

EDITORIAL

Benzalkonium chloride intoxication in cats

Richard Malik, Stephen W. Page, Graham Finlay-Jones, Dominic M. Barfield, Andy H. Sparkes

THE UK is fortunate to have a Veterinary Poisons Information Service (VPIS). A paper summarised on p 229 of this issue of *Veterinary Record* by Bates and Edwards (2014) concerning benzalkonium chloride (BAC) exposure in cats is testament to the

excellent database analyses VPIS conducts as part of its mission. It is pertinent that during the period studied, only one case of feline BAC intoxication was reported in the adverse drug reaction database of the Center for Veterinary Medicines in the USA, with another single case recorded by the Australian Pesticides and Veterinary Medicines Authority, while the VPIS recorded 245 cases.

Although the paper is retrospective, the data is sufficiently robust to paint an evidence-based clinical picture for both owners and the veterinary team confronted with the management of such patients. The number of cases Bates and Edwards reviewed is huge, reflecting the commonness and importance of this toxicosis, and the excellent record-keeping of this group.

The first question that springs from the paper is 'Why cats?' (or, 'Why not dogs?'). The answer is straightforward, at least in part. The intoxication reflects the behavioural predisposition of cats to groom any abnormal material from their coat or pads. This often gets them into trouble when they share the environment

Richard Malik, DVSC, DipVetAn, MVetClinStud, PhD, FACVSc, FASM,

Centre for Veterinary Education, University of Sydney, Sydney, NSW 2006, Australia

Stephen W. Page, BSc, BVSc, DipVetClinStud, MVetClinStud, MAppSc, MANZCVSc, Advanced Veterinary Therapeutics, PO Box 905, Newtown, NSW 2042, Australia

Graham Finlay-Jones, Associate Diploma of Engineering III, Pet Friendly Cleaning Services, Vaucluse Road, Vaucluse, NSW, Australia

Dominic M. Barfield, BSc, BVSc, MVet-Med, DACVECC, FHEA, Department of Clinical Science and Services, Royal Veterinary College, Hawkshead Lane, Hatfield, Hertfordshire AL97TA, UK

Andy H. Sparkes, BVSc, PhD, Veterinary Director, International Cat Care, Tisbury, UK
e-mail: richard.malik@sydney.edu.au

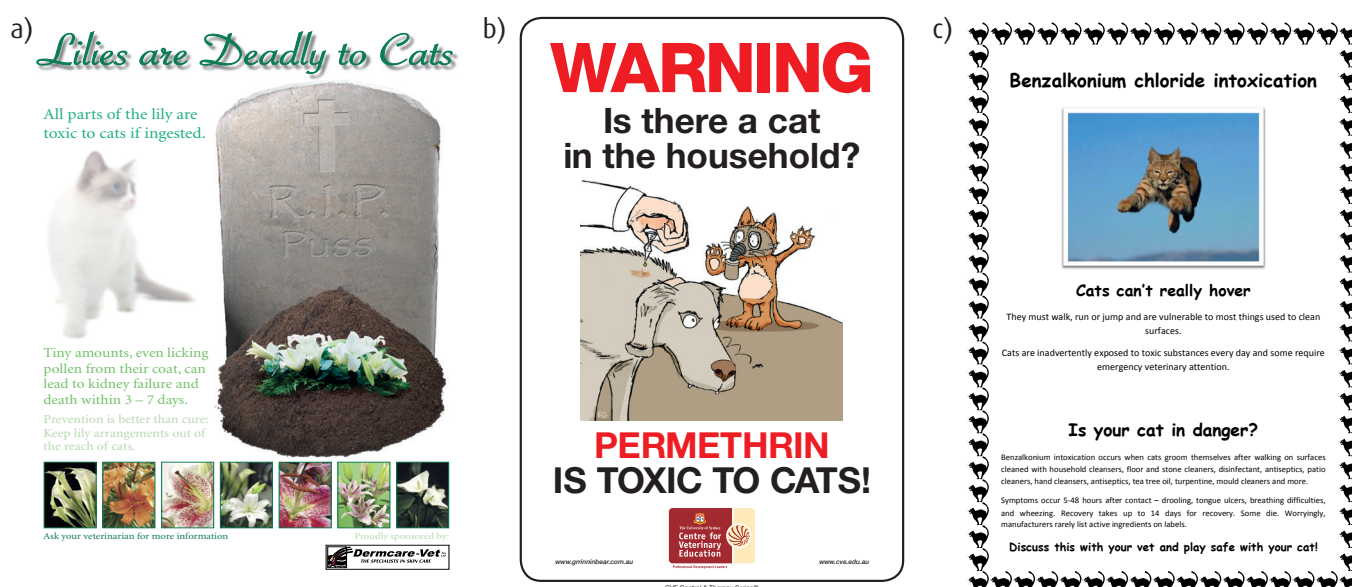


FIG 1: Emotive poster alerting cat owners to the danger of intoxication by lilies (a); humorous poster alerting cat owners to the danger of permethrin spot-on products to cats, including passive exposure from their canine companions (b); and the authors' first attempt at a poster warning owners of the dangers of surface cleaners and disinfectants (c)

with people who use different chemical agents to clean surfaces on which cats may walk or roll. It is the same reason why cats are at risk of lead intoxication from flaky paint (they groom it off their coat and ingest it) (Knight and Kumar 2003), why flea allergens in the coat can trigger severe secondary eosinophilic granuloma lesions on the lingual surface (Malik 2007), and why cats come to ingest illicit substances that mysteriously find their way onto their coat or paws (Barfield and others 2007).

This BAC toxidrome is a classic example of 'dose makes the poison'. As Bates and Edwards (2015) emphasise, BAC is widely used as an environmental disinfectant, and is included as an antibacterial agent in many ophthalmic, nasal, otic and nebuliser products. In Australia, it is included in a medicated shampoo authorised for use for dogs, cats and horses.

At low doses, BAC has a long history of safe use in humans and animals. However, as the received dose increases, so does the likelihood of adverse effects. Products for human use generally contain 0.004 to 0.01 per cent BAC, with concentrations higher than 0.1 per cent (or 1 g/l) considered potentially caustic and corrosive (Arugonda 1999, Kibble 2009, Hoffman and others 2014). BAC is a cationic surface-active agent that is cytotoxic at sufficient concentration (Eun and others 1994) and irritant to all exposed tissues including skin (Basketter and others 2004), nose (Riechelmann and others 2004), and airways (Swiercz and others 2013). In addition, BAC is well known to cause bronchoconstriction in humans, especially those with asthma (Miszkiel and others 1988), due to mast cell lysis and histamine release (Read and Kiefer 1979).

It has also been suggested that the surface active properties of BAC may decrease the normal protective mucus lining of the naso- and oropharynx (Hoffman and others 2014).

Bates and Edwards' case series is the first to comprehensively describe the dangers to cats of BAC in household cleaning products. The North American fascination with pot pourris has led to BAC being one of the most common toxicants in that jurisdiction (Richardson 1999, Merola and Dunayer 2006, Gwaltney-Brant 2013). Common to the experiences in both the UK and the USA are the over-representation of cats as intoxication victims.

The toxidrome is similar either side of the Atlantic. The cat's tongue bears the brunt of the exposure and is repeatedly exposed to injurious concentrations of BAC. Destruction of the epithelium of the dorsal lingual surface contributes to the subsequent symptomatology. With severe exposure, there is also injury to the oral cavity and possibly the pharynx and larynx, with additional upper respiratory signs. Finally, for reasons currently unclear, many of the cats develop a fever.

Apparently little can be done for affected cats by the time they present for veterinary attention, unless they are in respiratory distress, as the damage is already largely done. Sedation of the patient (if cardiovascularly stable), followed by washing in warm soapy water (soap is usually anionic and inactivates BAC) to remove any residual material on the coat and/or pads would be sensible, followed by drying the coat using a warm air blower (to avoid hypothermia). Analgesia should be provided using intravenous opioids such as methadone or buprenorphine,

avoiding non-steroidal anti-inflammatories in the short term. We note from Bates and Edwards' observations that many clinicians treat affected cats with corticosteroids.

Except possibly for cats that have laryngeal inflammation, we can see little justification for doing so, and these agents may delay healing and re-epithelisation in the oral cavity.

Although there might be a place for topical adsorbents such as sucralfate if the oesophagus is also compromised, cats do not always tolerate such measures and there is little evidence to support their use. They might, however, coat the lingual ulcers and thereby provide some relief of discomfort and facilitate healing.

Intravenous fluids are important to correct dehydration, attend to ongoing fluid requirements and correct any electrolyte abnormalities (for example, potassium supplementation). In moderate to severe cases, there is a strong case for feeding via a naso-oesophageal or oesophagostomy tube, as these cats can take over a week to resume eating (Bates and Edwards 2015). To not eat for such a period puts some cats at risk for developing hepatic lipidosis, especially if overweight at the outset. This is a serious complication, and one we have observed following this toxidrome.

