1. **NAME**: QUATERNARY AMMONIUM

1.1 Substance

Quaternary ammonium compounds

1.2 Group

Benzalkonium Chloride
Benzethonium Chloride
Cetalkonium Chloride
Cetrimide
Cetrimonium Bromide
Cetylpyridinium Chloride
Glycidyl Trimethyl Ammonium Chloride
Stearalkonium Chloride

1.3 Synonyms

Group:
QAC
Cationic surfactant
Cationic detergent

Benzalkonium Chloride:
Alkyldimethylbenzylammonium chlorides;
Zephiran chloride (R);
Alkyldimethyl quaternary ammonium chlorides;
Hyamine 3500;
Benzethonium Chloride:
Diisobutylphenoxyethoxyethyltrimethylbenzylammonium chloride;
Hyamine 1622(R)
Cetalkonium Chloride:
Benzylhexadecyldimethylammonium chloride;
Cetyltrimethylbenzylammonium chloride;
Hexadecyldimethylbenzylammonium chloride;
Triton K 12;

Cetrimide
Trimethyltetradecylammonium bromide + dodecyl and
hexadecyltrimethylammonium bromide
Cetrimonium Bromide:
Hexadecyltrimethylammonium bromide
Cetyltrimethylammonium bromide
Retarder LA

Cetylpyridinium Chloride:
1-Hexadecylpyridinium chloride;
CPC
Glycidyltrimethylammonium chloride:
(2,3-epoxypropyl) trimethylammonium chloride
Stearalkonium Chloride:
Benzyl dimethyl stearyl ammonium chloride;
Stearyldimethylbenzylammonium chloride;

1.4 Identification numbers

1.4.1 CAS number

Benzalkonium Chloride CAS 8001-54-5

1.4.2 Other numbers

Benzethonium Chloride CAS 121-54-0
Cetalkonium Chloride CAS 122-18-9
Cetrimide CAS 8044-71-1
Cetylpyridinium Chloride (anhydrous) CAS 123-03-5
Stearalkonium Chloride CAS 122-19-0
Cetrimonium Bromide CAS 57-09-0

2. SUMMARY

2.1 Main risk and target organs

Quaternary ammonium compounds can cause toxic effects by all routes of exposure including inhalation, ingestion, dermal application and irrigation of body cavities. Exposure to diluted solutions can cause mild and self-limited irritation. Concentrated solutions of quaternary ammonium compounds are corrosive and can cause burns to the skin and the mucous membranes. They can produce systemic toxicity due to their curare-like properties. They can also cause allergic reactions.

2.2 Summary of clinical effects

Mild to severe caustic burns of the skin and mucous membranes can occur depending on the agent and the concentration. Other signs may include: nausea, vomiting, abdominal pain, anxiety, restlessness.

2.3 Diagnosis

Diagnosis depends essentially on prior history and presentation of specific signs and symptoms. These may include gastrointestinal symptoms, pain, burning sensation or local ulceration depending on the site of exposure and the concentration of the solution.

2.4 First-aid measures and management principles

First aid measures include eyes and skin decontamination by immediate and prolonged irrigation with copious amounts of water or saline.
Treatment is symptomatic and supportive. There is no specific antidote.

Most ingestions of diluted solutions are benign, and mild irritation is self-limited. Only clinical observation and
symptomatic treatment are usually necessary. Emesis and gastric decontamination are not indicated.

After ingestion of concentrated solutions or large amounts, monitor and support respiratory and cardiovascular function. Early oesophagoscopy should be performed to assess the severity of burns.

3. PHYSICO-CHEMICAL PROPERTIES

3.1 Origin of substance

Quaternary ammonium compounds or cationic detergents are synthetic derivatives of ammonium chloride (Arena et al., 1964).

3.2 Chemical structure

General formula:
\[
\begin{array}{cc}
R_1 & R_3 \\
N & \ldots \\
R_2 & R_4
\end{array}
\]

Where \( R_1-4 \) represent(s) alkyl or aryl substituents and \( X \) represents a halogen, such as bromide, iodide, or chloride (Dreisbach & Robertson, 1987; Budavari, 1996).

