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Toxicological evaluation of "PURIFOG"

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Executive Summary

On behalf of Fonderia Mestieri SrL, a toxicological evaluation of the product "PURIFOG" related to its intended use was performed based on the available literature. The vendor of this product is UR FOG SrL (Via Giacinto Collegno 11, Torino 10143, Italy) and all compositional data were supplied by the vendor.
A bibliographical evaluation of the potential skin irritating, sensitizing, ocular and inhalation effects of the substances declared to be contained in the product was carried out.

Product to be evaluated

The product is a liquid mixture contained in a transparent plastic bag. The volume of the liquid is 200 mL. The liquid is a mixture of disinfectants and bactericidal/virucidal for sanitization of indoor spaces. It contains a mixture of dipropylene glycol, quaternary ammonium compounds, ethyl alcohol and water and is intended to be used as a micronized aerosol generated through a proper thermospray device.

Toxicological evaluation of "PURIFOG"

As declared by UR FOG SrL the composition of the mixture to be evaluated is reported in Table 1

Substance	CAS #	Percentage in the preparation w/w	Weight per bag (g)	Weight per gram of product (g)
Water				
Isopropanol				
Ethanol				
Dipropylene glycol				
Benzalkonium chloride (C10-C18 Alkyl)				
citrus aurantium dulcis oil				

Table 1. Ingredients contained in the preparation under evaluation, as declared by the Vendor (UR FOG SrL).

The suggested dose of this product by UR FOG SrL in the sanitization of indoor environments is 1 gram per cubic meter. The suggested released amount of the components per cubic meter is reported in the last column of Table 1.
The potential routes of exposure stemming from the intended use are: skin contact, eye contact, inhalation and intentional ingestion.
A bibliographical search of the current knowledge about the potential skin irritating, sensitizing, oral, eyes and inhalation effects of the ingredients was carried out through known and reliable public databases (mainly through the TOXNET database of NIH National Library of Medicine, now included in the PubChem and PubMed databases[1]) and in primary scientific literature trough PubMed, Scopus and WebOfScience databases
Every ingredient was evaluated for its own effect. No interaction and synergistic effects between ingredients was considered.

It is not possible to predict the human assumption of the single ingredients of the mixture through the different routes of exposure. However, taking into account the average volume of inspired as 7.5 liter of air per minute, and the suggested dose for indoor decontamination (1 gram of product per cubic meter), a reasonable estimate of the maximum inhaled quantity is 7.5 mg per minute of the whole mixture. For 1 hour exposure the maximum inhaled quantity of the various ingredients is reported in Table 2, taking into account a total volume of air inhaled of 500 litres and under the hypothesis that all the amount inhaled will deposit onto the respiratory apparatus and no decrease of the aerosol concentration takes place during the exposure time. The inhaled dose is at least 3 orders of magnitude lower than the estimated acute toxicity levels. As a consequence, with the current knowledge it is concluded that aerosolized PURIFOG, if used as suggested, do not represent a threat for human and animal healths for a single episode of 1 hour exposure. A reversible and mild irritation to the eyes can occur.

	Dipropilene glycol	Ethanol	isopropanol	Benzalkonium Chloride
mg per gram of product	786	15	85	10
Max inhaled dose, mg	393	7.5	42.5	5
Estimated LD50 (70kg bw)	350000	350000	200000	3500

Table 2. Estimated maximum amount of inhaled substance for the exposure of one hour to 1 g per cubic meter of aerosol (volume of inhaled air 500 litres).

Dipropylene Glycol (CAS# 25265-71-8)

The US National Toxicological Program (NTP) carried out a toxicological evaluation and a carcinogenesis study about dipropylene glycol.[2] The report analysed scientific literature on animal and human exposure data till to 2004. A review on the toxicity of propylene, dipropylene and tripropilene glycol vas recently published.[3]

TOXICITY SUMMARY[2,3]

Dipropylene glycol is a by-product of the manufacture of Propylene glycol and is used in industrial manufacturing applications and as a reactive intermediate to produce plasticizers, unsaturated polyester resins, polyurethane polyols and alkyd resins. It is also used as a solvent, with applications including: cosmetics and personal care products, pesticides, specialty deicers, inks and lubricants. In the professional, commercial service and consumer settings, Dipropylene glycol is used as a functional fluid (e.g. in hydraulic brake fluids, cutting fluids) and as an inert ingredient in pesticide formulations. These applications present a potential for inhalation exposure in addition to dermal exposure. In the consumer setting, dermal exposure, and to a lesser degree inhalation exposure are to be expected due to the formulation of Dipropylene glycol into cosmetic or fragrance products.
Dipropylene glycol technical grade typically has three structural isomers that can be discerned using NMR spectroscopy or using GC/MS. In addition, the structure contains 10 stereoisomers due to asymmetry from the chiral carbon.
Rats orally exposed to DPG at a dose of 5.01 g/kg bw exhibited no mortality. Decreased locomotor activity was observed, but no clinical signs were seen after 1 day. In another study, 20% mortality

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occurred in rats after a gavage dose of 10.4 mL/kg bw (10.6 g/kg bw), with 80% mortality seen at the extreme dose level of 17.9 mL/kg bw. No mortality was seen at a dose of 8.6 mL/kg bw (8.8 g/kg bw). In an acute dermal toxicity study, using occlusive patches in rabbits, 5.01 g/kg bw DPG resulted in no deaths and only slight erythema, which disappeared by the second day after treatment. No clinical signs were observed throughout the 14-day post exposure observation period. No acute toxicity was observed with high DPG aerosol exposure. A REACH summary of a 4 h inhalation aerosol exposure of rats to 2.34 mg DPG/L described no deaths or clinical signs with a 14-day follow-up period.
In summary, animal toxicology studies in multiple species across all routes of exposure indicate that lethality from exposure to the dipropylene glycol is only observed when animals are exposed to well above experimental limit doses. To achieve any observed acute toxic effects, the doses required must be high enough to be expressed in terms of percentages in air, water or food. The only reported exception is in cats where a reduction in red blood cell survival due to formation of Heinz bodies is observed. Dipropylene glycol is therefore considered as non-hazardous. No human fatalities are known to have occurred in relation to acute accidental or occupational exposures to dipropylene glycol. The compound should be considered to be essentially non-toxic upon acute exposure.