In our opinion, preventing small animal intoxications is more important than actually treating them, because you save the patient a deal of suffering, and you save the owner a great deal of money. There are good alternatives to BAC, for example, steam cleaning (Wood and others 2014), and BAC is far from the ideal disinfectant, especially in a veterinary environment (Traverse and Aceto 2015).

It is hard to blame manufacturers of antiseptics and patio cleaners for this unforeseen danger to cats, yet given the frequency with which cats can be affected, it might be prudent to lobby manufacturers to place a warning label on the product advising users of the danger to companion animals, wildlife, as well as small children, who might inadvertently come into contact with these agents. As veterinarians we certainly have a role to play, individually, within our own practices and as a profession.

Many agents are labelled for use by saturating the environment with diluted product and leaving surfaces to dry before allowing animals to re-enter the treated area. Diluting a product and then allowing the solvent to evaporate leads to reconcentration and the degree of potential exposure to cats is therefore increased. We could find no studies on the concentration of BAC on treated surfaces and the period of persistence. Without such knowledge it is impossible to predict the dose to which cats might be exposed.

Media veterinarians can broach this topic on a regular basis to make the danger of such products clear to pet owners and to give them a chance to avoid doing harm. But taking it a step further, we think an innovative way forward is to design a series of emotive cartoons to graphically warn cat-owners of the adverse impact these products can have, and display posters at the point of sale in retail outlets (ideally), and also in veterinary waiting rooms (eminently do-able).

We have used this conceptual framework in an attempt to reduce the occurrence of lily intoxication (Fig 1a) and

permethrin spot-on intoxications (Fig 1b), so it should not be difficult to come up with another series of posters (for example, Fig 1c) to remind people of the dangers of using quaternary ammonium cleaners, mould removers, patio cleaners, not to mention other topical irritants such as antiseptics, tea tree oil, pyrethroids and products containing turpentine (known as mineral spirits in North America). After all, cats only have nine lives!

In the UK, this might be a job for BSAVA. But looking wider, International Cat Care and WSAVA might take the message to Europe, Asia and Oceania, while the American Board of Feline Practitioners might be tasked with the job in North America. We should be proactive. We should think locally, but also act globally.

A full accompanying bibliography for the toxicology of benzalkonium chloride can be found alongside the online version of this article.

References

- ARUGONDA, S. K. (1999) Quaternary ammonium compounds. Poisons Information Monograph G022, International Programme on Chemical Safety
- BARFIELD, D. M., PEGRUM, S. A., SNOW, D. & MALIK, R. (2007) Pupillary dilation, tachycardia and abnormal behaviour in a young cat. Diagnosis: cocaine intoxication. *Journal of Feline Medicine and Surgery* **9**, 265-270
- BASKETTER, D. A., MARRIOTT, M., GILMOUR, N. J. & WHITE, I. R. (2004) Strong irritants masquerading as skin allergens: the case of benzalkonium chloride. *Contact Dermatitis* **50**, 213-217
- BATES, N. & EDWARDS, N. (2014) Benzalkonium chloride exposure in cats: a retrospective analysis of 245 cases reported to the Veterinary Poisons Information Service (VPIS). *Veterinary Record* doi: 10.1136/vr.102653
- EUN, H. C., CHUNG, J. H., JUNG, S. Y., CHO, K. H. & KIM, K. H. (1994) A comparative study of the cytotoxicity of skin irritants on cultured human oral and skin keratinocytes. *British Journal of Dermatology* **130**, 24-28
- GWALTNEY-BRANT, S. M. (2013) Miscellaneous indoor toxicants. In *Small Animal Toxicology* 3rd edn. M.E.P.A. Talcott. pp 291-308
- HOFFMAN, R. S., HOWLAND, M. A., LEWIN, N., NELSON, L. & GOLDFRANK, L. (2014) Goldfrank's Toxicologic Emergencies 10th ed. McGraw-Hill
- KIBBLE, A. H. (2009) Benzalkonium chloride. Handbook of Pharmaceutical Excipients. 6th ed. Eds R. C. Rowe, P. J. Sheskey, M. E. Quinn. Pharmaceutical Press, pp 56-58.
- KNIGHT, T. E. & KUMAR, M. S. (2003) Lead toxicosis in cats – a review. *Journal of Feline Medicine and Surgery* **5**, 249-255
- MALIK, R. (2007) Palatine erosive lesions – 'To Bleed or not to Bleed?' *Australian Veterinary Practitioner* **37**, 54-58
- MEROLA, V. M. & DUNAYER, E. K. (2006) The 10 most common toxicoses in cats. *Veterinary Medicine* **101**, 339-342
- MISZKIEL, K. A., BEASLEY, R., RAFFERTY, P. & HOLGATE, S. T. (1988) The contribution of histamine release to bronchoconstriction provoked by inhaled benzalkonium chloride in asthma. *British Journal of Clinical Pharmacology* **25**, 157-163
- READ, G. W. & KIEFER, E. F. (1979) Benzalkonium chloride: selective inhibitor of histamine release induced by compound 48/80 and other polyamines. *Journal of Pharmacology and Experimental Therapeutics* **211**, 711-715
- RICHARDSON, J. A. (1999) Potpourri hazards in cats. *Veterinary Medicine* **94**, 1010-1012
- RIEHELMANN, H., DEUTSCHLE, T., STUHLMEIER, A., GRONAU, S. & BÜRNER, H. (2004) Nasal toxicity of benzalkonium chloride. *American Journal of Rhinology* **18**, 291-299
- SWIERCZ, R., HALATEK, T., STETKIEWICZ, J., WASOWICZ, W., KUR, B., GRZELINSKA, Z. & MAJCHEREK, W. (2013) Toxic effect in the lungs of rats after inhalation exposure to benzalkonium chloride. *International Journal of Occupational Medical and Environmental Health* **26**, 647-656
- TRAVERSE, M. & ACETO, H. (2015) Environmental cleaning and disinfection. *Journal of Small Animal Practice* (In press). doi: 10.1016/j.cvsm.2014.11.011
- WOOD, C. L., TANNER, B. D., HIGGINS, L. A., DENNIS, J. S. & LUEMPFT, L. G., 3RD (2014) Effectiveness of a steam cleaning unit for disinfection in a veterinary hospital. *American Journal of Veterinary Research* **75**, 1083-1088

doi: 10.1136/vr.h1119

Benzalkonium chloride intoxication in cats

Richard Malik, Stephen W. Page, Graham Finlay-Jones, Dominic M. Barfield and Andy H. Sparkes

Veterinary Record 2015 176: 226-228
doi: 10.1136/vr.h1119

Updated information and services can be found at:
<http://veterinaryrecord.bmj.com/content/176/9/226>

These include:

**Supplementary
Material**

Supplementary material can be found at:
<http://veterinaryrecord.bmj.com/content/suppl/2015/02/26/vr.h1119.DC1.html>

References

This article cites 12 articles, 3 of which you can access for free at:
<http://veterinaryrecord.bmj.com/content/176/9/226#BIBL>

**Email alerting
service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
<http://group.bmj.com/group/rights-licensing/permissions>

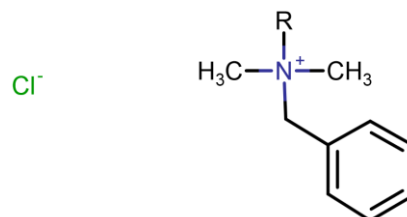
To order reprints go to:
<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:
<http://group.bmj.com/subscribe/>

Benzalkonium Chloride Bibliography

Benzalkonium chloride [INN:BAN:JAN:NF]

CAS RN: 8001-54-5



A mixture of alkylbenzyltrimethylammonium compounds, R = 8-18.

