACH OF CHILDREN

See First Aid and Other Precautions on Side Panel.

ACTIVE INGREDIENT:

Diisobutylphenoxyethoxyethyl dimethyl benzyl ammonium
chloride, monohydrate 98.8%

INERT INGREDIENTS 1.2%

EPA Reg. No. 707-116-AA 100.0%

EPA Est. No. 707-PA-1

FOR
FORMULATION
USE ONLY

NET CONTENTS

Minimum phenol coefficient—250
(S. typhosa—20°C—AOAC Method)

DIRECTIONS FOR USE

Benzethonium Chloride is a concentrate for formulating purposes only. Use only in accordance with the directions in the Technical Bulletin from the manufacturer.

NOTE: This product should not be used or compounded with any reducing or oxidizing agents (such as calcium hypochlorite, solid perchlorate, or nitric acid) since such admixtures may be explosive.

Do not use in conjunction with soap or any anionic wetting agent. In preparing packaging mixes containing Benzethonium Chloride use normal precautions for handling powdered materials likely to create a dust.

Use an exhaust fan to keep dust away from operators.

Provide goggles, gloves and respirators.

Under certain conditions, the use of protective creams may be advisable.

DANGER

This product is corrosive. Causes severe eye and skin damage. Do not get in eyes, on skin or on clothing. Protect eyes and skin when handling. Harmful or fatal if swallowed. Avoid contamination of food.

FIRST AID: In case of contact, immediately flush eyes or skin with plenty of water for at least 15 minutes. For eyes, call a physician. Remove and wash contaminated clothing before reuse.

If swallowed, drink promptly a large quantity of milk, egg whites, gelatin solution or if these are not available, drink large quantities of water. Avoid alcohol. Call a physician immediately.

NOTE TO PHYSICIAN: Probable mucosal damage may contraindicate the use of gastric lavage. Measures against circulatory shock as well as oxygen and measures to support breathing manually or mechanically may be needed. If persistent, convulsions may be controlled by the cautious intravenous injection of a short acting barbiturate drug.

Do not reuse empty container. Return to container, reconditioner or destroy by perforating or crushing and burying in a safe place.

This product is toxic to fish. Do not contaminate water by cleaning of equipment or disposal of waste.

NOTICE: Seller warrants that the product conforms to its chemical description and is reasonably fit for the purpose stated on the label when used in accordance with directions under normal conditions of use, but neither this warranty nor any other warranty of merchantability or fitness for a particular purpose, express or implied, extends to the use, storage or handling of this product contrary to label instructions, or under abnormal conditions, or under conditions not reasonably foreseeable to seller, and buyer assumes the risk of any such use.

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ACCEPTED

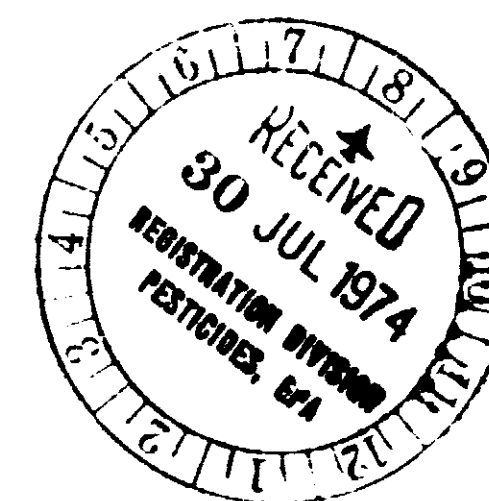
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UNDER THE FEDERAL INSECTICIDE

ROHM AND HAAS COMPANY

INDEPENDENCE MALL WEST

PHILADELPHIA, PENNSYLVANIA 19105



BENZETHONIUM CHLORIDE NF

GERMICIDE CONCENTRATE



BENZETHONIUM CHLORIDE NF

GERMICIDE CONCENTRATE

These suggestions and data are based on information we believe to be reliable. They are offered in good faith, but without guarantee, as conditions and methods of use of our products are beyond our control. We recommend that the prospective user determine the suitability of our materials and suggestions before adopting them on a commercial scale.