3.3 Physical properties

3.3.1 Colour

See 3.3.3

3.3.2 State/Form

See 3.3.3

3.3.3 Description

The quaternary ammonium compounds show a variety of physical, chemical, and biological properties and most compounds are soluble in water miscible solvents.

Benzalkonium chloride occurs as a white or yellowish white amorphous powder, a thick gel, or gelatinous flakes. It is hygroscopic, soapy to the touch and has a moldy aromatic odour and very bitter taste. Practically insoluble in ether; and very soluble in acetone, ethanol (95%), methanol, propanol and water (Wade & Weller, 1994). Aqueous solutions of benzalkonium chloride foam when shaken, have a low surface tension and possess detergent and emulsifying properties (Wade & Weller, 1994).

3.4 Hazardous characteristics

See 3.3.3.

4. USES/CIRCUMSTANCES OF POISONING
4.1 Uses

4.1.1 Uses

4.1.2 Description

Quaternary ammonium compounds are the active ingredients in disinfectants and sanitizers for homes, farms, hospitals, offices and public transportation vehicles. They are also used as algaecides and slimicides for swimming pools, industrial water reservoirs, and farm ponds. They are included in the last rinse in laundering by some hospitals, diaper services and various institutions.

Quaternary ammonium compounds are used in a variety of topical preparations in the treatment of minor infections of the eye, mouth and throat and as preservative in preparations for external use. Cetrimide and benzalkonium chloride are used as antiseptics for cleansing wounds, skin and burns (Reynolds, 1996).

Quaternary ammonium compounds are also used as surface active agents. These compounds are strongly adsorbed by many substances. The positive charge imparts antistatic properties to wool, cotton, and other cellulosic fibres as well as certain synthetic fibres. The compounds are used in hair conditioners, as softeners for textiles and paper products, and as pigment dispersers (Rietschel, 1995).

The concentration of quaternary ammonium compounds may vary from 0.005 % to 25 % or more.

4.2 High risk circumstances

Accidental poisoning can occur when quaternary ammonium compounds are stored in ordinary containers, and should be stored in distinctive bottles (never in soft drink bottles) in a safe place (Adelson & Sunshine, 1952).

Accidental poisoning has been infrequently described after irrigation of body cavities (Gilchrist, 1979; Baraka et al., 1980; Momblano et al., 1984).

Repeated occupational exposure after handling quaternary ammonium compounds as powders or solutions can produce sensitization (Shmunes & Levy, 1972; Oritiz-Prutos et al., 1996; Placucci et al., 1996; Krogstrup & Larsen, 1997).

4.3 Occupationally exposed populations

Physicians, nurses, dentists, veterinarians, pharmacists, and laboratory workers (Rietschel, 1995; Placucci et al., 1996). Housework and cleaning professionals.

5. ROUTES OF EXPOSURE
5.1 Oral

This is the most common route of entry (Vale & Meredith, 1985).

5.2 Inhalation

Quaternary ammonium compounds are commonly used in inhalers and nasal sprays as a wetting agent and as a preservative (Kuboyama et al., 1997; Beasley et al., 1998).

5.3 Dermal

Accidental spillage of quaternary ammonium compounds on skin and clothes is common because these compounds are present in various household preparations eg, shampoos, dish washing material, disinfectants, cleaning agents, and eye and nasal preparations. Dermal absorption is very low except through damaged skin (Nicola et al., 1997; Fisher & Stillman, 1972).

5.4 Eye

This route of entry may occur (Reynolds, 1996).

5.5 Parenteral

Haemolysis after intravenous injection of quaternary ammonium compounds has been reported (Reynolds, 1996).

5.6 Others

Irrigation of body cavities:
- intra-uterine administration may cause haemolysis (Reynolds, 1996)
- irrigation with cetrimide solutions in the treatment of hydatid cysts has produced systemic toxicity (Gilchrist, 1979; Baraka et al., 1980; Momblano et al., 1984).

6. KINETICS

6.1 Absorption by route of exposure

Oral exposure:
Quaternary ammonium compounds are poorly absorbed by oral route (Craig & Stitzel, 1994).

Dermal exposure:
Systemic effects from percutaneous absorption through intact skin are rare (Wilson & Burr, 1975).