<http://chem.sis.nlm.nih.gov/chemidplus/rn/8001-54-5>

CITATION	ABSTRACT/NOTES	KEY WORDS
Adelson, L. and I. Sunshine (1952). "Fatal poisoning due to a cationic detergent of the quaternary ammonium compound type." <u>Am J Clin Pathol</u> 22 (7): 656-661.	[Gosselin et al, III-66]	Toxicity QAC human
Adriaens, E., et al. (2001). "The mucosal toxicity of different benzalkonium chloride analogues evaluated with an alternative test using slugs." <u>Pharm Res</u> 18 (7): 937-942.	PURPOSE: The objective of this study was to evaluate the mucosal toxicity of different benzalkonium chloride (BAC) analogues using slugs as the alternative test organism. METHODS: The effect of different BAC analogues on the mucosal tissue of slugs was determined from the protein, lactate dehydrogenase, and alkaline phosphatase released from the foot mucosa after treatment. Additionally, mucus production and reduction in body weight of the slugs were measured. The eye irritation potency of the molecules was evaluated with the Bovine Corneal Opacity and Permeability (BCOP) assay. The antimicrobial activity of the different BAC analogues was also assessed. RESULTS: All BAC analogues induced severe damage to the mucosal epithelium of the slugs, and the irritation increased with decreasing alkyl chain length: BAC-C16 < BAC-C14 < BAC-C12 approximately BAC-mix. A similar ranking was obtained with the BCOP assay for eye irritation. The relative order of activities among the three BAC analogues was the same, i.e., BAC-C14 > or = BAC-C16 > BAC-C12. The BAC-C14 exhibited higher activity than the BAC-mix. CONCLUSIONS: The toxicity and activity of BAC analogues depend on the alkyl chain length. The use of BAC-C14 as a conservative agent in pharmaceutical preparations instead of the BAC-mix should be considered.	MOA BAC chain length
Akutsu, I., et al. (1989). "[A case of acute benzalkonium chloride		Toxicity BAC human

CITATION	ABSTRACT/NOTES	KEY WORDS
intoxication]." <u>Nihon Naika Gakkai Zasshi</u> 78 (11): 1613-1614.		
Alfredson, B. V., et al. (1951). "Toxicity studies on alkydimethyl-benzylammonium chloride in rats and in dogs." <u>J Am Pharm Assoc Am Pharm Assoc</u> 40 (8): 263-267.		Toxicity BAC dog
Aronson, J. K. (2014). Chapter 24 - Antiseptic drugs and disinfectants. <u>Side Effects of Drugs Annual</u> . J. K. Aronson, Elsevier. Volume 35 : 435-445.	Abstract The Side Effects of Drugs Annuals form a series of volumes in which the adverse effects of drugs and adverse reactions to them are surveyed. The series supplements the contents of Meyler's Side Effects of Drugs: the International Encyclopedia of Adverse Drug Reactions and Interactions. This review of the 2011 publications on antiseptic drugs and disinfectants covers aldehydes (formaldehyde and glutaral), the bisbiguanide chlorhexidine, boric acid, cationic surfactants (benzalkonium compounds, ethylene oxide, and triclosan), halogens (fluorides and sodium hypochlorite), hydrogen peroxide, the iodophor povidone-iodine, and phenols.	Toxicity QAC human
Arugonda, S. K. (1999). Quaternary ammonium compounds. Poisons Information Monograph G022., International Programme on Chemical Safety.	http://www.inchem.org/documents/pims/chemical/pimg022.htm	Review QAC
Aursnes, J. (1982). "Ototoxic effect of quaternary ammonium compounds." <u>Acta Otolaryngol</u> 93 (5-6): 421-433.	In earlier investigations by the author it has been shown that chlorhexidine, when introduced into the middle ear of guinea pigs, caused serious damage to the inner ear. The present investigation was performed in order to study if the quaternary ammonium compounds benzethonium chloride and benzalkonium chloride, frequently used for skin disinfection, can also induce inner ear damage when introduced into the tympanic cavity of guinea pigs. The disinfectants in question, at a concentration of 0.1% and in a solution of aqua dest. or 70% alcohol, were introduced into the animals' middle ear for exposure times of 10, 30, or 60 min. The animals were sacrificed 2 or 9 weeks after the exposure and the organ of Corti and vestibular neuroepithelia were studied as surface preparations with phase contrast microscopy. It was found that most of the ears exposed to the disinfectants had suffered damage, affecting both the vestibular and cochlear parts of the inner ear. The extent of the damage was related both to the duration of exposure and to the length of the animals' survival after the exposure. Furthermore it was found that the tympanic cavity and the perilymphatic spaces of vestibulum and cochlea were pathologically changed.	Toxicity ototoxicity
Barlow, D. W., et al. (1995). "Ototoxicity of topical otomicrobial agents." <u>Acta Otolaryngol</u> 115 (2): 231-235.	Topical antimicrobial solutions are used commonly for prevention or treatment of purulent otorrhea even though most solutions contain ototoxic agents. This study compares the cochlear and middle ear toxicity of cortisporin otic solution (COS), 0.3% gentamicin ophthalmic solution (GOS), benzalkonium chloride (0.026% and 0.05%), and 1.0% Ofloxacin, a new quinolone antibiotic. Saline 0.9% was used as a control. The agent was instilled daily for 7 days into the bulla of juvenile guinea pigs. The animals were sacrificed on the 14th day. The organ of Corti was examined using surface preparation light microscopy and scanning electron microscopy. The tympanic membrane (TM) and adjacent	Toxicity ototoxicity

CITATION	ABSTRACT/NOTES	KEY WORDS
	middle ear mucosa were examined with light microscopy. The average cochlear hair cell damage was 66% for COS, 6.5% for GOS, and 1% for Ofloxacin, benzalkonium and saline. COS and benzalkonium 0.05% produced moderate mucosal thickening and inflammation. However, this was not statistically different from the mild mucosal thickening produced by saline, GOS, Ofloxacin and 0.026% benzalkonium. There was statistically significant mild to moderate thickening of the TM for all agents compared to the saline control.	
Basketter, D. A., et al. (2004). "Strong irritants masquerading as skin allergens: the case of benzalkonium chloride." <u>Contact Dermatitis</u> 50 (4): 213-217.	Chemicals may possess a number of hazards to human health including the ability to cause skin irritation and contact allergy. Identification and characterization of these properties should fall within predictive toxicology, but information derived from human exposure, including clinical experience, is also of importance. In this context, it is of interest to review the case of benzalkonium chloride, a cationic surfactant. This chemical is a well-known skin irritant, but on occasions it has also been reported to have allergenic properties, typically on the basis of positive diagnostic patch test data. Because the accumulated knowledge concerning the properties of a chemical is employed as the basis for its regulatory classification (e.g. in Europe), as well as for informing the clinical community with respect to the diagnosis of irritant versus allergic contact dermatitis (ACD), it is important to distinguish properly which chemicals are simply irritants from those which are both irritant and allergenic on skin. A review of the information on benzalkonium chloride confirms that it is a significant skin irritant. However, both predictive test results and clinical data lead to the conclusion that benzalkonium chloride is, at most, an extremely rare allergen, except perhaps in the eye, but with many supposed cases of ACD being likely to arise from the misinterpretation of patch test data. As a consequence, this substance should not normally be regarded as, or classified as, a significant skin sensitizer.	Toxicity BAC human skin irritant
Bates, N. and N. Edwards (2014). "Benzalkonium chloride exposure in cats: a retrospective analysis of 245 cases reported to the Veterinary Poisons Information Service (VPIS)." <u>Veterinary Record</u> .	Benzalkonium chloride is commonly found in household products. This retrospective study examined 245 cases of feline exposure to benzalkonium chloride-containing products reported to the Veterinary Poisons Information Service (VPIS). A single route of exposure was reported in 188 cats (ingestion 126, skin 58, buccal 4); 57 cats had multiple routes. The common products involved were household antibacterial cleaners (43.6 per cent), household disinfectants (22.3 per cent) and patio cleaners (17.5 per cent). The most common signs were hypersalivation/drooling (53.9 per cent), tongue ulceration (40.4 per cent), hyperthermia (40.4 per cent) and oral ulceration (22.9 per cent). The mean time recorded for onset of the first clinical sign was 6.4 hours (range five minutes to 48 hours, median 4.5 hours, n=60), however, the VPIS was not contacted until 14.0±13.2 hours after exposure (n=120). This figure also reflects the time of presentation. The most common treatments given were antibiotics (82.0 per cent), fluids (50.2 per cent), analgesia (45.3 per cent), gastroprotectants (31.0 per cent), dermal decontamination (24.1 per cent) and steroids (22.7 per cent). 13 cats (5.3 per cent) received syringe or nasogastric feeding. Of 245 cats, 12 (4.9 per cent) remained asymptomatic, 230 (93.9 per cent) recovered and three died (1.2 per cent). The time to recovery ranged from 1 to 360 hours (n=67) with a mean of 100.4±82.0 hours (4.2±3.4 days, median 72 hours).	Toxicity BAC cat
Baudouin, C., et al. (2010). "Preservatives in eyedrops: the good, the bad and the ugly." <u>Prog Retin Eye Res</u> 29 (4): 312-334.	There is a large body of evidence from experimental and clinical studies showing that the long-term use of topical drugs may induce ocular surface changes, causing ocular discomfort, tear film instability, conjunctival inflammation, subconjunctival fibrosis, epithelial apoptosis, corneal surface impairment, and the potential risk of failure for further glaucoma surgery. Subclinical inflammation has also been described in patients receiving antiglaucoma treatments for long periods of time. However, the mechanisms involved, i.e., allergic, toxic, or inflammatory, as well as the respective	Toxicity BAC human eye