Skin irritating and sensitizing effects[3]

In experimental animals, dipropylene glycol was considered not acutely toxic by dermal exposure. No mortality occurred when dipropylene glycol was applied on the skin of rabbits at doses of 5 or 20 g/Kg. Dipropylene glycol is only slightly irritating for the skin of rabbits. Ten application of dipropylene glycol to the skin of rabbits in 12 days produced negligible irritation. In another study, dipropylene glycol was reported to cause only mild skin irritation in rabbits exposed to 0.5 g in a 24 hours dermal application test.
Dipropylene glycol does not produce allergic skin reaction or sensitization in humans after a 48 hours closed patch test
Dipropylene glycol does not produce allergic skin reactions or sensitization in humans. It did not produce irritation in human subjects after a 48-hour closed patch test when administered at a concentration of 20% in petrolatum (mineral oil). Dipropylene glycol did not produce allergic skin reactions in 503 human volunteers with eczema tested for sensitivity to dipropylene glyco. Patients were exposed to 10% dipropylene glycol for 2 days. Only one patient had a positive patch test reaction to dipropylene glycol.
In a 48-hour closed patch test using a shaving preparation containing 7.2% dipropylene glycol, mild irritation was observed in 6 of 101 subjects after the first exposure and in 8 of 101 subjects after repeating the application 2 weeks later. Repeated applications of the shaving preparation did not have a sensitizing effect in 50 volunteers treated occlusively for 24 or 48 hours, 3 times per week over a 3-week period. No photosensitizing properties could be detected after ultraviolet irradiation. Likewise, no effects were observed in 59 patients exposed to the shaving preparation for a 4-week period.
The repeated application of a 20% formulation of dipropylene glycol in petrolatum did not have a sensitizing effect on 25 human volunteers. Exposure to dipropylene glycol consisted of five consecutive treatments, each lasting 48 hours; another 48-hour repeat treatment occurred 1 to 14 days after the fifth consecutive treatment.

Reproductive and Developmental Toxicology[3]

The National Toxicology Program conducted developmental toxicity studies of dipropylene glycol in rats and rabbits. Dipropylene glycol did not cause fetal toxicity or teratogenicity when administered

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by gavage to timed pregnant Sprague-Dawley (CD®) rats (20 to 25 per group) at doses of 800, 2,000 or 5,000 mg/kg per day on days 6 to 15 of gestation. Dams were necropsied on gestation day 20. One of 25 pregnant rats in the 2,000 mg/kg group and 2 of 22 pregnant rats in the 5,000 mg/kg group died before day 20. Reduced body weight gain, reduced feed consumption, and increased water consumption were observed in 5,000 mg/kg dams. Although maternal toxicity was observed in rats administered 2,000 or 5,000 mg/kg, developmental toxicity in the fetuses was not observed. Dipropylene glycol did not affect resorptions, fetal viability, fetal body weight, or fetal external, visceral, or skeletal alterations. Small increases in the numbers of fetal malformations were seen in mice injected subcutaneously with propylene glycol. Twenty-one pregnant ICR/Jcl female mice (9 to 12 weeks old) were injected with 0.01 mg/g on day 9, 10, or 11 of gestation, the period of sensitivity to the induction of fetal deaths and malformations in this strain. The following malformations were noted in 5 of 226 living fetuses (2%): open eyelid (three fetuses), polydactyly (one fetus), and cleft palate (one fetus). However, three fetuses with malformations (open eyelid, polydactyly, and exencephalus) were also noted among 1,026 living fetuses in the untreated control group.
No reproductive or developmental toxicity studies of dipropylene glycol in humans were found in the literature

Skin, Eye, and Respiratory Irritations[3]

Mildly irritating to the eyes.
May cause primary skin irritation in some people, possibly due to dehydration, but the material is not a sensitizer.
May cause transitory stinging, blepharospasm, and lacrimation.

Ethanol (CAS # 64-17-5)

Toxicity Summary[4]

HUMAN STUDIES: Ethanol is a central nervous system (CNS) depressant. It enhances the inhibitory effects of gamma-aminobutyric acid (GABA) at the GABA-A receptor and competitively inhibits the binding of glycine at the N-methyl-d-aspartate receptor (it disrupts excitatory glutaminergic neurotransmission). Ethanol also stimulates release of other inhibitory neurotransmitters, such as dopamine and serotonin. The most common clinical signs of ethanol toxicosis are ataxia, lethargy, vomiting, and recumbency. In more severe cases, hypothermia, disorientation, vocalization, hypotension, tremors, tachycardia, acidosis, diarrhea, respiratory depression, coma, seizures, and death may occur. Alcohol is directly irritating to the stomach and causes vomiting. High ethanol blood levels also stimulate emesis. The concern with vomiting during intoxication is that at high blood ethanol concentrations, the muscles that control the epiglottis become slow to react or even paralyzed. This increases the risk for aspiration. Ethanol intoxication reduces peripheral oxygen delivery and metabolism and causes mitochondrial oxidative dysfunction, potentially resulting in shock or hypoxia in an acutely intoxicated patient. Hypothermia may result from multiple mechanisms. Peripheral vasodilation, CNS depression, ethanol interference with the thermoregulator mechanism, and/or impaired behavioral responses to a cold environment all lead to a lowered body temperature. Moderate ethanol intake appears to reduce the risk of myocardial infarction and other heart diseases. However, high spirits consumption was associated with increased risk of cancer mortality in women. Consumption of alcoholic beverages (beer, in particular) is associated with an increased risk for rectal but not colon cancer. Beer is a commonly consumed alcoholic beverage

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among reproductive-age adults. Beer drinking males have an increased risk of contributing to pregnancy waste. Women consume beer before and after pregnancy recognition. Binge drinking appears to be a common drinking behavior, and those who binge drink have an increased risk of impaired fetal growth and offspring behavior. Beer consumption by lactating women might temporarily impair motor function of nursing infants. The rate of ethanol metabolism varies among individuals. Studies of twins indicate that interindividual variability in the rate of ethanol metabolism may be genetically controlled. The main pathway for ethanol oxidation in humans is to acetaldehyde via alcohol dehydrogenase pathway. Acetaldehyde is oxidized further to acetic acid by aldehyde dehydrogenase. Asians are known to be sensitive to the health effects of ethanol; the sensitivity has been attributed to different forms of the enzyme acetaldehyde dehydrogenase. Alcohol ingestion by Asians resulted in marked elevations of blood acetaldehyde levels ranging from 0.4 to 3 mg/L, and individuals developed facial flushing and tachycardia as a direct consequence of elevated blood acetaldehyde levels. ANIMAL STUDIES: A drop full-strength ethanol on rabbit eyes causes reversible injury graded only 3 on a scale of 10 after 24 hr. Application of 70% alcohol to rabbit corneas injures and temporarily loosens the corneal epithelium, but the recovery is complete. When rats were dosed with ethanol by oral gavage with 8 to 15 g/kg/day over 4 months and fed a diet containing 25% of total calories as fat, focal necrosis, inflammation, and fibrosis were observed in the liver. Nine baboons fed ethanol at 50% of total calories developed fatty liver, and four animals developed hepatitis within 9 to 12 months. Rabbits exposed to saturated vapors of ethanol for periods ranging from 25 to 365 days developed cirrhosis of the liver. Rats were given a single intraperitoneal dose of diethylnitrosamine followed by treatment with ethanol in drinking water for 12 to 18 months. Ethanol was an effective promoter of liver tumors. Cynomolgus monkeys administered up to 5 g/kg bw ethanol daily on gestation days 20-150 revealed an increase in pregnancy wastage (abortions and still births) but no structural malformation or facial change. Ethanol, and not acetaldehyde, has been implicated as the causative agent of the teratogenic effects in laboratory animals. Oral coadministration of 100 mg/kg of 4-methylpyrazole, an inhibitor of alcohol dehydrogenase, with 6 g/kg of ethanol intraperitoneally on gestation day 10 dramatically increased the embryotoxicity of ethanol in mice. Ethanol is not mutagenic in Salmonella typhimurium strains TA 97, TA 98, TA 100, TA 1535, TA 1537, or TA 1538 in the presence or absence of metabolic activation. In the presence of a metabolic activation system, ethanol is slightly mutagenic to Salmonella strain TA 102, a strain considered to respond to the presence of oxygen radicals. Ethanol did not induce mutations in mouse lymphoma L5178Y TK+/- cells and did not induce micronuclei in Chinese hamster V79 cells in the absence of metabolic activation. No chromosomal aberrations or sister chromatid exchanges were observed in Chinese hamster ovary cells treated with ethanol. ECOTOXICITY STUDIES: The zebrafish were exposed to different concentrations (control, 0.01, 0.1, and 1%) of ethanol from blastula stage to 144 hour-post-fertilization (hpf). No effect on survival was observed except the 1% ethanol group suffered 89% mortality during 108-120 hpf. No developmental defects were observed at the 0.01 and 0.1% concentrations, but significantly higher deformity rates occurred with 1% ethanol. Hyperactivity and less tortuous swimming paths were observed in all ethanol concentrations.