Parenteral:
Systemic absorption is possible. (Wilson & Burr, 1975).

6.2 Distribution by route of exposure

No data available
6.3 Biological half-life by route of exposure

No data available

6.4 Metabolism

No data available

6.5 Elimination and excretion

Poorly absorbed by oral route and therefore relatively large amounts of the agent are eliminated in faeces (Craig & Stitzel, 1994).

7. TOXICOLOGY

7.1 Mode of action

Local corrosive injury may result from the caustic nature of these compounds. Quaternary ammonium compounds have curare-like depolarising properties (Van Berkel & de Wolff, 1988).

Benzalkonium chloride may cause bronchoconstriction by releasing spasmogenic mediators from the mast cells within the bronchial wall and stimulating cholinergic and noncholinergic nerves to produce bronchoconstriction (Graf et al., 1995; Hallen & Graf, 1995).

7.2 Toxicity

7.2.1 Human data

7.2.1.1 Adults

Human fatalities can occur following an oral dose of 100 to 400 mg/kg or a parenteral dose of 5 to 15 mg/kg (Ellenhorn et al., 1997). According to Arena (1964), the fatal dose of quaternary ammonium compounds was estimated to be 1 to 3 g.

7.2.1.2 Children

No data available

7.2.2 Relevant animal data

LD50 of benzalkonium chloride varies according to the species of animal and also depends on the route of exposure (Wade & Weller, 1994).

<table>
<thead>
<tr>
<th>Animal, route</th>
<th>LD50 (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guinea pig, oral</td>
<td>200</td>
</tr>
<tr>
<td>Mouse, ip</td>
<td>10</td>
</tr>
<tr>
<td>Mouse, iv</td>
<td>10</td>
</tr>
<tr>
<td>Mouse, oral</td>
<td>175</td>
</tr>
<tr>
<td>Mouse, sc</td>
<td>62</td>
</tr>
<tr>
<td>Rat, ip</td>
<td>14.5</td>
</tr>
<tr>
<td>Rat, iv</td>
<td>13.9</td>
</tr>
</tbody>
</table>
Nasal lesions were induced by the intranasal administration of 0.5 to 0.10% of benzalkonium chloride in rats (Kuboyama et al., 1997). Extensive inner ear destruction occurred after a comparatively short period of middle ear exposure to quaternary ammonium compounds in guinea pigs (Aursnes, 1982).

7.2.3 Relevant in vitro data

Tanada et al. (1991) studied the adsorption removal of benzalkonium chloride by granular activated carbon for medical waste water treatment; they found significant correlation between the amount of benzalkonium chloride adsorbed in less than 1000 ppm of equilibrium concentration and the micropore volume of activated carbon.

7.2.4 Workplace standards

No data available

7.2.5 Acceptable daily intake (ADI) and other guideline levels

No data available

7.3 Carcinogenicity

No data available

7.4 Teratogenicity

No data available

7.5 Mutagenicity

No data available

7.6 Interactions

Some studies indicate that the presence of alcohol potentiates the lethal effect (Adelson & Sunshine, 1952).

8. TOXICOLOGICAL ANALYSES AND BIOMEDICAL INVESTIGATIONS

8.1 Material sampling plan

8.1.1 Sampling and specimen collection
  8.1.1.1 Toxicological analyses
  8.1.1.2 Biomedical analyses
  8.1.1.3 Arterial blood gas analysis
  8.1.1.4 Haematological analyses
  8.1.1.5 Other (unspecified) analyses

8.1.2 Storage of laboratory samples and specimens
  8.1.2.1 Toxicological analyses
  8.1.2.2 Biomedical analyses
8.1.2.3 Arterial blood gas analysis
8.1.2.4 Haematological analyses
8.1.2.5 Other (unspecified) analyses

8.1.3 Transport of laboratory samples and specimens
8.1.3.1 Toxicological analyses
8.1.3.2 Biomedical analyses
8.1.3.3 Arterial blood gas analysis
8.1.3.4 Haematological analyses
8.1.3.5 Other (unspecified) analyses