Suggestions for uses of our products or the inclusion of descriptive material from patents and the citation of specific patents in this publication should not be understood as recommending the use of our products in violation of any patent or as permission or license to use any patents of the Rohm and Haas Company

This bulletin is intended to provide the reader with complete, up-to-date information on this very important antimicrobial compound. Sections are presented on:

- National Formulary Description
- Antimicrobial Activity Data
 - Phenol Coefficients
 - A.O.A.C. Use Dilution
 - Microbiostatic and Microbicidal Titers
- Effect of Hard Water on Antimicrobial Activity
- Chemical and Physical Properties
- Surface Tension
- Precautionary Data
- Toxicological Data
- Bibliography
- Federal Registration

INTRODUCTION

Benzethonium Chloride NF¹ is a crystalline quaternary ammonium germicide offered as colorless crystals and manufactured to meet the quality standards set forth in the National Formulary.

This highly effective crystalline quaternary germicide is especially suited for formulating dry powdered products. Its high degree of purity makes it an excellent candidate for use in cosmetic and pharmaceutical products. By mixing Benzethonium Chloride crystals with inert, compatible diluents, powdered disinfectants or sanitizers can be prepared.

Pharmaceutical formulations are subject to the New Drug Regulations of the Federal Food, Drug, and Cosmetic Act, as amended, pertaining to the safety and effectiveness of such products.

Convenience and exactness of dosage contribute to the popularity of tablets. Benzethonium Chloride can be made into sanitizing tablets containing up to 50 percent active quaternary. This product has a relatively low hard water ceiling and sequestering agents should be employed to improve efficiency in hard water. The tablet manufacturer should evaluate his final composition by the AOAC Germicidal and Detergent Sanitizer Test to assure proper sanitizing performance in his marketing area. Other excipients such as lactose, ammonium sulfate, sodium bicarbonate, citric acid and other highly soluble substances may be used to optimize the physical properties of the finished tablet.

Disinfectants for surgical instruments, barbers' tools, and dentures can be prepared in the form of aqueous concentrates, powders, or tablets. A quaternary concentration of 1000 ppm is required for instrument disinfection. Formulators must provide required data to support registration of their specific formulations.

Benzethonium Chloride is a true deodorant which destroys obnoxious odors instead of masking them. Odors due to microbial decomposition also may be eliminated by the destruction of the microorganisms.

A 1:1000 dilution of active ingredient of Benzethonium Chloride product, applied by mopping, spraying, or sponging, will quickly control cooking odors, odors of putrefaction, personal illness, and odors in public rooms without contributing a chemical or disinfectant odor.

In suitable formulations Benzethonium Chloride provides bactericidal and deodorant properties for a number of diverse applications. The crystalline form of Benzethonium Chloride is readily soluble in water and a number of solvents. It can be formulated into powdered or liquid products for industrial, or household type sanitizers and disinfectants. This product may also prove useful in products as a preservative or as an antimicrobial agent for topical applications.

¹National Formulary, Thirteenth Edition Monograph, Benzethonium Chloride, Page 77, American Pharmaceutical Association publisher, Washington, DC 1970.

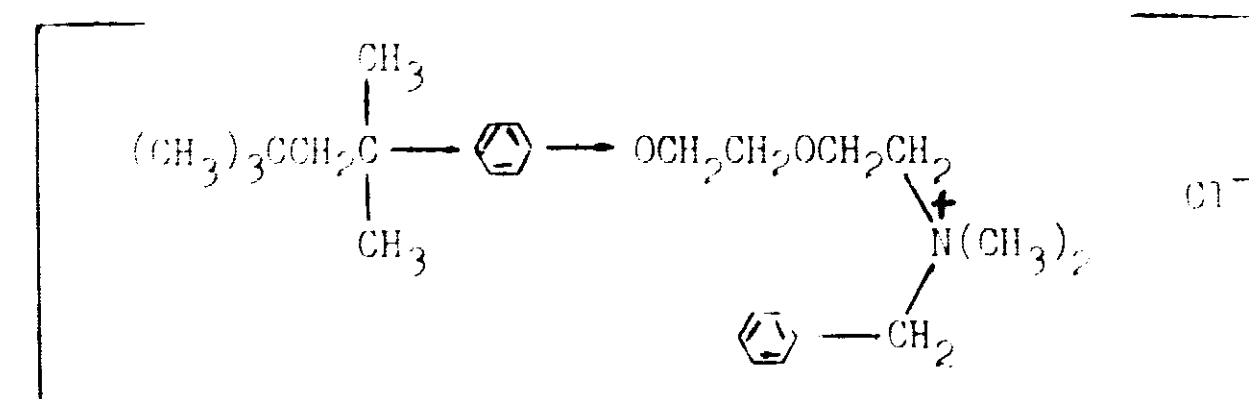
NATIONAL FORMULARY DESCRIPTION

For the convenience of readers, data from the National Formulary, Thirteenth Edition page 77 - Monographs are presented with the permission of the publisher.