IRRITATION AND SENSITIZATION EFFECTS ON SKIN

Cutaneous reactions to ethanol, 1-propanol, 2-propanol and acetaldehyde were evaluated by Haddock et al in a control group and in patients before and while they were receiving disulfiram therapy.[5] Local cutaneous erythema was observed from parch tests with ethanol, 1-propanol and 2-propanol in hydrated skin, and from acetaldehyde in dry skin. Erithema resulting from topically applied alcohols occurred in a dose related manner and was caused by a direct vasodilatory effect on the cutaneous microvasculature.

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Potential skin irritating effects of ethanol were investigated by Bingham et al.[6] Human subjects reported no apparent skin irritation when applied to the forearm of human subjects in a modified Draize test. No irritation was noted when ethanol was applied to the forearm openly for 21 days, whereas 21-days occlusive test caused erythema and induration toward the end of the exposure period. There have been infrequent reports of skin sensitization reactions attributed to ethanol. Ethanol is a weak sensitizer in a patch test.
Non human toxicity vaues are reported below[4].
LD50 Mouse subcutaneous 8285 mg/kg
LDLo Dog subcutaneous: 6600 mg/kg
Ethyl alcohol was considered mildly toxic by skin contact.[4]

ORAL ADMINISTRATION

Falk M. et al administered orally to rats by means of an intragastric tube ethanol (0.6/100 g) in order to evaluate potential toxic effect of this alcohol. [4] The administration caused an accumulation of secretory vescicles laden with very low density lipoprotein (VlDL) particles which were seen 90 min after administration and later disappeared.
Pankov et al performed a single ethanol administration in rat. [4] In response to alcohol administration the catecholamine secretion from the adrenal medulla was enhanced as evaluated by urinary catecholamine excretion in rats. The threshold dose of 87 mmol/Kg also produced a transient increase in blood sugar concentration. Experiments with chronic ethanol treated rats showìied that the increase of urinary catecholamine excretion following 87 mmol/Kg disappeared occasionally, whereas the increase following repeated administration of 130 mmol(Kg is permanent. Morphologic evaluation revealed enlargement of the adrenal medulla, changes of cells and nuclei as well as a distinct reduction of chromaffin reaction.

EFFECTS ON EYES

Grant et al treated rabbit eyes with a drop of ethanol 96%[4]. The treatment caused reversible injury graded only 3 on a scale of 10 after 24 hours. Application of 70% alcohol to rabbit corneas injurres and temporaly loosens the corneal epithelium, but the recovery was complete. Repeated application (7 drops) of 40 to 80% alcohol to rabbit eyes over an unspecified but presumably longer time caused loss of corneal epithelium and endothelium, followed by hemorrhages in the conjunctiva, and infiltration and vascularization of the corneal stroma.

INHALATION EFFECTS

The effect of inhalation exposure to ethyl alcohol were studied by Bingham et al[4]. In a nontolerant human subject, the inhalation exposure to 1380 ppm ethanol for 39 min resulted in no effects at 28 min, but headaches and slight numbness at 33 min. At 3340 ppmv for 100 min, sensation of warmth and coldness, nasal irritation, headaches and numbness were reported. When exposed to 8840 ppmv for 64 min, the subjects complained of a momentary intolerable odor and difficulty in breathing, conjunctival and nasal irritation, a feeling of warmth, headache, drowsiness and fatigue. In tolerant individuals, the symptoms are less sever, and the time required to produce them is greater then in intolerant individuals. For instance, a human subject tolerant to alcohol reported slight headaches after 20 min exposure to 5030 ppmv fo 120 minutes. Intoxication has been seen among humans subjected to inhalation of vapors from hot alcohol.

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In a study reported by Grant[4], alcohol vapor exposure at sufficiently high concentration may cause prompt stinging and watering of the eyes, but there appear to be no reports on eye injury from industrial exposure to alcohol vapors. Human volunteers exposed to alcohol vapor have observed at concentrations of 0.7 to 1% vapor in air the smell of alcohol was at first unbearable, although unpleasant later, and that the eyes began to burn with increased intensity after several minutes. A vapor concentration of 0.25% (2500 ppmv) had no notable effect on the eyes.

NON HUMAN AND HUMAN ACUTE TOXICITY (ORAL, INHALATION)

Non Human toxicity values are reported below.[4]
LD50 Mouse iv 2.0 g/L
LD50 Mouse sc 8.3 g/L
LD50 Mouse ip 0.9 g/L
LC50 Mouse inhalation 39 g/m^3/4 hr
LD50 Mouse oral 3.4 g/L
LD50 Rat iv 1.4 g/L
LD50 Rat ip 3.8 g/L
LC50 Rat inhalation 20000 ppm/ 10 hr
LD50 Rat oral 7.0 g/L
LD50 Rat oral 10.6 g/kg
LD50 Guinea pig oral 5.6 g/kg
LD50 Rat oral 9.9 g/kg
LD50 Rat (young adult) oral 17.8 g/kg
LD50 Rat (14 days old) oral 6.2 g/kg
LD50 Rat (older adults) oral 11.5 g/kg
LD50 Dog oral 5.5 g/kg

Human toxicity values are reported below:
LDLo Infant (0-1 year) subcutaneous: 7060 mg/Kg
LDLo Human oral: 1400 mg/Kg
LDLo Child (1-13 years): 2000 mg/Kg
TDLo Man oral: 700 mg/Kg
TDLo woman oral: 256 g/Kg/12 weeks

2-propanol (isopropanol, CAS# 67-63-0)

TOXICITY SUMMARY[7]

Isopropyl alcohol is an aliphatic alcohol hydrocarbon. It is prepared from propylene, which is obtained in the cracking of petroleum or by the reduction of acetone. It is a colorless liquid which is soluble in water, alcohol, ether, acetone, benzene and chloroform. It is insoluble in salt solutions. It has a slight odor resembling a mixture of ethanol and acetone and has a slight bitter taste. It is used in antifreeze, industrial solvent, solvent for gums, shellac, essential oils, in quick drying oils, creosote and resins; extraction of alkaloids; in quick drying inks; in denaturing ethyl alcohol; in body rubs, hand lotions, after shave lotions, cosmetics and pharmaceuticals; in manufacture of acetone, glycerol, isopropyl acetate; antiseptic; rubefacient ; and pharmaceutical aid. HUMAN EXPOSURE: Toxic effects include