8.2 Toxicological Analyses and Their Interpretation
8.2.1 Tests on toxic ingredient(s) of material
  8.2.1.1 Simple Qualitative Test(s)
  8.2.1.2 Advanced Qualitative Confirmation Test(s)
  8.2.1.3 Simple Quantitative Method(s)
  8.2.1.4 Advanced Quantitative Method(s)

8.2.2 Tests for biological specimens
  8.2.2.1 Simple Qualitative Test(s)
  8.2.2.2 Advanced Qualitative Confirmation Test(s)
  8.2.2.3 Simple Quantitative Method(s)
  8.2.2.4 Advanced Quantitative Method(s)
  8.2.2.5 Other Dedicated Method(s)

8.2.3 Interpretation of toxicological analyses

8.3 Biomedical investigations and their interpretation
8.3.1 Biochemical analysis
  8.3.1.1 Blood, plasma or serum
  8.3.1.2 Urine
  8.3.1.3 Other fluids
8.3.2 Arterial blood gas analyses
8.3.3 Haematological analyses
8.3.4 Interpretation of biomedical investigations

8.4 Other biomedical (diagnostic) investigations and their interpretation

8.5 Overall interpretation of all toxicological analyses and toxicological investigations

Specific laboratory determination for quaternary ammonium compounds are not usually available or necessary for the treatment of the patient. In severe cases, a complete blood count (haemoglobin, red blood cells, leukocytes with differential count), methaemoglobin determination, glucose, electrolytes, renal and hepatic function and arterial blood gases should be performed; chest X-ray and ECG should also be obtained.

9. CLINICAL EFFECTS

9.1 Acute poisoning

9.1.1 Ingestion

Serious toxicity is unlikely with benzalkonium chloride because of the low concentrations found in most preparations (Vale & Meredith, 1985). However, in higher concentrations, mild to severe caustic burns can occur on the lips, tongue, mouth, throat, hypopharynx, oesophagus, stomach depending on the agent and concentration of the solution (Chataigner et al., 1991; Chan, 1994). They may be accompanied by hypersalivation, vomiting, haematemesis, diarrhoea and confusion (van Berkel & de
Wolff, 1988). Metabolic acidosis may also occur (Arena, 1964). In severe cases there may be hypotension, shock, respiratory paralysis, convulsions, coma and cardiopulmonary arrest (Mathieu-Nolf et al., 1985). Fatalities have been reported (Chataigner et al., 1991; Hitosugi et al., 1998).

9.1.2 Inhalation

Prolongation of mucociliary clearance occurred, shortly after application of benzalkonium chloride but there was no detectable effect on nasal mucosal function after two weeks of regular use (McMahon et al., 1997).

Some studies state that benzalkonium chloride containing nasal preparations can cause nasal stiffness, nasal mucosa swelling, and bronchoconstriction in asthmatic patients (Reynolds, 1996).

9.1.3 Skin exposure

Dermal burns have been reported with concentrated cetrimide, including solutions of 12 and 17.5% (Mercer, 1983; Nicola et al., 1997). 1% solution of cetrimide produced necrosis when applied to the dermis of a 77-year-old woman (August, 1975).

Caustic action can occur with benzalkonium chloride with preparation diluted 1:2,000 or 1:5,000, and with dilution of at least 1:20,000 (Wilson & Burr, 1975).

9.1.4 Eye contact

Eye exposure may result in mild discomfort (0.1% solution) to very serious corneal damage (10% solution) depending on the agent and the concentration. High concentrations of benzalkonium chloride can cause ocular toxicity in human eyes (Reynolds, 1996). Some investigations indicate that quaternary ammonium compounds can cause ocular inflammation (Swan, 1944; Rietschel, 1995).

9.1.5 Parenteral exposure

Intravenous administration of quaternary ammonium compounds may cause haemolysis (Reynolds, 1996).

9.1.6 Other

Intra-uterine administration may cause haemolysis (Reynolds, 1996). Irrigation with cetrimide solutions in the treatment of hydatid cysts has produced chemical peritonitis (Gilchrist, 1979), methaemoglobinemia with cyanosis (Baraka et al., 1980) and metabolic acidosis (Momblano et al., 1984).
9.2 Chronic poisoning

9.2.1 Ingestion

Small amounts of quaternary ammonium compounds are ingested from dish washing detergents used in the kitchen. Repeated measurements and calculations indicate an average oral intake of surfactants of about 100 mg/man/year, this level does not cause toxicity (Gloxhuber et al., 1974).