National Formulary XIII

Monographs-77

Benzethonium Chloride



Benzyltrimethyl [2- [2- [p-(1,1,3,3-tetramethylbutyl) phenoxy] ethoxy] ethyl] ammonium Chloride

$C_{27}H_{42}ClNO_2$

Mol. wt. 448.09

Benzethonium Chloride contains not less than 97.0 percent and not more than 103.0 percent of $C_{27}H_{42}ClNO_2$, calculated on the dried basis.

Description - Benzethonium Chloride occurs as colorless crystals. It has a mild odor and has a very bitter taste. Its one-in-one hundred solution is slightly alkaline to litmus.

Solubility - Benzethonium Chloride is soluble in water, in alcohol, and in chloroform. It is only slightly soluble in ether.

Identification -

- To 1 ml of a solution of Benzethonium Chloride (1 in 100) add 2 ml of alcohol, 0.5 ml of diluted nitric acid and 1 ml of silver nitrate T.S.: a white precipitate, which is insoluble in diluted nitric acid but soluble in diluted ammonia solution, is formed.
- A solution of Benzethonium Chloride (1 in 100) forms precipitates with diluted nitric acid and with mercuric chloride T.S., both of which dissolve upon the addition of alcohol.
- Dissolve 100 mg of Benzethonium Chloride in 1 ml of sulfuric acid, add 100 mg of potassium nitrate, and heat on a steam bath for 3 minutes. Cautionally dilute the solution with water to 10 ml, add 100 mg of granulated zinc, and warm the mixture for 10 minutes. Cool, add 100 mg of sodium nitrite to 1 ml of the clear liquid, and add this mixture to 10 mg of naphthol sodium disulfonate in 1 ml of stronger ammonia water: the solution turns orange-red, and a brown precipitate may appear.

Melting range, page 814 - Benzethonium Chloride, dried at $100^{\circ}C$ for 4 hours, melts between 152° and $160^{\circ}C$.

Loss on drying, page 814 - Dry Benzethonium Chloride at $100^{\circ}C$ for 4 hours: it loses not more than 5 percent of its weight.

Residue on ignition, page 858 - Benzethonium Chloride yields not more than 0.1 percent of residue on ignition.

Ammonium compounds - To 5 ml of a solution of Benzethonium Chloride (1 in 50) add 1 ml of sodium hydroxide T.S., and heat to boiling: the odor of ammonia is not perceptible.

Assay - Dissolve about 300 mg of Benzethonium Chloride, accurately weighed, in 25 ml of water contained in a glass-stoppered, 250-ml flask. Add 0.4 ml of bromophenol blue solution (1 in 2000), 10 ml of chloroform, and 1 ml of sodium hydroxide T.S. Titrate with 0.02 M sodium tetraphenylboron until the blue color disappears from the chloroform layer. Add the last portions of the sodium tetraphenylboron solution dropwise, agitating vigorously after each addition. Each ml of 0.02 M sodium tetraphenylboron is equivalent to 8.962 mg of $C_{27}H_{42}ClNO_2$.

Packaging and storage - Preserve Benzethonium Chloride in tight, light-resistant containers.

CATEGORY - Local anti-infective.

APPLICATION - Topical, as a 1:750 solution to the skin or 1:5000 solution nasally.

CHEMICAL AND PHYSICAL PROPERTIES

Composition Benzethonium Chloride is diisobutylphenoxyethoxyethyl dimethyl benzyl ammonium chloride with a molecular weight of 448.1. The material is hygroscopic and will pick up moisture over a prolonged period of time to form a monohydrate with a molecular weight of 466.1. The equilibrium value for moisture content is approximately 4 percent.