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central nervous depression, liver, kidney, cardiovascular depression and brain damage. It can cause drowsiness, ataxia, stupor, coma and respiratory depression, irritation of mucous membranes and eyes, gastritis, gastric hemorrhage, vomiting, pancreatitis, cold clammy skin, hypothermia, miosis, tachycardia, slow and noisy respiration. High risk of circumstances of poisoning: Accidental ingestion of rubbing alcohols/toiletries by children. There is a potential exposure from dermal and inhalation exposure in children during isopropyl alcohol sponging for control of fever. Intentional ingestion for alcoholic effect or in suicide attempts. Occupational or accidental exposure to liquid or its vapor in industrial applications. Individuals exposed to isopropyl alcohol include the following: workers in the pharmaceutical industry, cosmetic industry, chemical industry, petroleum workers, laboratory workers, printers, painters and carpenters and cabinet makers. There is little absorption through intact skin. Isopropyl alcohol is a potent eye and skin irritant. 80% of an oral dose is absorbed within 30 minutes. Absorption is complete within 2 hours although this may be delayed in a large overdose. Alveolar concentration is correlated to the environmental concentration at any given time. Isopropyl alcohol is absorbed through intact skin on prolonged exposure. Isopropyl alcohol distributes in body water with an apparent volume of distribution of 0.6-0.7 L/kg. 20-50% of an absorbed dose is excreted unchanged. Most isopropyl alcohol is oxidized in the liver by alcohol dehydrogenase to acetone, formate and finally carbon dioxide. Acetone is slowly eliminated by the lung (40%) or kidney. Clinically insignificant excretion occurs into the stomach and saliva. Related keto acids are not produced in sufficient quantities to cause a severe metabolic acidosis. Inebriation, peripheral vasodilation has occurred. In children, hypoglycemia is particularly severe when poisoning following fasting, exercise or chronic malnutrition Lactic acidosis may occur in patients with severe liver disease, pancreatitis or receiving biguanide therapy or as a result of the hypovolemia which frequently accompanies severe intoxication. However, unlike the other toxic alcohols, isopropanol rarely causes death and is associated with ketosis without acidosis. Treatment of isopropanol ingestions are typically supportive therapy and ingestions are rarely lethal.[8]
Concerning animal studies, Isopropyl alcohol most closely follows first order kinetics, with a half life of 2.5 to 3.2 hours. The elimination half life of the active metabolite acetone is significantly prolonged to about 5 hours in rats. In rat hepatocytes the following has been observed: marked depletion of glutathione, increased malondialdehyde production, decreased protein sulfhydryls content and leakage of lactic dehydrogenase with loss of membrane activity.

Skin, Eye, and Respiratory Irritations

Mild irritation of the eyes, nose and throat was induced in human subjects exposed for 3 to 5 min to 400 ppm of isopropyl alcohol.[9]
The vapors are mildly irritating to the eyes, nose, and throat.[10]
SINCE ISOPROPYL ALCOHOL HAS GREATER FAT-SOLVENT EFFECTS THAN ETHYL ALCOHOL, REPEATED USE HAS A DRYING EFFECT ON THE SKIN.[11]
ISOPROPYL ALCOHOL IS NOT A DERMAL IRRITANT, ALTHOUGH SEVERE CASES OF ALLERGIC CONTACT DERMATITIS HAVE BEEN REPORTED.[12]
SINCE ISOPROPYL ALCOHOL HAS GREATER FAT-SOLVENT EFFECTS THAN ETHYL ALCOHOL, REPEATED USE HAS A DRYING EFFECT ON THE SKIN.[13]

Oral Administration

ACCORDING TO CLINICAL EXPERIENCE ISOPROPYL ALCOHOL IS MORE TOXIC THAN ETHYL ALCOHOL AND LESS TOXIC THAN METHYL ALCOHOL. ITS ACUTE POTENCY AS CENTRAL NERVOUS DEPRESSANT IS

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ABOUT TWICE THAT OF ETHANOL. PROBABLE LETHAL ORAL DOSE FOR ADULT IS 8 OZ (240 ML), BUT AS LITTLE AS 20 ML IN WATER CAN PRODUCE SYMPTOMS.[14]
Although a dose of 240 to 250 mL has been proposed as lethal to humans, children and adults have survived much greater doses. For example, ingestion of 1L 70% isopropyl alcohol solution was survived with hemodialysis. Children have survived isopropanol levels of up to 500 mg/dL.[15]
A single lethal dose for a human is about 250 mL, although as little as 100 mL can be fatal.[16]
ONE MONKEY WAS GIVEN ISOPROPYL alcohol. EXAMINER HAD IMPRESSION OF CONGESTION OR HYPEREMIA OF OPTIC NERVEHEADS AFTER FIRST DOSE, THERE APPEARED TO BE NO DISTURBANCE OF THE EYES. IN SAME STUDY SEVERAL RABBITS WERE GIVEN ISOPROPYL ALC BY STOMACH TUBE and RATHER STRANGE OPHTHALMOSCOPIC OBSERVATIONS WERE REPORTED, CONSISTING OF BLURRING OR CUPPING OF OPTIC DISCS IN SOME ANIMALS.[17]

ISOPROPANOL, 50 MMOL/KG BY GASTRIC TUBE, INDUCED TRIACYLGLYCEROL ACCUMULATION IN LIVER OF FEMALE WISTAR RATS. AFTER ADMIN, LIVER PALMITATE-(14)C UPTAKE INCR WHEREAS HEPATIC PALMITATE OXIDN TO (14)CO2 WAS IMPAIRED & PALMITATE ESTERIFICATION INTO TRIACYLGLYCEROL WAS ENHANCED.[18]
Non-human toxicity values are:[19]
LD50 Dog oral 4797 mg/kg
LD50 Dog oral 4830 mg/kg
LD50 Rabbit oral 7990 mg/kg
LD50 Rabbit oral 6410 mg/kg
LD50 Rabbit oral 5030 mg/kg
LD50 Mouse oral 3600 mg/kg
LD50 Mouse oral 4475 mg/kg
LD50 Rat oral 5500 mg/kg
LD50 Rat oral 4710 mg/kg
LD50 Rat oral 5840 mg/kg
LD50 Rat oral 5280 mg/kg
LD50 Rat oral 5045 mg/kg
LC50 Rat ip 2830 mg/kg
LD50 Rat ip 2735 mg/kg
LD50 Mouse ip 4477 mg/kg
LC50 Rat iv 1088 mg/kg
LD50 Rat iv 1099 mg/kg
LD50 Mouse iv 1509 mg/kg
LD50 Rabbit dermal 12870 mg/kg
LD50 Rabbit skin 12,800 mg/kg