9.2.2 Inhalation

Occupational asthma has been reported after prolonged exposure to benzalkonium chloride (Bernstein et al., 1994).

9.2.3 Skin exposure

People exposed to quaternary ammonium compounds can exhibit irritant contact dermatitis, particularly with benzalkonium chloride (Shmunes & Levy, 1972; Oriz-Frutos et al., 1996; Placucci et al., 1996; Krogsrud & Larsen, 1997).

9.2.4 Eye contact

No data available

9.2.5 Parenteral exposure

No data available

9.2.6 Others

No data available

9.3 Course, prognosis, cause of death

Poisonings due to diluted solutions usually are mild and self-limited. In high concentrations, mild to severe caustic burns can occur. If there is improvement in symptoms after initial treatment then the patient is likely to survive if adequate treatment is continued. Death in case of heavy exposure is usually related to cardiorespiratory collapse, bronchoconstriction or acute pulmonary oedema (Ellenhorn, 1997). In severe cases death may occur within 1 or 3 hours after ingestion (Chataigner et al., 1991; Hitosugi et al., 1998).

9.4 Systemic description of clinical effects

9.4.1 Cardiovascular

In acute cases hypotension and cardiac arrest can occur (Mathieu-Nolf et al., 1985; Nicola et al., 1997).

9.4.2 Respiratory
In acute cases pulmonary oedema resulting from aspiration, dyspnea and cyanosis due to paralysis of the respiratory muscles, bronchoconstriction, cough can occur (Adelson & Sunshine, 1952; Chataigner et al., 1991; Chan, 1994).

Several cases of bronchoconstriction resulting from nebulised benzalkonium chloride as a preservative in corticosteroid preparations have been reported (Beasley et al., 1986; Beasley et al., 1987; Beasley et al., 1998). Occupational asthma has been reported after prolonged exposure to benzalkonium chloride (Bernstein et al., 1994).

9.4.3 Neurological

9.4.3.1 Central nervous system

In acute exposure, central nervous depression progressing to coma may occur and can be preceded by excitement and convulsions (Gloxhuber et al., 1974; Reynolds, 1996).

9.4.3.2 Peripheral nervous system

No data available

9.4.3.3 Autonomic nervous system

No data available

9.4.3.4 Skeletal and smooth muscle

Quaternary ammonium compounds have depolarising muscle relaxant properties and can produce paralysis of the respiratory muscles (Reynolds, 1996).

9.4.4 Gastrointestinal

In acute exposure vomiting, diarrhoea, and abdominal pain may occur. Ingestion of concentrated solution may produce local ulceration on lips, mouth, pharynx, oesophagus, stomach and intestines (Vale & Meredith, 1985; Chataigner et al., 1991).

9.4.5 Hepatic

In acute exposure hepatic necrosis and elevated liver function tests have been reported (Adelson & Sunshine, 1952).

9.4.6 Acid-base

In acute and severe cases metabolic acidosis has been reported (Adelson & Sunshine, 1952; Momblano et al., 1984).

9.4.7 Hematological
Haemolysis and methaemoglobinaemia have been reported in a woman following irrigation with 0.1\% cetrimide in the treatment of hydatid cysts (Baraka et al., 1980). Intra-uterine administration of quaternary ammonium compounds may cause haemolysis (Reynolds, 1996).

10. MANAGEMENT

10.1 General principles

Treatment is symptomatic and supportive. There is no specific antidote. Most ingestions of diluted solutions are benign, mild irritation is self-limited and only clinical observation and symptomatic treatment are usually necessary. Gastric decontamination is not indicated.

10.2 Life-supportive procedures and symptomatic treatment

When clinically indicated, expansion of circulatory blood volume, vasoactive drugs, supplemental oxygen, artificial ventilation and treatment of seizures should be promptly instituted. Endoscopy should be performed as soon as possible and within 24 hours. Symptomatic treatment may include bronchodilators, antiemetics and methaemoglobinemia treatment when indicated.