Its Chemical Abstracts 9th Collective Index name is:

N,N-dimethyl-N- [2- [2- [4- (1,1,3,3-tetramethylbutyl) phenoxy] ethoxy] ethyl] benzenemethanaminium chloride.

The Chemical Abstracts Registry number is 121-64-0.

Appearance A white, free-flowing powder.

Density 77.5 lbs./ft.³

Solubility Benzethonium Chloride is soluble in water, the lower alcohols, glycols, ethylene glycol monomethyl ether, tetrachloroethane, and miscible in ethylene dichloride and carbon tetrachloride.

Compatibility Benzethonium Chloride compatibility has been determined by mixing dilute solutions of the germicide and solutions of substances with which it might be combined in formulations. Presence or absence of turbidity indicates physical compatibilities, however, final formulations should be carefully evaluated for both physical and bactericidal stability.

Compatible

Acetic acid
Aluminum chloride
Borax
Calcium chloride
Citric acid
Nonionic wetting agents
Polyoxyalkylene lanolin
Potassium hydroxide
Sodium acetate
Sodium bicarbonate
Sodium hydroxide
Sodium nitrate
Sodium sulfate
Tetrasodium pyrophosphate
Trisodium phosphate

Partially Compatible

Potassium iodide
Sodium hexametaphosphate*
Sodium metasilicate
Sodium tetraphosphate*
Sodium tripolyphosphate*

Incompatible

Anionic wetting agents
Potassium chromate
Potassium dichromate
Soaps
Sodium heptaphosphate

*Only in dilute solutions or in the presence of sufficient nonionic wetting agents or other suitable solubilizer.

WARNING: Surface active agents, whether anionic, nonionic, or cationic, should not be used or compounded with oxidizing agents such as calcium hypochlorite, nitric acid or solid perchlorates, since mixtures of these materials with most organic compounds may be explosive.

SURFACE TENSION

Surface Tension and Interfacial Tension Data

Figures in Dynes Per Centimeter

Benzethonium Chloride Active Concentration

	<u>1.0%</u>	<u>0.1%</u>	<u>0.01%</u>	<u>0.001%</u>
Surface Tension	33	30	45	55
Interfacial Tension*	4.9	2.6	15.8	25.8

*Interfacial tension vs. Atreol No. 9. All data via Cenco duNouy tensiometer at 25°C.

ANTIMICROBIAL ACTIVITY DATA

PHENOL COEFFICIENTS

The bactericidal dilutions of Benzethonium Chloride and calculated phenol coefficients for a variety of microorganisms are listed below. The bactericidal dilutions are those dilutions of active ingredients which kill in 10 minutes but not in 5 minutes according to the AOAC Phenol Coefficient procedure as described in the Official Methods of Analysis of the AOAC. Appropriate modifications of the culture media were made for those organisms having special growth requirements. The phenol coefficient values for quaternary ammonium chlorides cannot be used to determine disinfectant concentrations, but are offered only as a guide for assessing the relative cidal potency of a product against various types of microorganisms.

Benzethonium Chloride

AOAC Phenol Coefficient

Ten Minute Cidal Dilution of Active Ingredient

<u>Organism</u>	<u>Benzethonium Chloride</u>	<u>Phenol</u>	<u>Phenol Coefficient</u>
<u>Salmonella typhosa</u>	1:25,000	1:90	275
<u>Salmonella pullorum</u>	1:18,000	1:90	200
<u>Salmonella gallinarum</u>	1:10,000	1:80	125
<u>Salmonella paratyphi</u>	1:10,000	1:85	110
<u>Salmonella typhimurium</u>	1:17,500	1:80	215
<u>Listeria monocytogenes</u>	1:40,700	1:80	543
<u>Salmonella choleraesuis</u>	1:17,500	1:80	215
<u>Escherichia coli</u>	1:20,000	1:80	250
<u>Klebsiella pneumoniae</u>	1:10,000	1:90	111
<u>Brucella abortus</u>	1:40,000	1:100	400
<u>Shigella sonnei</u>	1:30,000	1:90	333
<u>Listeurella multocida</u>	1:40,700	1:110	473
<u>Proteus vulgaris</u>	1: 4,200	1:70	60