INHALATION EFFECTS

It has good warning properties because it causes a mild irritation of the eyes, nose, & throat at a concn level of 400 ppm.[20] 400 PPM VALUE IS CONSIDERED TO BE LOW ENOUGH NOT TO CAUSE CNS DEPRESSION ALTHOUGH SLIGHT IRRITATION MAY OCCUR.[21]
Acute inhalation exposure to isopropanol can produce central nervous system depression that may be prolonged by acetone, a metabolite of isopropanol. Lethalities have occurred in very young and newborn children. Ingestion of isopropanol has been implicated in the deaths of a number of adults, particularly among alcoholics. Pulmonary congestion was the most frequent postmortem finding and is typical, although not diagnostic or specific, of deaths involving drug-induced central nervous system depression.[22]

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Persons with pre-existing skin disorders may be more susceptible to the effects of this agent. ... In persons with impaired pulmonary function, especially those with obstructive airway diseases, the breathing of isopropyl alcohol might cause exacerbation of symptoms due to its irritant properties.[23]

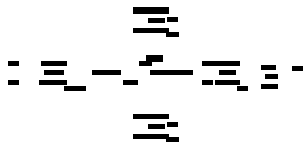
Acute Exposure through Inhalation of 400 ppm (1000 mg/m^3) isopropanol by guinea pigs for 24 hours reduced the ciliary activity in the nasal mucosa, but recovery was complete within two weeks. Higher concentrations produced damage that required longer to repair.[24]
The non-human toxicity values for inhalation are
LC50 Mouse inhalation 53 mg/L 2 hr[25]
LC50 Rat inhalation 51.045 mg/L 8 hr[26]
LC50 Rat inhalation 72.6 mg/L 4 hr[27]

Quaternary ammonium compounds (CAS# 63449-41-2, 68424-95-3, 68424-85-1)

INTRODUCTION

Quaternary ammonium compounds (QACs) are cationic surfactants. They are synthetic organically tetra-substituted ammonium compounds, where the R substituents are alkyl or heterocyclic radicals. A common characteristic of these synthetic compounds is that they have one long-chain hydrophobic alkyl group. The products used in the technical field are normally not distinct individual compounds, but mixtures of homologues, in which the average chain length and the distribution of chain lengths in the lipophilic parts of the molecules may vary according to the starting materials used. The most well investigated compound is benzalkonium chloride.
In 1988, EPA suggested the QACs clustered into four groups, so that the toxicity studies would be facilitated by selecting one representative from each group for testing[28].
Below is given the structural formula for one representative of each of the four groups:

Group I: Straight-chain alkyl or hydroxyalkyl QACs
(e.g. CAS no.124-03-8, Hexadecyl ethyl dimethyl ammonium bromide; CAS no. 1119-97-7 , Tetradecyl trimethyl ammonium bromide; CAS no. 57-09-0, Hexadecyl trimethyl ammonium bromide; CAS no. 112-03-8, Octadecyl trimethyl ammonium chloride; CAS no. 1120-02-1, Octadecyl trimethyl ammonium bromide; CAS no. 1119-94-4, Dodecyl trimethyl ammonium bromide; mixtures like Dialkyl(C8-C18)dimethyl ammonium chloride, CAS no. 68424-95-3)



Hexadecyl trimethyl ammonium bromide (CTAB)

Group II: Alkyl dimethyl benzyl ammonium compounds

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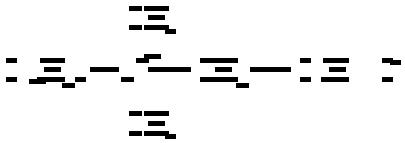
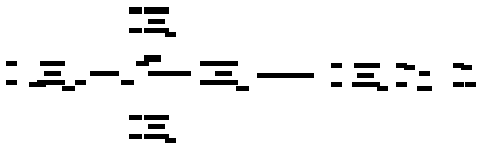
(e.g. CAS no. 139-08-2, Tetradecyl dimethyl benzyl ammonium chloride (Benzalkonium chloride); CAS no. 122-18-9, Hexadecyl dimethyl benzyl ammonium chloride; mixtures like, benzyl-C12-16-alkyldimethyl, chlorides, CAS no. 68424-85-1).



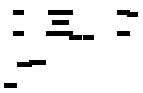
Tetradecyl dimethyl benzyl ammonium chloride (benzalkonium chloride)

Group III: Alkyl [di- and tri- chlorobenzyl] dimethyl ammonium compounds



Tetradecyl dimethyl dichlorobenzyl ammonium chloride

Group IV: Heterocyclic ammonium compounds



1-Hexadecylpyridinium chloride (cetylpyridinium chloride)

QACs are white, crystalline powders. Low molecular weight QACs are very soluble in water, but slightly or not at all soluble in solvents such as ether, petrol and benzene. As the molecular weight and chain lengths increases, the solubility in polar solvents (e.g. water) decreases and the solubility in non-polar solvents increases.[29]

QACs are synthesised industrially by alkylation of tertiary amines with alkyl halides or other alkylating species.
QACs are used as antiseptics, bactericides, fungicides, sanitisers, and softeners, but are also used in deodorants and as conditioning agents in hair cosmetics. The compounds are normally applied in concentrations between 0.01 and 1%. Concentrations in the low range are used in pharmaceutical products as topical antiseptics (skin, conjunctivae and mucous membranes). Benzalkonium chloride is a common used preservative in ophthalmic and nasal solutions.
In general, QACs within the field of antiseptics etc. contain alkyl chain lengths in the range C8 to C16 as these show good antimicrobial activities. For the use as softeners and hair conditioning agents chain lengths between C16 to C18 are used. The QACs are most effective against micro-organisms at neutral or slightly alkaline pH and become virtually inactive below pH 3.5. They are incompatible with anionic detergents such as soap, and demonstrate a high degree of binding to non-ionic surfactants [36,29,33]

The general population are exposed to QACs directly through their use in disinfectants, hair conditioning agents and fabric softening agents, and indirectly through food stuffs due to the use to clean food contact surfaces.

TOXICOKINETICS

Absorption, distribution and elimination

Oral intake

Rats received orally 14C-labeled hexadecyl trimethyl ammonium bromide (CTAB, group I). About 80% of the dose of radioactivity was found in the gastrointestinal tract 8 hours after the administration, only small amounts were found in the blood plasma and about 2% of the administrated radioactivity was excreted in the bile during the first 12 hours after treatment. The low levels of radioactivity in the plasma and bile, together with the large amount of radioactivity found in the gastrointestinal tract indicated poor intestinal absorption of CTAB. Only small amounts of radioactivity were found in the liver, kidneys, spleen, heart, lung and skeletal muscles. Within three days of ingestion 92% of the radioactivity was excreted via the faeces and 1% via urine[30].

Dermal, mucosal and eye application

Benzalkonium chloride was not detected in either venous blood or breast milk from woman using vaginal tampons containing 60 mg benzalkonium chloride (Bleau 1983 in 35),
Following the instillation of a C14 benzalkonium chloride solution onto the corneal surface of rabbits, radioactivity was detected in the corneal epithelium, endothelium and stroma, and in conjunctivae. No radioactive material was found in the aqueous humour or any other tissues, including the blood (Green 1986 in 35).
Although the absorption of QACs through normal skin probably is of less importance[31,33], studies with excised guinea pig skin have shown that the permeability constants strongly depends on the exposure time and type of skin[32].