CITATION	ABSTRACT/NOTES	KEY WORDS
	roles of the active compound and the preservative in inducing the toxic and/or proinflammatory effects of ophthalmic solutions, is still being debated. The most frequently used preservative, benzalkonium chloride (BAK), has consistently demonstrated its toxic effects in laboratory, experimental, and clinical studies. As a quaternary ammonium, this compound has been shown to cause tear film instability, loss of goblet cells, conjunctival squamous metaplasia and apoptosis, disruption of the corneal epithelium barrier, and damage to deeper ocular tissues. The mechanisms causing these effects have not been fully elucidated, although the involvement of immunoinflammatory reactions with the release of proinflammatory cytokines, apoptosis, oxidative stress, as well as direct interactions with the lipid components of the tear film and cell membranes have been well established. Preservative-induced adverse effects are therefore far from being restricted to only allergic reactions, and side effects are often very difficult to identify because they mostly occur in a delayed or poorly specific manner. Care should therefore be taken to avoid the long-term use of preservatives, otherwise a less toxic alternative to BAK should be developed, as this weakly allergenic but highly toxic compound exerts dose- and time-dependent effects. On the basis of all these experimental and clinical reports, it would be advisable to use benzalkonium-free solutions whenever possible, especially in patients with the greatest exposure to high doses or prolonged treatments, in those suffering from preexisting or concomitant ocular surface diseases, and those experiencing side effects related to the ocular surface. Indeed, mild symptoms should not be underestimated, neglected, or denied, because they may very well be the apparent manifestations of more severe, potentially threatening subclinical reactions that may later cause major concerns.	
Baur, X., et al. (2012). "Bronchial asthma and COPD due to irritants in the workplace - an evidence-based approach." <u>J Occup Med Toxicol</u> 7(1): 19.	BACKGROUND: Respiratory irritants represent a major cause of occupational obstructive airway diseases. We provide an overview of the evidence related to irritative agents causing occupational asthma or occupational COPD. METHODS: We searched MEDLINE via PubMed. Reference lists of relevant reviews were also screened. The SIGN grading system was used to rate the quality of each study. The modified RCGP three-star system was used to grade the body of evidence for each irritant agent regarding its causative role in either occupational asthma or occupational COPD. RESULTS: A total of 474 relevant papers were identified, covering 188 individual agents, professions or work-sites. The focus of most of the studies and the predominant diagnosis was occupational asthma, whereas occupational COPD arose only incidentally. The highest level assigned using the SIGN grading was 2+ (well-conducted systematic review, cohort or case-control study with a low risk of confounding or bias). According to the modified RCGP three-star grading, the strongest evidence of association with an individual agent, profession or work-site ("**") was found for 17 agents or work-sites, including benzene-1,2,4-tricarboxylic acid-1,2-anhydride, chlorine, platinum salt, isocyanates, cement dust, grain dust, animal farming, environmental tobacco smoke, welding fumes or construction work. Phthalic anhydride, glutaraldehyde, sulphur dioxide, cotton dust, cleaning agents, potrooms, farming (various), foundries were found to be moderately associated with occupational asthma or occupational COPD ("*[+]"). CONCLUSION: This study let us assume that irritant-induced occupational asthma and especially occupational COPD are considerably underreported. Defining the evidence of the many additional occupational irritants for causing airway disorders will be the subject of continued studies with implications for diagnostics and preventive measures.	Toxicity OHS
Beasley, R., et al. (2001). "Call for worldwide withdrawal of		Toxicity BAC human

CITATION	ABSTRACT/NOTES	KEY WORDS
benzalkonium chloride from nebulizer solutions." <u>J Allergy Clin Immunol</u> 107 (2): 222-223.		nebuliser
Bernstein, J. A., et al. (1994). "A combined respiratory and cutaneous hypersensitivity syndrome induced by work exposure to quaternary amines." <u>J Allergy Clin Immunol</u> 94 (2 Pt 1): 257-259.	The quaternary amine, benzalkonium chloride, has been associated with cutaneous and mucosal delayed hypersensitivity reactions and with paradoxical bronchoconstriction after use of aerosolized asthma medications. Until now, quaternary amines have not been reported to cause occupational asthma. We describe a case of occupational asthma caused by prolonged exposure to a cleaning solution containing benzalkonium chloride in the workplace. Single-blind, placebo-controlled, open-room challenges were performed to determine the specific agent responsible for the patient's symptoms. Pulmonary function and epicutaneous challenge tests were also performed. The patient had positive responses to challenges with a liquid toilet bowl cleaner containing benzalkonium chloride but was unreactive to other agents tested. Removal from the workplace resulted in complete resolution of symptoms. The exact mechanisms responsible for occupational asthma induced by quaternary amines remain unknown; however, this case emphasizes the importance of recognizing reactive chemicals as possible causes.	Toxicity OHS
BIBRA (1989). Toxicity profile Benzalkonium chloride. . Carshalton, Surrey, Great Britain, British Industrial Biological Research Association.		Review BAC
Bilbrey, S. A., et al. (1989). "Chemical burns caused by benzalkonium chloride in eight surgical cases." <u>Journal of the American Animal Hospital Association</u> 25 (1): 31-34.		Toxicity BAC dog
Blank, I. H., et al. (1964). "Penetration of cationic surfactants into skin." <u>J Invest Dermatol</u> 42 : 363-366.		PK QAC skin
Boucher, M., et al. (1992). "Possible association of benzalkonium chloride in nebulizer solutions with respiratory arrest." <u>Ann Pharmacother</u> 26 (6): 772-774.	OBJECTIVE: To report a case of possible association of benzalkonium chloride in nebulizer solutions with respiratory arrest and to review the involvement of various preservative agents in paradoxical bronchoconstrictive reactions. DATA SOURCES: Reference articles, case reports, and editorials are identified in the text. DATA SYNTHESIS: Many pharmacologic agents are available for nebulization. In addition to the active drug, these nebulizer solutions may contain preservatives. We describe a case of respiratory arrest in a 64-year-old man following nebulization therapy with albuterol and ipratropium solutions. These solutions contain benzalkonium chloride as a preservative. We are aware of only one report describing two deaths associated with such a severe reaction attributable to nebulization therapy. However, many reports of milder paradoxical bronchoconstriction are available in the medical literature.	Toxicity BAC human nebuliser

CITATION	ABSTRACT/NOTES	KEY WORDS
	CONCLUSIONS: Clinicians should be aware of the possibility of paradoxical bronchoconstrictive reactions when patients are treated with nebulized bronchodilators.	
Buffet-Bataillon, S., et al. (2012). "Emergence of resistance to antibacterial agents: the role of quaternary ammonium compounds--a critical review." <u>Int J Antimicrob Agents</u> 39 (5): 381-389.	Quaternary ammonium compounds (QACs) are widely distributed in hospitals, industry and cosmetics. Little attention has been focused on the potential impact of QACs on the emergence of antibiotic resistance in patients and the environment. To assess this issue, we conducted a literature review on QAC chemical structure, fields of application, mechanism of action, susceptibility testing, prevalence, and co- or cross-resistance to antibiotics. Special attention was paid to the effects of QACs on microflora; in particular, the issue of the potential of QACs for applying selective pressure on multiple-antibiotic-resistant organisms was raised. It was found that there is a lack of standardised procedures for interpreting susceptibility test results. QACs have different impacts on the minimum inhibitory concentrations of antibacterials depending on the antibacterial compound investigated, the resistance genes involved, the measuring methodology and the interpretative criteria. The unmet needs for adequate detection of reduced susceptibility to QACs and antibiotics include (i) a consensus definition for resistance, (ii) epidemiological cut-off values and (iii) clinical resistance breakpoints. This review advocates the design of international guidelines for QAC use.	Resistance QAC
Burge, P. S. and M. N. Richardson (1994). "Occupational asthma due to indirect exposure to lauryl dimethyl benzyl ammonium chloride used in a floor cleaner." <u>Thorax</u> 49 (8): 842-843.	The case is described of a 44 year old pharmacist who developed severe occupational asthma threatening his continued employment, confirmed by serial measurement of peak expiratory flow at home and work. The cause was found to be the cleaning agent used in his office when it was unoccupied. Bronchial challenge testing identified the specific agent to which he was sensitised as lauryl dimethyl benzyl ammonium chloride, a constituent of the floor cleaner. Substitution of this floor cleaner by a simple detergent cleaner led to a substantial improvement in his asthma, confirmed by repeated serial peak flow measurements.	Toxicity OHS
Caloni, F., et al. (2014). "Epidemiological study (2006–2012) on the poisoning of small animals by human and veterinary drugs." <u>Veterinary Record</u> 174 (9): 222.	A retrospective study was conducted on the exposure of dogs and cats to drugs, reported to the Poison Control Centre of Milan (Centro Antiveleni di Milano (CAV)) between January 2006 and December 2012. Calls related to drugs for human use and veterinary drugs accounted for 23.7 per cent of total inquiries (1415) received by CAV and mostly involved dogs (70 per cent of enquiries). Exposure to drugs for human use accounted for 79 per cent of cases involving dogs, whereas veterinary drugs were the main culprit (77 per cent) in the case of cats. The most common class of drugs for human use proved to be CNS drugs (26.8 per cent), followed by NSAIDs (19.6 per cent) and cardiovascular and endocrine drugs (12.9 per cent each). The majority of calls (95.2 per cent) related to veterinary drugs involved dogs and cats exposed to parasiticides. The outcome was reported in only 58.2 per cent of cases, and fatal poisoning accounted for 8.7 per cent of these cases. Epidemiological data from this Italian survey provide useful information on animal exposure to drugs. The knowledge of agents involved in poisoning episodes can help veterinarians make the correct diagnosis and institute preventive measures to possibly reduce animal exposure to drugs.	Toxicity review dog cat
Campbell, A. and M. Chapman (2008). Benzalkonium Chloride. <u>Handbook of Poisoning in Dogs</u>	This chapter contains section titled: * Type of Product * Presentation * Occurrence of poisoning incidences * Toxicity * Clinical effects * Treatment * References and further reading	Review BAC dog cat