<u>Organism</u>	<u>Benzethonium Chloride</u>	<u>Phenol</u>	<u>Phenol Coefficient</u>
<u>Staphylococcus aureus</u>	1:25,000	1:60	410
<u>Saccharomyces cerevisiae</u>	1:35,000	1:100	350
<u>Streptococcus pyogenes C-203</u>	1:18,000	1:80	225
<u>Streptococcus fecalis</u>	1:10,000	1:60	154
<u>Streptococcus viridans</u>	1:40,000	1:90	444
<u>Listerella monocytogenes</u>	1:60,000	1:70	860
<u>Clostridium sporogenes</u>	1:10,000	1:90	111
<u>Pseudomonas aeruginosa PRD-10</u>	1:49,000	1:70	700
<u>Lactobacillus casei</u>	1: 8,000	1:80	100

Microbiostatic and Microbicidal Titers of
Benzethonium Chloride

Dilution of Active Ingredient

<u>Organism</u>	<u>Bactericidal</u>	<u>Bacteriostatic</u>
<u>Streptococcus pyogenes C-203</u>	1: 50,000	1: 50,000
<u>Streptococcus viridans</u>	1:200,000	1:400,000
<u>Escherichia coli</u>	1: 16,000	1: 16,000
<u>Salmonella gallinarum</u>	1: 32,000	1: 32,000
<u>Salmonella choleraesuis</u>	1: 32,000	1: 32,000
<u>Salmonella typhimurium</u>	1: 16,000	1: 16,000
<u>Pseudomonas aeruginosa PRD-10</u>	1: 8,000	1: 8,000
<u>Lactobacillus casei</u>	1: 50,000	1:100,000
<u>Shigella sonnei</u>	1: 16,000	1: 32,000
<u>Klebsiella pneumoniae</u>	1: 16,000	1: 16,000
<u>Saccharomyces cerevisiae</u>	1:100,000	1:100,000
<u>Lityrosporum ovale</u>	1:800,000	1:800,000
<u>Trichophyton interdigitale</u>	1: 70,000	1: 40,000
<u>Monilia albicans</u>	1:400,000	1:800,000
<u>Aspergillus niger</u>	1:400,000	1:800,000

EFFECT OF HARD WATER ON ANTIMICROBIAL ACTIVITY

Benzethonium Chloride retains its effectiveness as a hard surface disinfectant and as a preservative in the presence of hard water, however, its speed of action is slowed by the presence of calcium and magnesium salts. The effectiveness of hard surface sanitizers is determined by the AOAC Germicidal and Detergent Sanitizer Test. Since this procedure requires a 200 ppm active quaternary solution to kill 99.999 percent of an E. coli culture in 30 seconds, speed of kill becomes a critical factor in selecting a sanitizing agent.

As indicated below, the hard water ceiling of Benzethonium Chloride is relatively low. It should be compounded with inorganic or organic sequestering agents to improve sanitizing performance under hard water conditions.

Product - Benzethonium Chloride

Limiting Water Hardness as ppm
CaCO₃ AOAC Germicidal &
Detergent Sanitizer Test

200 ppm Active Solution - - - - -

A.O.A.C. USE DILUTION

The A.O.A.C. Use Dilution Confirmation Procedure is used to determine the effective disinfectant concentration for hard surfaces using the two basic index bacteria, Staphylococcus aureus and Salmonella choleraesuis. If the product is to be used in hospitals, the effective disinfectant use dilution for Pseudomonas aeruginosa PRD-10 must be also determined.

The effective disinfectant concentrations of Benzethonium Chloride for these microorganisms are:

<u>Organism</u>	<u>Disinfectant Concentration of Active Ingredient</u>	<u>Disinfectant Dilution of Active Ingredient</u>
<u>Staphylococcus aureus</u>	500	1:2000
<u>Salmonella choleraesuis</u>	500	1:2000
<u>Pseudomonas aeruginosa PRD-10</u>	1000	1:1000

MICROBIOSTATIC AND MICROBICIDAL TITERS

The maximum microbiostatic and microbicidal dilutions of Benzethonium Chloride are determined by means of serial dilutions in broth tubes inoculated with a fresh culture of organism to be tested. After 24 hours incubation, transfers are made from the tubes not showing growth to fresh broth containing a quaternary inactivator. After an additional 24 hours incubation (total incubation time of 48 hours) the initial set of tubes is reexamined for growth. The highest dilution of active ingredient preventing growth in the subculture tubes (quaternary inactivator present) after a total incubation time of 48 hours is the microbicidal titer.