Toxicological mechanism

The cationic surface active compounds are in general more toxic than the anionic and non-ionic surfactants. The positively-charged cationic portion is the functional part of the molecule and the local irritation effects of QACs appear to result from the quaternary ammonium cation.
Due to their relative ability to solubilise phospholipids and cholesterol in lipid membranes, QACs affect cell permeability which may lead to cell death. Further QACs denature proteins as cationic materials precipitate protein and are accompanied by generalised tissue irritation.
It has been suggested that the shown decrease in acute toxicity of QACs with chain lengths above C16 is due to decreased water solubility[31, 32,33, 34].
In general it appears that QACs with a single long-chain alkyl groups are more toxic and irritating than those with two such substitutions. Only the first mentioned are useful as germicides/detergents (Gosselin 1984).
The straight chain aliphatic QACs have been shown to release histamine from minced guinea pig lung tissue[31]. However, studies with benzalkonium chloride have shown that the effect on histamine release depends on the concentration of the solution. When cell suspensions (11% mast cells) from rats were exposed to low concentrations, a decrease in histamine release was seen. When exposed to high concentrations the opposite result was obtained[35].
In addition, QACs may show curare-like properties, a muscular paralysis with no involvement of the central nervous system. This is most often associated with lethal doses[31, 36].

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HUMAN TOXICITY

The toxicity of QACs in general is not well established, although several human fatalities have been ascribed to them. Far from all of the compounds have been put through toxicological investigation and specific investigations are used to characterise the toxicological properties of the QACs. As mentioned before, the QACs has been clustered into four groups[28], so that the toxicity would be facilitated by selecting one member from each group for testing.
The major part of the present data refer to investigation on benzalkonium chloride/alkyl dimethyl benzyl ammonium chloride which belong to group II. In the literature the generic term alkyl dimethyl benzyl ammonium chloride is often used as a general term for benzalkonium chloride.

Short term/single exposure

At least 10 human fatalities (9 adults and one child) implicating QACs are medically recorded as resulting from alkyl dimethyl benzyl ammonium chloride (C8-C18) solutions of 10 to 15% that were introduced into the victims via oral ingestion, intramuscular, intravenous or intrauterine instillation (Gleason 1969 in - 36).

Inhalation

Five deep breaths of benzalkonium chloride (4 mg/ml in 0.9% sodium chloride, nebulised) caused constrictions of the airways in asthmatic persons. The mechanism of this effect is unclear, but it was not considered by the investigators to be an allergic response[37].

Oral intake

Ingestion of 100-400 mg/kg b.w. of alkyl dimethyl benzyl ammonium chloride (10-15% solutions) caused rapid death within a few minutes to three hours in five persons. Superficial necrosis of mucous membranes was seen in the upper alimentary tract and erosion, ulceration and petecchial haemorrhages were seen throughout the small intestine. Severe changes were seen in the liver, kidneys and heart. Even in the case of prompt death lesions were seen in these organs. In addition glottic and pulmonary oedema was reported[31, 33].
In humans poisoning paralysis is not a well established phenomenon. However, curare-like paralysis was reported in three persons poisoned with dimethyl benzyl ammonium chloride (benzalkonium chloride).[33] (Gosselin 1984).
For group I TOXICITY RATINGS: 3 AND 4. 3 = MODERATELY TOXIC: PROBABLE ORAL LETHAL DOSE (HUMAN) 0.5-5 G/KG, BETWEEN 1 OZ AND 1 PINT (OR 1 LB) FOR 70 KG PERSON (150 LB). 4 = VERY TOXIC: PROBABLE ORAL LETHAL DOSE (HUMAN) 50-500 MG/KG, BETWEEN 1 TEASPOON AND 1 OZ FOR 70 KG PERSON (150 LB).[38]

Dermal application skin irritation

From human testing of different QACs the generalised conclusion is obtained that all the compounds investigated to date exhibit similar toxicological properties.
It has been concluded that the maximum concentration that did not produce irritating effect on intact skin is 0.1%. Irritation became manifest in the 1-10% range. Concentrations below 0.1% have caused irritation in persons with contact dermatitis or broken skin.[35,31,36,39]

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Sensitisation

Topical mucosal application of QACs may produce sensitisation. Reports on case stories and patch test have shown that compounds such as benzalkonium chloride (group II), cetalkonium chloride (group II) and cetrimide (group I) may possibly act as sensitisers [35,39,31,36,40]. However, in general it is suggested that QACs have a low potential for sensitising man[40].

In several studies patients from dermatological clinics have been patch tested with 0.1% benzalkonium chloride (according to standard international procedures). It was shown that the compound was able to induce skin sensitisation in about 0.5-5.5 % of the patients[41], [42], [43] (see also Camarasa 1979 in 35).

In patch studies carried out in the general population and in healthy volunteers, no sensitivity to 0,1 % benzalkonium chloride was detected[39, 44].

It is difficult to distinguish between an allergic and an irritative skin reaction due to the inherent skin irritating effect of QACs.

Mucous membranes and eye

A 0.1% benzalkonium chloride instilled into the eye produced burning and stinging reactions. In general, a 0.02% solution seems without irritating effect. A few cases of unpleasant reactions have been reported at this concentration, however only conjunctival redness and not corneal damage has been described. 0.01% did not cause any damage.[39,35]

Intrauterine instillation of alkyl dimethyl benzyl ammonium chloride in the range of 5-15 mg /kg/b.w. (10-15% solutions) has led to death[39].

Intramuscular or intravenous administration

Intramuscular or intravenous administration of 5-15 mg alkyl dimethyl benzyl ammonium chloride /kg/b.w. (10-15% solutions) caused death. In total five deaths are reported due to intramuscular, intravenous or intrauterine administration. Three of the persons who received intravenous injections died within 21-46 hours. Another person survived for 15 days[33].

Long term/repeated exposure

Inhalation

A group of 196 farmers (with or without respiratory symptoms) were evaluated for the relationship between exposure to QACs (unspecified, exposure levels not given) and respiratory disorders by testing for lung function and bronchial responsiveness to histamine. After histamine provocation statistically significant associations were found between the prevalence of mild bronchial responsiveness (including asthma-like symptoms) and the use of QACs as disinfectant. The association seems even stronger in people without respiratory symptoms[45].

Oral intake

No data have been found.

Dermal application

No data have been found.

Reproductive / developmental effects

No data have been found.

Genotoxic effects

No data have been found.

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Carcinogenic effects
No data have been found.

TOXICITY, ANIMAL DATA

The toxicological data available for most of the QACs are limited (see Human toxicity). However, studies have been performed on some of the widely used compounds. The most investigated QACs belong to group II as particularly benzalkonium chlorides have been studied.

Short term/single exposure
The acute toxicity of QACs varies with the compound and, especially, the route of administration. For some substances the LD50 value is several hundreds times lower by the i.p. or i.v. than the oral route, *whereas toxicities between the congeners only differ in the range of two to five times*.
At least some QACs are significantly more toxic in 50% dimethyl sulfoxide than in plain water when given orally[32, 36, 33].
Probably all common QAC derivatives produce similar toxic reactions, but as tested in laboratory animals the oral mean lethal dose varies with the compound between the approximate limits given below[33,36].