CITATION	ABSTRACT/NOTES	KEY WORDS
and Cats, Blackwell Science Ltd: 17-19.		
Chataigner, D., et al. (1991). "[Acute accidental poisoning with hospital disinfectant. 45 cases of which 13 with fatal outcome]." <u>Presse Med</u> 20 (16): 741-743.	Airsane HP 800 is a disinfectant widely used in hospitals as a powder to be diluted in water. It mainly contains a mixture of quaternary ammonium compounds. Forty five cases of acute accidental poisoning with this product have been reported to the Paris Poison Centre. All the victims were mentally disturbed patients: 2 were young adults hospitalized in psychiatric units and the other 43 were old people hospitalized for senile dementia. All ingested the solid preparation which was left in their room by hospital workers who did not know it was dangerous. Corrosive burns of the mouth, pharynx, oesophagus and sometimes of the respiratory tract were produced in most patients. Thirteen of them died. All were old persons. Ten had inhalation pneumonitis and died of acute respiratory distress one hour to twelve days after taking the powder. Progressive deterioration was responsible for the death of the other three between the 19th and 40th days. These severe accidental poisonings could easily be prevented by a better information of hospital workers, and by storing the disinfectant and preparing the solution beyond the reach of patients.	Toxicity QAC human fatal
Chen, Y., et al. (2014). "Acute toxicity of the cationic surfactant C12-benzalkonium in different bioassays: how test design affects bioavailability and effect concentrations." <u>Environ Toxicol Chem</u> 33 (3): 606-615.	Using an ion-exchange-based solid-phase microextraction (SPME) method, the freely dissolved concentrations of C12-benzalkonium were measured in different toxicity assays, including 1) immobilization of <i>Daphnia magna</i> in the presence or absence of dissolved humic acid; 2) mortality of <i>Lumbriculus variegatus</i> in the presence or absence of a suspension of Organisation for Economic Co-Operation and Development (OECD) sediment; 3) photosystem II inhibition of green algae <i>Chlorella vulgaris</i> ; and 4) viability of in vitro rainbow trout gill cell line (RTgill-W1) in the presence or absence of serum proteins. Furthermore, the loss from chemical adsorption to the different test vessels used in these tests was also determined. The C12-benzalkonium sorption isotherms to the different sorbent phases were established as well. Our results show that the freely dissolved concentration is a better indicator of the actual exposure concentration than the nominal or total concentration in most test assays. <i>Daphnia</i> was the most sensitive species to C12-benzalkonium. The acute <i>Daphnia</i> and <i>Lumbriculus</i> tests both showed no enhanced toxicity from possible ingestion of sorbed C12-benzalkonium in comparison with water-only exposure, which is in accordance with the equilibrium partitioning theory. Moreover, the present study demonstrates that commonly used sorbent phases can strongly affect bioavailability and observed effect concentrations for C12-benzalkonium. Even stronger effects of decreased actual exposure concentrations resulting from sorption to test vessels, cells, and sorbent phases can be expected for more hydrophobic cationic surfactants.	Toxicity BAC bioassay
Chiambaretta, F., et al. (1997). "[Allergy and preservatives. Apropos of 3 cases of allergy to benzalkonium chloride]." <u>J Fr Ophtalmol</u> 20 (1): 8-16.	BACKGROUND: Ophthalmologists are not always aware of the hypersensitising potential of benzalkonium chloride (preservative widely used in ophthalmology). OBSERVATIONS: Hypersensitivity to benzalkonium chloride was asserted by allergologic exploration in the three cases reported. Contact allergy, a frequent phenomenon, was diagnosed in two cases. The third case represents one of the few cases described in ophthalmology of immediate hypersensitivity associated to vital risk: chemosis and angioneurotic edema is reported in a woman who had been already presented an anaphylactic shock to a quaternary ammonium family anaesthetic. DISCUSSION: The ocular allergologic evaluation is specified. Risk to benzalkonium chloride sensitisation factors (ophthalmology, presence of benzalkonium chloride in numerous daily used products) are reviewed. The risk of severe immediate allergy is increased due to the relationship	Toxicity BAC human eye

CITATION	ABSTRACT/NOTES	KEY WORDS
	of benzalkonium chloride to other quaternary ammonium compounds. CONCLUSION: Best risk prevention remains allergen eviction.	
Christensen, N. (1980). "QAC poisoning from drinking apparatus." <u>Vet Rec</u> 107 (15): 363.		Toxicity QAC animal
CIR Expert Panel (1989). "Final Report on the Safety Assessment of Benzalkonium Chloride." <u>Journal of the American College of Toxicology</u> 8 (4): 589-625.	Benzalkonium Chloride is a mixture of alkylbenzyltrimethylammonium chlorides. The ingredient is used in cosmetic products as a foaming cleansing and bactericidal agent at concentrations up to 5.0%. The compound was nonmutagenic in several different cell assays. It is a skin and ocular irritant at concentrations greater than 0.1%. This cosmetic ingredient is not a sensitizer to normal humans at concentrations of 0.1%, but may be to individuals with diseased skin. It is concluded that Benzalkonium Chloride can be safely used as an antimicrobial agent at concentrations up to 0.1%. [CIR Cosmetic Ingredient Review]	Review BAC
Coppock, R. W., et al. (1988). "The toxicology of detergents, bleaches, antiseptics and disinfectants in small animals." <u>Vet Hum Toxicol</u> 30 (5): 463-473.	Small animals are exposed to a variety of household products. The most common route of exposure is oral by direct ingestion or from grooming soiled fur and feet. The majority of household products are complex chemical mixtures. The clinician must determine the body burden of toxic or potentially toxic substances and the potential for a combination of chemicals to produce intoxication in a particular species and then plan a course of action. Toxicoses of selected household and commercial products are discussed in detail. Animals are exposed to a variety of antiseptics by numerous routes. Potential for iatrogenic intoxication from antiseptics is also discussed. An abridged version of this article will be published in the 10th edition of CURRENT VETERINARY THERAPY: SMALL ANIMAL PRACTICE, RW Kirk, editor, WB Saunders Co, Philadelphia, PA.	Review disinfectants small animals
Coulston, F., et al. (1961). "Toxicology of benzalkonium chloride given orally in milk or water to rats and dogs." <u>Toxicol Appl Pharmacol</u> 3 : 584-594.		Toxicity BAC rat dog
Cummins, L. M. and E. T. Kimura (1971). "Safety evaluation of selenium sulfide antidandruff shampoos." <u>Toxicol Appl Pharmacol</u> 20 (1): 89-96.		Toxicity BAC rat LD50
Dabezies, O. H., et al. (1966). "Evaluation of a stronger concentration of preservative (benzalkonium chloride) in contact lens soaking solution." <u>Eye Ear Nose Throat Mon</u>		Toxicity BAC human eye