PRECAUTIONARY DATA
FOR LABELLING

DANGER

Keep out of reach of children. Corrosive. Causes severe eye and skin damage. Do not get in eyes, on skin or on clothing. Wear goggles or face shield and rubber gloves when handling. Harmful or fatal if swallowed. Avoid contamination of food.

FIRST AID

In case of contact, immediately flush eyes or skin with plenty of water for at least 15 minutes. For eyes, call a physician. Remove and wash contaminated clothing before reuse.

If swallowed, drink promptly a large quantity of milk, egg whites, gelatin solution or if these are not available, drink large quantities of water. Avoid alcohol. Call a physician immediately.

NOTE TO PHYSICIAN

Probable mucosal damage may contraindicate the use of gastric lavage. Measures against circulatory shock as well as oxygen and measures to support breathing manually or mechanically may be needed. If persistent, convulsions may be controlled by the cautious intravenous injection of a short-acting barbiturate drug.

TOXICOLOGICAL DATA

EVALUATION OF BENZETHONIUM CHLORIDE TOXICITY

Acute Toxicity

In rats, Benzethonium Chloride administered orally was shown to be toxic, having an LD₅₀ of 420 $\pm$ 25 mg/kg. Following oral dosing, deaths occurred between 24 and 60 hours. Symptoms of toxicity prior to death were limited to severe depression.

Intraperitoneal and intravenous administrations of Benzethonium Chloride to rats resulted in LD₅₀'s of 33.1 $\pm$ 2.5 mg/kg and 19.1 $\pm$ 0.8 mg/kg respectively.

Eye irritation studies indicated that Benzethonium Chloride in concentrations of 1 percent, 5 percent, and 10 percent produced progressively greater irritation which was manifested by varying degrees of erythema and conjunctivitis. A 0.01 percent solution instilled into the eye produced no irritation. The higher concentrations, similarly, produced no irritation when the eyes were washed immediately after instillation.

On mucosal tissue 0.1 percent solutions produced no irritation, while some irritation resulted from application of a 0.2 percent solution.

On the skin of rabbits and dogs, solutions of 1.0 percent concentration caused erythema, blanching and edema. A single application of 0.6 percent solution was nonirritating to the skin of dogs.

SUBACUTE TOXICITY

Benzethonium Chloride was applied to the skin of rabbits daily, 5 days per week for 4 weeks. A concentration of 0.1 percent Benzethonium Chloride in water was applied. No dermal or systemic effects were observed at this dilution, but a 1 percent solution produced erythema and edema persisting for 48 hours.

CHRONIC TOXICITY

Benzethonium Chloride was administered to rats in their diets for 1 year at levels of 0, 50, 100, 1500, 3000, and 6000 ppm. At the 3000 ppm level some growth retardation was observed. Histopathologically, the testes of the male rats at the 1500 and 3000 ppm levels were atrophied. Otherwise, no aberrations were observed in appearance and behavior, in hematological studies, or in tissues.

Chronic dietary administration for one year to dogs at levels of 0, 1, 10, and 100 ppm produced no adverse effects on growth, survival, hematology, or tissues.

BIBLIOGRAPHY

A listing of published references on the properties and application of Benzethonium Chloride is available upon request.

FEDERAL REGISTRATION

Formulations involving the use of Benzethonium Chloride which involve treatment of humans require testing and approval of the Federal Food, Drug and Cosmetic Act Agency. The F.D.A. has received data on Benzethonium Chloride from Rohm and Haas under their Master File Number 2127 which should be referred to in any New Drug Application.

Formulations of all products with microbicidal claims (except drugs) must be registered with the Environmental Protection Agency. Applications for registration must be accompanied by five copies of the proposed label, and should be sent to the Director, Pesticides Registration Division, Environmental Protection Agency, Washington, D.C. 20540. The expedite handling of such applications, reference should be made to EPA File No. 700-100-1 and to the fact that the active principle is a Pesticide and Drug Company product.