Inhalation
Wistar rats were exposed to an alkyl dimethyl ethyl benzyl ammonium compound at a concentration of 5.4 mg/litre (maximum attainable) for one hour. This concentration lead to 100% death[31].
A whole-body inhalation study on cetylpyridinium chloride has been reported. This is a heterocyclic QAC belonging to group IV. Groups of five rats per sex were exposed to air containing 0, 0.05, 0.07, 0.13 and 0.29 mg cetylpyridinium chloride dust/l for four hours (equal to 50, 70, 130 and 290 mg dust/m3). The particle size was less than 5 µm. The LC50 was 0.09 mg/l (90 mg/m3) with upper and lower 95% confidence limits at 0.13 and 0.07 mg/l respectively. Deaths occurred in all treated groups (2/10, 1/10, 8/10 and 10/10). No deaths were seen among controls and all the deaths occurred within 4 days of exposure. Nasal discharge and chromodacryorrhoea (red discoloration around the nares) was found in all exposed groups and during the first week transient laboured breathing/respiratory difficulty (most pronounced at the higher exposure levels) was seen. The remaining animals were killed after 14 days. Besides lesions in the eyes (see below), no gross lesions attributed to the treatment were seen in these animals. Histopathological examination of lungs and other major organs were not carried out.[46] The author has calculated that the total cetylpyrimidinium chloride exposure at the LC50 level (0.09 mg/l) was about 4-8 mg/kg b.w. and based upon this it was inferred that cetylpyrimidinium chloride could be more toxic by inhalation exposure than by oral or dermal exposure.

Oral administration LD50
LD50 values for QACs have been reported within the range of 250-1000 mg/kg for rats, 150-1000 mg/kg for mice, 150-300 mg/kg for guinea pigs and about 500 mg/kg b.w. for rabbits and dogs[31,32].
The ranges observed reflect differences in the study designs of these rather old experiments as well as differences between the various QACs.
The oral route of administration was characterised by delayed deaths, gastrointestinal lesions and respiratory and central nervous system depression. It was also found that given into a full stomach,

the QACs lead to lower mortality and fewer gastrointestinal symptoms. This support the suggestion of an irritating effect.[31,32,36,33,39]

In an attempt to elucidate the relationship between structure and toxicity of QACs, various homologues alkyl dimethyl benzyl ammonium chloride (C8-C19) were investigated with respect to LD50 in mice. *The results indicated that increasing chain length beyond C16 decreased the acute toxicity markedly and that even numbered members appeared to be more toxic than those with odd numbered carbon chains*. It was suggested that the decrease in toxicity above C16 was due to decreased water solubility.[31]

Dermal application LD50

Only a few LD50 data are available. For benzalkonium unspecified (group II) a LD50 at about 1500 mg/kg b.w. for rats has been reported. In mice a LD50 value at 1600 mg/kg b.w. for octadecyl trimethyl ammonium chloride (group I) and in rabbits a LD50 at 7700 mg/kg b.w. for cetylpyridinium chloride (group IV) have been obtained.

CTAB (group I) given subcutaneously to rabbits and guinea pigs lead to a LD50 at about 100 mg/kg. Unspecified alkyl dimethyl benzyl ammonium chloride (group II) applicated subcutaneously gave rise to values in the range of 60 (mice) to 400 (rats).[39,47].

0.1, 1.5, 6.5 and 50% solutions of benzalkonium chloride were applied on the fur (0.05 ml and then rubbed in) of two strains of mice. Each dilution was applied to 8 mice. 29 of 96 mice receiving 6.5 and 50% solutions (approximately 160 and 1250 mg/kg b.w./day) died within 72 hours after the application. Weight reduction was seen in the 6.5 and 50% groups, but not at lower levels. Necropsy of animals which died revealed discoloration of the subcutis on application site and absence of content in the gastrointestinal tract. The cause of death was not apparent.[35]

Skin irritation

From animal testing (rabbits, guinea pigs, rats and mice) of different QACs within groups I and II the generalised conclusion is obtained that all the QACs investigated to date exhibit similar skin irritating properties. In general, the maximum concentration that did not produce effect on intact skin is 0.1%. Solutions of 0.3-5% induces reactions ranging from skin irritation (erythema) to necrosis.[33,39,36]

Sensitisation

Various protocols involving repeated dermal or intradermal applications of benzalkonium chloride and challenge with 0.01-0.3% solutions have shown that benzalkonium chloride is able to induce sensitisation in guinea pigs and mice[35,39]. Older studies performed on other QACs did not reveal any signs of sensitising effect[31].

Mucous membranes and eye

Various studies concerning toxic effect of benzalkonium chloride to the eye have been performed. Instillation of different concentrations of benzalkonium chloride solutions in the rabbit eye have revealed that microscopic changes in the corneal epithelium can be induced at levels 0.01% or more. 0.001% is without damaging effect[35].

Examination of five groups I or II QACs showed that 0.063-0.125% was the "threshold irritant concentration" range.[31]

Investigation of two QACs -alkyl dimethyl benzyl ammonium chloride and cetylpyridinium chloride- showed that instillation of a 330 ppm (0.033%) solution was the maximum concentration which did not produce irritation in rabbit eyes[36].

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Eye irritation due to airborne cetylpyridinium chloride (group IV) has been reported once (see 4.1, inhalation above). Groups of five rats per sex were exposed to air containing 0, 0.05, 0.07, 0.13 and 0.29 mg cetylpyridinium chloride dust/l for four hours (equal to 50, 70, 130 and 290 mg dust/m3). Eye irritation was found in one or more animals per sex in all groups, except the controls. Lesions of the cornea, iris and/or conjunctiva were found in 4/10, 4/10, 6/10 and 6/10, respectively. All the ocular lesions were reversible[46]. In general, the longer chain alkyl trimethyl ammonium compounds are less irritating to the eye than the shorter chain homologues (C18<C12) and the dialkyl dimethyl ammonium compounds are less irritating than the corresponding mono alkyl trimethyl ammonium compounds.
Other tests for mucous membrane irritation occasionally applied to study the QACs include a penile irritation test. Seven group I QACs were tested (alkyl trimethyl ammonium compounds) in such assay. Irritating effect were seen after application of a 1-10% solutions[31].