CITATION	ABSTRACT/NOTES	KEY WORDS
45(10): 78 passim.		
Damour, O., et al. (1992). "Cytotoxicity evaluation of antiseptics and antibiotics on cultured human fibroblasts and keratinocytes." <u>Burns</u> 18(6): 479-485.	Infection is the greatest problem in burn patients and topical antimicrobial agents must be chosen with great care, especially when cultured skin is grafted. We examined the cytotoxic effect of six antiseptics and six antibiotics commonly used on cultured human fibroblasts and keratinocytes. Cultured cells were exposed for 15 min to Hibitane (chlorhexidine), Biseptine (chlorhexidine+benzalkonium chloride+benzyl alcohol), Benzalkonium Chloride, Yellow Betadine (polyvidone-iodine+nonoxinol), Betadine Scrub (polyvidone-iodine+quaternary ammonium) and Green Betadine (polyvidone-iodine) and viability was determined using the MTT test. At therapeutic concentrations all the antiseptics are cytotoxic for fibroblasts and keratinocytes. Additionally the cells were exposed for 48 h to vancomycin, colistin, amikacin, imipenem, pefloxacin, piperacillin and cell viability was determined using the MTT test. The concentrations of antibiotics corresponding to the plasma peak obtained after therapeutic application were not cytotoxic to the tested cells. The CD50 was much higher than the MIC (from 125 to 875 times for keratinocytes and from 1400 to 5900 times for fibroblasts). These data suggest that commonly applied antiseptics must not be used before grafting cultured skin grafts. After grafting any infection can be controlled with topical applications of appropriate antibiotics.	Toxicity BAC cytotoxicity
Day, M. J. and R. J. Washabau (2013). Chapter 55 - Esophagus. <u>Canine and Feline Gastroenterology</u>. M. J. Day and R. J. Washabau. Saint Louis, W.B. Saunders: 570-605.	Corrosive injury to the esophagus can result from several oral medications and ingested chemicals. The severity of the injury depends on chemical concentration, pH, duration of contact with the mucosa, and distribution of the lesion (e.g., focal vs. diffuse injury). Oral tablet and capsule medications with high acidity, especially doxycycline and clindamycin in cats, can cause severe focal esophagitis and strictures. 35-39 The corrosive effects of these medications are worse in cats because of the slower esophageal propagation velocity in this species (compared with the dog), and prolonged mucosal contact time when tablets or capsules are administered as a "dry swallow." 40,41 Ingested chemical irritants are usually concentrates that have highly acidic, alkaline, or oxidant properties. This should be suspected when esophagitis is accompanied by stomatitis and oropharyngeal ulcerations (mucositis). Examples include chlorine granules, button batteries, and undiluted quaternary ammonium disinfectants such as benzalkonium chloride that cats can lick from their paws and haircoat. 42,43	Toxicity BAC cat
Deutschle, T., et al. (2006). "In vitro genotoxicity and cytotoxicity of benzalkonium chloride." <u>Toxicol In Vitro</u> 20(8): 1472-1477.	Benzalkonium chloride (BAC) acts as a preservative in numerous nasal preparations. Possible genotoxic and cytotoxic effects of BAC in human respiratory epithelial BEAS-2B cells should be investigated in vitro. Cell cultures were exposed for 2h to BAC in concentrations ranging from 0.002% to 0.05%. Methyl methanesulfonate served as positive control, PBS as negative control. The tail moment of single-cell gel-electrophoresis (SCGE) was used to assess BAC-induced DNA damage. Cell viability was measured by trypan blue dye exclusion staining. Additionally, the critical micellar concentration (CMC) of BAC in PBS was detected. The tail moment increased dose dependently with the maximum value at 0.02%, and declined for higher concentrations. Nearly all cells died at low BAC concentrations up to 0.01%. Above this concentration cell viability increased. The CMC of BAC in PBS was estimated to be 0.02%. BAC caused relevant DNA changes in respiratory epithelial cells in vitro at concentrations commonly employed in commercially available nasal preparations. Some of the exposed cells survived. In further studies it could be considered to look whether these cells would still be able to proliferate and possibly fix the damage that they have possibly accumulated into an actual mutation using for example the induction of micronuclei.	Toxicity BAC cytotoxicity

CITATION	ABSTRACT/NOTES	KEY WORDS
Dhillon, A. S., et al. (1982). "Quaternary ammonium compound toxicity in chickens." <u>Avian Dis</u> 26 (4): 928-931.	Two commercial White Leghorn flocks of 41,000 and 57,000 25-week-old hens experienced death losses of 676 and 1,089 birds in a week. Six birds from each flock were presented for necropsy to the Animal Disease Diagnostic Laboratory at Purdue University with a clinical history of excessive deaths, unsatisfactory production, and dehydration. Gross lesions were present on the tongue and on oral and pharyngeal mucosa as uniformly pale or white areas with interspersed multifocal sites of ulceration. Other changes were cyanotic, shriveled combs and wattles and ruptured ovarian follicles with concurrent egg yolk peritonitis. Microscopic examination revealed large areas of coagulative necrosis with multifocal epithelial ulceration of the oral and pharyngeal mucosae. There was an intense inflammatory, heterophilic response at the periphery of affected areas. Alterations in the abdominal viscera were limited to egg yolk peritonitis. The high death rate and oral lesions were attributed to accidental use of excessive levels of a quaternary ammonium disinfectant in the drinking water.	Toxicity QAC chicken
Di Stefano, F., et al. (2003). "Cavitating BOOP associated with myeloperoxidase deficiency in a floor cleaner with an incidental heavy exposure to benzalkonium compounds." <u>J Occup Health</u> 45 (3): 182-184.		Toxicity OHS
Dolan, L. C., et al. (2013). "Safety studies conducted on a sanitizing agent containing benzalkonium chloride." <u>J Food Sci</u> 78 (1): T119-127.	Free N Clear is a sanitizing agent composed of United States Pharmacopeial Convention grade benzalkonium chloride (BAC), acetic acid, and methylparaben. Free N Clear is proposed for use as a sanitizing agent at a 1: 50 dilution (2% solution), which contains approximately 100 ppm BAC. As part of a program to assess its safety, a 2% solution of Free N Clear (diluted Free N Clear) was administered by gavage to Sprague-Dawley rats for 91d and tested for genetic toxicity in vitro and in vivo. In the 91d study, the no observable adverse-effect level of diluted Free N Clear in male and female Sprague-Dawley rats is 5000 mg/kg bw/day, the highest dose administered. Diluted Free N Clear was not mutagenic in a bacterial reverse mutation assay that tested concentrations extending into the toxic range, and did not increase the frequency of micronucleated polychromatic erythrocytes in bone marrow cells of male or female Sprague-Dawley rats when tested at the maximum permissible dose volume of 20 mL/kg bw. The results support safety of Free N Clear, when used at the concentration proposed for use. PRACTICAL APPLICATION: The significance of these findings will allow for the development of Free N Clear as a potential sanitizing agent for food.	Review BAC
Domagk, G. (1935). "Eine neue Klasse von Desinfektionsmitteln." <u>Deutsche Medizinische Wochenschrift</u> 61 : 829-832.	"Zephirol" is an aqueous solution of an alkyl-dimethyl-benzyl-ammonium-chloride. It has high disinfecting power and its aqueous solutions are colourless and odourless. In common with most other disinfectants, its disinfecting power is slightly reduced in media containing protein-G. D. SHEARER.	Review BAC
Domagk, G. (1938). Preserving and disinfecting media. United States Patent Office. United		Review QAC (first patent)

CITATION	ABSTRACT/NOTES	KEY WORDS
States of America, Alba Pharmaceutical Company, New York.		
Durepaire, R., et al. (1970). "[Balinitis caused by quaternary ammonium compounds]." <u>Bull Soc Fr Dermatol Syphiligr</u> 77 (4): 470-473.		Toxicity QAC human
Euerby, M. R. (1985). "High performance liquid chromatography of benzalkonium chlorides--variation in commercial preparations." <u>J Clin Hosp Pharm</u> 10 (1): 73-77.	High performance liquid chromatography (HPLC) has been used to identify and determine the various alkyl benzyldimethylammonium chloride homologues (C10 to C16) present in commercial benzalkonium chloride preparations. The assay is especially suited for routine quality control work since it has proved to be quick and easily reproducible. It has been found that there can be a large degree of variation in the quality of differing benzalkonium chloride sources.	Quality BAC
Eun, H. C., et al. (1994). "A comparative study of the cytotoxicity of skin irritants on cultured human oral and skin keratinocytes." <u>Br J Dermatol</u> 130 (1): 24-28.	The cytotoxicity of irritants on human oral and skin keratinocyte culture models was compared. Keratinocytes were exposed to sodium lauryl sulphate and benzalkonium chloride at concentrations of 10(-4)-10(-7) M for 24 h. Cytotoxicity was evaluated by changes in mitochondrial metabolic activity (MTT assay) and plasma membrane integrity (LDH leakage). Our results showed that oral and skin keratinocytes are equally sensitive to the irritants tested. There were marked similarities in susceptibility between each cell type cultured from six individuals. The immunohistochemical staining pattern of both cell types resembled that of the basal cell. These observations suggest that the skin keratinocyte culture model may be useful in evaluating the cytotoxicity of agents which are irritants on either the skin or oral mucosa.	Toxicity BAC cytotoxicity
Ferk, F., et al. (2007). "Benzalkonium chloride (BAC) and dimethyldioctadecyl-ammonium bromide (DDAB), two common quaternary ammonium compounds, cause genotoxic effects in mammalian and plant cells at environmentally relevant concentrations." <u>Mutagenesis</u> 22 (6): 363-370.	Quaternary ammonium compounds (QACs) are cationic surfactants that are widely used as disinfectants. In the present study, we tested two important representatives, namely, benzalkonium chloride (BAC) and dimethyldioctadecyl-ammonium bromide (DDAB) in four genotoxicity tests, namely, in the Salmonella/microsome assay with strains TA 98, TA 100 and TA 102, in the single-cell gel electrophoresis (SCGE) assay with primary rat hepatocytes and in micronucleus (MN) assays with peripheral human lymphocytes and with root tip cells of Vicia faba. In the bacterial experiments, consistently negative results were obtained in the dose range between 0.001 and 110 microg per plate in the presence and absence of metabolic activation while significant induction of DNA migration was detected in the liver cells. With BAC, a moderate but significant effect was found with an exposure concentration of 1.0 mg/l while DDAB caused damage at lower doses (0.3 mg/l). The effects were not altered when the nuclei were treated with formamidopyridine glycosylase, indicating that they are not due to formation of oxidized purines. The MN assays with blood cells were carried out under identical conditions to the SCGE experiments and a significant increase was seen at the highest dose levels (BAC: 1.0 and 3.0 mg/l; DDAB: 1 mg/l). Both compounds also caused significant induction of MN as well as inhibition of cell division in plant cells, the lowest effective levels were 1.0 and	Toxicity BAC cytotoxicity