Treatment of contact dermatitis and other injuries should be performed.

10.3 Decontamination

Ingestion
A significant ingestion is unlikely if spontaneous emesis has already occurred. Do not induce emesis or perform gastric lavage because of the risk for corrosive injury and production of foam (AACT & EAPCCT, 1997). For significant ingestions, consideration may be given to aspirating the stomach contents; however, the risk of gastrointestinal injury could be further compromised by this procedure. If undertaken, this should be performed cautiously through a thin, flexible nasogastric tube. In severe cases, activated charcoal may be considered; however, although there are in vitro data demonstrating the adsorption of benzalkonium chloride by activated charcoal (Tanada et al., 1991), its effective use in the medical management of severe quaternary ammonium poisonings has not been confirmed. Furthermore this may mask endoscopy evaluation.

Eyes and skin
Irrigate with copious amounts of tepid water or saline. Consult an ophthalmologist if eye pain persists or if there is significant corneal injury on fluorescein examination (Olson, 1999).
10.4 Enhanced elimination

Elimination methods have not been shown to be effective (Olson, 1999).

10.5 Antidote treatment

10.5.1 Adults
There is no specific antidote

10.5.2 Children
There is no specific antidote

10.6 Management discussion

For significant ingestions, consideration may be given to aspirating the stomach contents; however, the risk of gastrointestinal injury could be further compromised by this procedure. If undertaken, this should be performed cautiously through a thin, flexible nasogastric tube. Although there are in vitro data demonstrating the adsorption of benzalkonium chloride by activated charcoal (Tanada et al., 1991), its effective use in the medical management of severe quaternary ammonium poisonings has not been confirmed. Furthermore this may mask endoscopy evaluation.

11. ILLUSTRATIVE CASES

11.1 Case reports from the literature

Child, oral ingestion
Two and a half-month-old twins were mistakenly given an 11% solution of benzalkonium chloride orally for candidiasis. They had been prescribed a 1:50,000 dilution. Within 24 hours both children had developed irritability, fever, anorexia, dehydration, cough, circumoral erythema, drooling and numerous oral and pharyngeal lesions. One twin developed chemical pneumonitis. Both twins were given IV fluids and antibiotic support and recovered (Nicola et al., 1997).

Children, oral ingestion
Five normal newborn breast fed babies were accidentally fed a dilute antiseptic solution (chlorhexidine 0.05% with cetrimide 1%) in place of sterile water, developing caustic burns of the lips, mouth and tongue within minutes; one baby became quite severely ill due to acute pulmonary oedema, but all survived without sequele (Mucklow, 1988).

Adult, oral ingestion
While in a tavern, a 45-year-old woman, was served a drink made up of 3/4 of an ounce of whisky and 2.5 ounces of supposed ginger ale (but it was hyamine 2389). She swallowed a mouthful (approximately 1 ounce) and immediately complained of feeling ill and vomited. She died approximately 25 minutes after ingesting the drink (Adelson & Sunshine, 1952).

Adults, skin exposure
Two physicians were reported to have become sensitized to
benzalkonium chloride from handling instruments soaked in the disinfectant for cold sterilization. They developed allergic conjunctivitis from the presence of benzalkonium chloride in ophthalmic solutions (Fisher & Stillman, 1972; Rietschel, 1995).

Adult, skin exposure
A physician developed a severe allergic conjunctivitis from an ophthalmic solution containing benzalkonium chloride. The conjunctivitis became worse with the use of another preparation containing this preservative (Fisher & Stillman, 1972).

12. ADDITIONAL INFORMATION

12.1 Specific preventive measures

Quaternary ammonium compounds should not be stored in soft drink containers and should be stored in specific bottles and in a safe place. While handling these compounds care should be necessary.

12.2 Other

No data available

13. REFERENCES


Arena JM (1964) Poisoning and other health hazards associated with use of detergents. JAMA, 190:56-58.


Mucklow ES (1988) Accidental feeding of a dilute antiseptic solution (chlorhexidine 0.05% with cetrimide 1%) to five babies. Human Toxicol, 7:567-569.


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