LD and LC50 reported values for Benzyldimethyldecylammonium chloride[48]

Organism	Test Type	Route	Dose	Effect	Reference
rat	LD50	skin	1420 mg/kg (1420 mg/kg)	BEHAVIORAL: SOMNOLENCE (GENERAL DEPRESSED ACTIVITY); BLOOD: HEMORRHAGE	Pharmaceutical Chemistry Journal, 12(1593), 1978
mouse	LD50	oral	150 mg/kg (150 mg/kg)	BEHAVIORAL: SOMNOLENCE (GENERAL DEPRESSED ACTIVITY); BLOOD: HEMORRHAGE	Pharmaceutical Chemistry Journal, 12(1593), 1978
mouse	LD50	intravenous	16 mg/kg (16 mg/kg)		Journal of the American Pharmaceutical Association, Scientific Edition., 38(428), 1949

LD and LC50 reported values for Dimethyldioctadecylammonium chloride[49]

Organism	Test Type	Route	Dose	Effect	Reference
rat	LD50	oral	11300 mg/kg (11300 mg/kg)	BEHAVIORAL: SOMNOLENCE (GENERAL DEPRESSED ACTIVITY); GASTROINTESTINAL: HYPERMOTILITY, DIARRHEA; SKIN AND APPENDAGES (SKIN): HAIR: OTHER	Eisei Shikenjo Hokoku. Bulletin of the Institute of Hygienic Sciences., (101)(152), 1983 [PMID:6675765]
rat	LD50	oral	11,300 mg/kg		Lewis, R.J. Sax's Dangerous Properties of Industrial Materials. 9th ed. Volumes 1-3. New York, NY: Van Nostrand Reinhold, 1996., p. 1428

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Long term/repeated exposure

Inhalation

An inhalation toxicity study of an aerosolised hair conditioner containing an effective benzalkonium chloride concentration at 0.1% has been carried out in rats and hamsters. 12 CD rats and 12 golden hamsters were exposed to 9.9 mg conditioner/m3 five days a week, four hours/day, for 14 weeks (9.9 mg conditioner corresponds to 9.9 µ g benzalkonium chloride/m3). Body weights, haematological and biochemistry data were recorded, and gross and histopathological examination were conducted. No changes related to inhalation of the benzalkonium chloride conditioner were seen in any of the species.[35]

Oral administration

Rats

The most widely investigated group is the alkyl dimethyl benzyl ammonium chlorides, particularly benzalkonium chloride. Many long term studies have been carried out, however, they are all of a very old date and do not meet the requirements of today's quality guidelines.

Osborn-Mendel rats were fed 0.063, 0.125, 0.25 and 0.5% alkyl dimethyl benzyl ammonium chloride (group II) in the diet for two years. The measured toxicity parameters were growth rate, food consumption, mortality, and gross and microscopic (at least ten tissues) pathological examination. Suppression of growth occurred even at the lowest concentration (about 63 mg/kg b.w./day). For the remaining parameters toxic effects were seen at the 0.25% level. At about this level (250 mg/kg b.w./day) pathologic changes were reported including diarrhoea and bloating of the abdomen, brown syrupy material in the intestine, distension of the coecum and foci of haemorrhagic necrosis in the gastro-intestinal tract. All rats at the 0.5% level died within 10 weeks[31,39].

In another two years study, however, using a larger number of animals (12/sex), levels of 0.015, 0.031, 0.062, 0.125, 0.25 and 0.5% alkyl dimethyl benzyl ammonium chloride in the diet were tested. This study revealed that alkyl dimethyl benzyl ammonium chloride at 0.125% (125 mg/kg b.w./day) in the diet did not affect the growth, food consumption, blood picture or histopathology of the treated animals. At the 0.5% level only 50% of the animals survived 50 days. The pathological findings at this level were in agreement with Fitzhugh (1948) in that diarrhoea, brown viscid contents in the upper intestinal tract and acute gastritis were observed. Histopathological investigation revealed mucosal necrosis of the gastrointestinal tract[31].

In these long-term studies the alkyl dimethyl benzyl ammonium chloride were fed in the diet. To obviate the difficulties concerning calculation of the exact doses administered to the animals, studies with benzalkonium chloride given by gavage were carried out. Rats were given the compound at 50 and 100 mg/kg b.w./day for 12 weeks with water or milk as vehicle. The compound was well tolerated at 50 mg/kg b.w./day, but depression of weight gain was seen at 100 mg/kg b.w./day when water was used as vehicle[31]. It is not clear if tissue examination was performed in this study.

In a rat study doses of 5, 12.5 and 25 mg benzalkonium chloride /kg b.w./day given by gavage for two years lead to decrease in body weight at the highest dose level and increased cell growth in the gastric mucosa (probably at all dose levels)[31,39].

CTAB (group I) was offered to 10 SD rats of each sexes in concentrations of 0.007, 0.014 and 0.032% in drinking water for one year. These concentrations were calculated to deliver doses of approximately 10, 20 and 45 mg/kg b.w./day. The compound was well tolerated at the two lowest dose levels. At the highest dose level reduction in body weight, wetting and discoloration of the fur in the ventral region, decreased relative liver weight and increased relative coecum weight were seen. No compound related haematological or gross pathologic changes were seen and no microscopic alterations were found in the wall of stomach and small intestine of treated rats. No other tissues were histopathological examined[50].

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Dogs

Dogs fed alkyl dimethyl benzyl ammonium chloride in the diet for 15 weeks at levels of 0.031, 0.062, 0.125, 0.25, 0.5 and 1.0% showed that 0.125% (approximately 30 mg/kg b.w./day) was the level without toxic effect. At the 0.25% level decreased body weight and food consumption were seen. Dogs fed the 0.5 and 1% levels died. As in the rats, the pathological changes were restricted to the gastrointestinal tract and included haemorrhage and necrosis in the gastrointestinal mucosa[31].
In another study dogs (6 animals/dose) were given doses of 12.5, 25 and 50 mg benzalkonium chloride/kg b.w./day by gavage for 52 weeks with water or milk as vehicle. The benzalkonium chloride was given as a 10% solution. Deaths occurred among dogs at the two highest dose levels, but only when water was used as vehicle. The toxic effects seen at these levels - salivation, emesis and enteritis - were most intense in the dogs given the compound in water. When water was used as vehicle, intestinal congestion and inflammation was seen even in the dogs receiving 12.5 mg/kg b.w./day. These observations were, however, regarded as minor changes[35].

Guinea pig

Groups of 20 guinea pigs were given 5, 12.5 or 25 mg alkyl dimethyl benzyl ammonium chloride by gavage for one year. No overt adverse effects or cellular changes in the major organs (not further specified) were seen[35].
The above mentioned repeated toxicity studies do not cover all the studies carried out on group I and II QACs, but include the data which seems most pertinent. For the remaining studies not described above, the reported non-toxic (unspecified) levels are within the same range -or even higher- than those stated above[31].

Dermal application

Application (probably uncovered) of benzalkonium chloride at 10 mg/kg b.w./day or more five times per week for three months to rats caused changes in the blood picture, liver and kidney damage and changes in certain organ weights[39].
In a dermal study involving 100 female Swiss mice and ten New Zealand rabbits (both males and females), half of the mice and rabbits were treated with 8.5% benzalkonium chloride and the remaining half with 17% for about 80 weeks. An untreated group consisting of 100 mice and 19 rabbits served as controls. The solutions were applied uncovered twice a week (0.02 ml) on shaved dorsal skin (mice) or ear (rabbit). The highest dose level corresponds to approximately 85 mg/kg b.w./day for mice and 0.85 mg/kg/day for rabbits. Complete necropsy was performed on each animal. Skin samples and lesions in the lung, liver, kidneys were examined microscopically. Benzalkonium chloride caused ulceration, inflammation and scarring at the application site at both dose levels. No effects were seen on survival. The study indicated lack of systemic toxicity[51].

Torino, 24 april 2020

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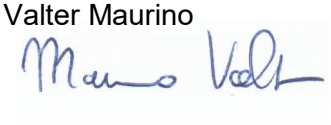

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