CITATION	ABSTRACT/NOTES	KEY WORDS
	10 mg/l for DDAB and BAC, respectively. Our findings show that both chemicals induce moderate but significant genotoxic effects in eukaryotic cells at concentrations which are found in wastewaters and indicate that their release into the environment may cause genetic damage in exposed organisms. Furthermore, the direct contact of humans to QAC-containing detergents and pharmaceuticals that contain substantially higher concentrations than those which were required to cause effects in eukaryotic cells in the present study should be studied further in regard to potential DNA-damaging effects in man.	
Fitzhugh, O. G. and A. A. Nelson (1948). "Chronic oral toxicities of surface-active agents." <u>J Am Pharm Assoc Am Pharm Assoc</u> 37 (1): 29-32.		Toxicity QAC
Furrer, P., et al. (2002). "Ocular tolerance of preservatives and alternatives." <u>Eur J Pharm Biopharm</u> 53 (3): 263-280.	Eye drops are multiple dosage forms protected against microbial contamination by means of preservatives. However, the ocular tolerance of these chemicals can vary and this may result in adverse toxic or allergic reactions. This overview presents the pharmacopoeial requirements for the preservation of eye drops, the factors affecting ocular tolerance as well as the adverse external ocular effects induced by preservatives. The alternatives to the use of preservatives are also discussed, including the recent progress in eye drops packaging.	Toxicity BAC human eye
Gall, H. (1979). "[Toxic contact dermatitis due to the quaternary ammonium compound benzalkonium chloride (author's transl)]." <u>Derm Beruf Umwelt</u> 27 (5): 139-140.	A 20-year-old soldier caught an eczematous contact dermatitis on the left ear after the protection of hearing "Selektone" had been adapted. The protection of hearing had been disinfected before in a Zephirol solution 1% aqueous. Zephirol contains the quaternary ammonium compound Benzalkonium chloride. The problems of patch testing with Benzalkonium chloride are discussed.	Toxicity BAC human dermatitis
Gasset, A. R. (1977). "Benzalkonium chloride toxicity to the human cornea." <u>Am J Ophthalmol</u> 84 (2): 169-171.	A 36-year-old woman fitted with a soft contact lens after an uneventful extracapsular cataract extraction was wearing her aphakic lens successfully until she switched her lens-soaking solution to an isotonic solution of boric acid, potassium chloride, and sodium carbonate preserved with benzalkonium chloride and edetic acid. After three days her eye became inflamed and vision decreased. No endothelial damage was apparent and the anterior chamber showed 2+ cell and flare reaction. Three weeks after removal of the lens and fitting with an aphakic lens visual acuity was 6/9 (20/30). Study of the preservative by a semiquantitative dilution method together with the clinical evidence in this case proved the cytotoxic effect of benzalkonium chloride when used to sterilize soft contact lenses.	Toxicity BAC human eye
Gonzalez, M., et al. (2014). "Asthma among workers in healthcare settings: role of disinfection with quaternary ammonium compounds." <u>Clin Exp Allergy</u> 44 (3): 393-406.	INTRODUCTION: An increased incidence of asthma has been reported among healthcare workers. The role of quaternary ammonium compounds (QACs), commonly used in cleaning/disinfection products, has not been clearly defined. The aim of this study was to analyse associations between asthma and occupational exposure to disinfectants, especially QACs. METHODS: The study was performed on a stratified random sample of the various healthcare departments of 7 healthcare settings. The study included: questionnaire, physical examination and specific IgE assays. Occupational exposure assessment was performed by means of a work questionnaire, workplace studies and a review of products ingredients. Data were analysed by logistic regression. RESULTS: Response rate was 77%;	Toxicity OHS

CITATION	ABSTRACT/NOTES	KEY WORDS
	543 workers (89% female) participated; 37.1% were registered nurses (RNs), 16.4% auxiliary nurses (ANs), 17.3% cleaners; 32.8% were atopic. 335 participants were exposed to QACs. Nursing professionals reported a significantly higher risk of reported physician-diagnosed asthma and, for RNs, of nasal symptoms at work than administrative staff working in healthcare sector. This risk was particularly marked during disinfection tasks and when exposure to QACs. Exposure to QACs increased significantly the risk of reported physician-diagnosed asthma and nasal symptoms at work (adjusted OR = 7.5 and 3.2, respectively). No significant association was found with other exposures such as latex glove use, chlorinated products/bleach or glutaraldehyde. CONCLUSION: RNs and ANs presented a higher risk of reported asthma than administrative staff. The highest risk was associated with tasks involving dilution of disinfection products by manual mixing, suggesting possible exposure to repeated peaks of concentrated products known to be strong respiratory irritants. Workplace interventions should be conducted to more clearly determine QAC exposure and improve disinfection procedures.	
Gosselin, R. E., et al. (1984). <u>Clinical toxicology of commercial products (fifth ed)</u>. Baltimore Williams & Wilkins.		Review BAC
Graf, P., et al. (1995). "Benzalkonium chloride in a decongestant nasal spray aggravates rhinitis medicamentosa in healthy volunteers." <u>Clin Exp Allergy</u> 25(5): 395-400.	A randomized double-blind parallel study with 20 healthy volunteers was performed to research the effect of a preservative in a decongestant nasal spray on the development of rhinitis medicamentosa. Ten subjects received oxymetazoline nasal spray with benzalkonium chloride and the others used oxymetazoline nasal spray without the preservative three times daily for 30 days. Before starting the course of treatment and after its conclusion, recordings of the mucosal surface positions were made with rhinostereometry followed by histamine challenge tests. Symptoms of nasal stuffiness were estimated on visual analogue scales (0-100) in the morning and the evening just before using the nasal spray. After 30 days, rebound swelling and nasal stuffiness were found in both groups. In the group receiving oxymetazoline nasal spray with benzalkonium chloride the mean rebound swelling was 1.1 mm and the estimated mean evening symptom score for nasal stuffiness was 43. In the group without benzalkonium chloride the corresponding variables were significantly less marked, with a mean rebound swelling of 0.5 mm ($P < 0.05$) and a mean evening symptom score of 25 ($P < 0.05$). The increase in histamine sensitivity in both groups was interpreted as a sign of nasal hyperreactivity. A new type of nasal spray bottle was used that has been shown to prevent bacterial contamination. In conclusion, the long-term use of benzalkonium chloride in oxymetazoline nasal spray accentuates the severity of rhinitis medicamentosa in healthy volunteers.	Toxicity BAC human rhinitis
Grier, R. L. (1967). "Quaternary ammonium compound toxicosis in the dog." <u>J Am Vet Med Assoc</u> 150(9): 984-987.		Toxicity QAC dog
Gwaltney-Brant, S. M. (2013). Chapter 24 - Miscellaneous Indoor Toxicants. <u>Small Animal</u>	Cationic Detergents and Potpourris Cationic detergents are used as fabric softeners, liquid potpourris, germicides, and sanitizers and are considered highly or extremely toxic. The American Society for the Prevention of Cruelty to Animals Animal Poison Control Center (ASPCA-APCC) reports that exposures to liquid potpourri are the sixth most	Toxicity BAC cat

CITATION	ABSTRACT/NOTES	KEY WORDS
<u>Toxicology (Third Edition)</u>. M. E. P. A. Talcott. Saint Louis, W.B. Saunders: 291-308.	common toxicosis reported in cats.⁷ In addition to the cationic detergents, potpourris contain essential oils that are well absorbed dermally and through mucous membranes and can cause mucous membrane and GI irritation, along with central nervous system depression and dermal hypersensitivity and irritation. The cationic surfactants are quaternary ammonium compounds with aryl or alkyl substituent groups, one of which is often a long hydrophobic carbon chain. Generally a halogen, such as bromide, iodide, or chloride, is also attached. These agents include benzethonium chloride, benzalkonium chloride, alkyl dimethyl 3,4-dichlorobenzene, and cetyl pyridinium chloride.⁴ Toxicoses in animals and humans have been reported from quaternary ammonium compounds.⁸⁻¹⁰ The observed toxicity of cationic detergents can be divided into local effects, depending on concentration and systemic effects, which are dose related.¹⁰ Cationic detergent concentrations as low as 1% are damaging to mucous membranes, and solutions containing more than 7.5% of cationic detergents may cause corrosive burns of the mouth, pharynx, and esophagus. Quaternary ammonium compounds are absorbed from the gastrointestinal tract, but several factors modify this systemic absorption. Ethanol and isopropanol, which are often found in cationic detergent preparations, significantly enhance gastrointestinal absorption. In contrast, food and chyme in the stomach reduce absorption by forming unabsorbable complexes.²⁻¹¹ Percutaneous absorption through intact skin is not a major route of absorption for these compounds, although quaternary ammonium compounds may be absorbed through damaged skin.² Ingestion of these detergents from licking or grooming irritated skin surfaces and paws is also a significant exposure pathway for dogs and cats. A mechanism explaining the systemic effects of cationic detergent toxicity has not been established. There are conflicting reports of cholinesterase inhibition caused by quaternary ammonium compounds.³ These compounds also possess ganglionic blocking potential and a curare-like action that causes paralysis of the neuromuscular junctions of striated muscles.^{2,3,10} This hypothesis is supported by the structural similarities between quaternary ammonium compounds and decamethonium, a neuromuscular blocking agent, and hexamethonium, a ganglionic blocking agent.³ The principal clinical signs of these poisonings are profuse salivation, vomiting with possible hematemesis, muscle weakness, fasciculations, central nervous system (CNS) and respiratory depression, fever, seizures, collapse, and coma. These effects are very similar to, and must be differentiated from, those of pesticide poisonings. In cats, exposures to liquid potpourri products resulted in hypersalivation, hyperthermia, vomiting or retching, depression, dyspnea and abnormal respiratory sounds, and oral ulcers.¹² Cationic detergent ingestions usually result in corrosive damage to the mucous membranes of the mouth, tongue, pharynx, and esophagus. Shock may develop early or as the toxicosis progresses. Hair loss and skin ulcerations are frequently seen in cats,⁹ and inflammatory lesions of the paws are reported in dogs after exposure to quaternary ammonium compounds.⁸ Ocular exposure may result in clinical effects of mild discomfort to very serious corneal damage, depending on the concentration of the detergent. Treatment of ingestions requires the giving of milk, water, or egg whites. Vomiting should not be induced when the concentration of cationic detergent in the product consumed is greater than 7.5%. Oral dilution may be followed by the administration of activated charcoal and a saline cathartic. Esophagoscopy for evaluation of the degree of corrosive damage is appropriate if stridor, dysphagia, or prolonged hypersalivation is present. General supportive care should include maintenance of respiration, adequate caloric intake (e.g., placement of a percutaneous esophageal gastric [PEG] tube), GI protectants	

CITATION	ABSTRACT/NOTES	KEY WORDS
	(e.g., sucralfate), antibiotics, analgesics (e.g., butorphanol tartrate, fentanyl), corticosteroids, intravenous (IV) fluid therapy (monitor blood gas and acid-base status, and serum electrolytes), and treatment of any seizures that may occur. Patients should be monitored closely for shock. Any exposed skin should be gently but thoroughly washed with soap and water. The eyes should be thoroughly evaluated, and if ocular exposure has occurred, the eyes should be lavaged with isothermic isotonic saline for 20 to 30 minutes. Corneal ulcers should be promptly and persistently treated if present. ²	
Hann, S., et al. (2007). "Flexural allergic contact dermatitis to benzalkonium chloride in antiseptic bath oil." <u>Br J Dermatol</u> 157 (4): 795-798.	Benzalkonium chloride (BAK) is an acknowledged irritant but has also been identified as a cause of allergic contact dermatitis. The antiseptic bath emollient Oilatum Plus (Stiefel, High Wycombe, U.K.) contains a relatively high concentration of 6% BAK. We describe six patients who presented with flexural eczema, particularly involving the anogenital area, who had a history of using Oilatum Plus. Patch testing showed all six to have a type 4 allergy to BAK as well as other allergens. Avoidance of Oilatum Plus led to a resolution of the flexural eczema in each case.	Toxicity BAC human dermatitis
Hegstad, K., et al. (2010). "Does the wide use of quaternary ammonium compounds enhance the selection and spread of antimicrobial resistance and thus threaten our health?" <u>Microb Drug Resist</u> 16 (2): 91-104.	Quaternary ammonium compounds (QACs) are widely used biocides that possess antimicrobial effect against a broad range of microorganisms. These compounds are used for numerous industrial purposes, water treatment, antifungal treatment in horticulture, as well as in pharmaceutical and everyday consumer products as preserving agents, foam boosters, and detergents. Resistance toward QACs is widespread among a diverse range of microorganisms and is facilitated by several mechanisms such as modifications in the membrane composition, expression of stress response and repair systems, or expression of efflux pump genes. Development of resistance in both pathogenic and nonpathogenic bacteria has been related to application in human medicine and the food industry. QACs in cosmetic products will inevitably come into intimate contact with the skin or mucosal linings in the mouth and thus are likely to add to the selection pressure toward more QAC-resistant microorganisms among the skin or mouth flora. There is increasing evidence of coresistance and cross-resistance between QACs and a range of other clinically important antibiotics and disinfectants. Use of QACs may have driven the fixation and spread of certain resistance cassette collectors (class 1 integrons), currently responsible for a major part of antimicrobial resistance in gram-negative bacteria. More indiscriminate use of QACs such as in cosmetic products may drive the selection of further new genetic elements that will aid in the persistence and spread of antimicrobial resistance and thus in limiting our treatment options for microbial infections.	Resistance QAC
Hitosugi, M., et al. (1998). "A case of fatal benzalkonium chloride poisoning." <u>Int J Legal Med</u> 111 (5): 265-266.	Five elderly persons with senile dementia accidentally ingested Hoesmin, a 10% aqueous solution of benzalkonium chloride (BAC). The condition of one patient, an 84-year-old woman whose lips and oral cavity became erythematous, gradually deteriorated. Although gastric lavage was performed, the patient died 3 h after ingestion of Hoesmin. Autopsy revealed corrosive changes of the mucosal surfaces of the tongue, pharynx, larynx, esophagus and stomach which may have come in contact with BAC. In addition, BAC was detected in the serum. We conclude that the patient died of BAC poisoning. Fatal BAC poisoning is rare and autopsy findings in only a few cases of BAC poisoning have been reported. Our findings emphasize the risk of oral ingestion of BAC.	Toxicity BAC human ingestion fatal
Hitt, M. E. and D. L. Zoran (2008). Chapter 27 - Diseases of the Oral Cavity and Pharynx.		Toxicity BAC cat

CITATION	ABSTRACT/NOTES	KEY WORDS
<u>Handbook of Small Animal Practice (Fifth Edition)</u>. R. V. Morgan. Saint Louis, W.B. Saunders: 295-308.		
Hoffman, R. S., et al. (2014). <u>Goldfrank's toxicologic emergencies (10th edition)</u>. New York, McGraw-Hill.		Review BAC
Holle, G. E. (1991). "Changes in the structure and regeneration mode of the rat small intestinal mucosa following benzalkonium chloride treatment." <u>Gastroenterology</u> 101(5): 1264-1273.	Tritiated thymidine was administered IP to rats that had been exposed to benzalkonium chloride in the duodenum, jejunum, and ileum, resulting in neuronal ablation. Epithelial cell proliferation and migration were studied 21 and 7 days after treatment. Significant hyperplasia and hypertrophy of the villi and crypts was seen from day 7 on. This was half as pronounced as that of the muscle layer, whose maximal percent increase was not seen until day 21. In the crypt, the proliferation had increased significantly (65% 3H index corrected) and its zone had expanded proportionally to the total crypt depth. After an average of 36 hours in the ileum (48 hours in normal rats), labeled cells reached the tip of the lengthened villi, reflecting significantly accelerated migration. Concerning the distributional pattern of the labeled cells in the crypt, a nonsignificant shift to the lower two thirds of the crypt could be distinguished. From this the author concludes that treatment with benzalkonium chloride influences the proliferation and migration of the epithelial cells in the treated area. These alterations may result from loss of the myenteric plexus, but other factors cannot be excluded.	Toxicity BAC rat intestine
Huang, C., et al. (2014). "[Toxicity research status of benzalkonium chloride on ocular surface]." <u>Zhonghua Yan Ke Za Zhi</u> 50(4): 303-306.	Benzalkonium chloride (BAC) is the most commonly used preservative in ophthalmic preparations. So far large bodies of clinical and experimental studies have shown that use of topical drugs containing BAC can induce a series of ocular surface diseases, such as apoptosis. However, recently, some clinical studies have shown that ocular toxicity in patients treated with eye drops containing BAC has not apparent correlated with BAC. Some scholars consider that the limitations of the research lead people to recognize the BAC toxicity exaggeratedly. Here we summarize numerous clinical and experimental studies of BAC in the past few years, and focus on reviewing recent researches of the toxic effect of BAC on ocular surface.	Toxicity BAC human eye
Innocenti, A. (1978). "[Occupational asthma due to benzalkonium chloride]." <u>Med Lav</u> 69(6): 713-715.		Toxicity OHS
Jaganathan, L. and R. Boopathy (2000). "Distinct Effect of Benzalkonium Chloride on the Esterase and Aryl Acylamidase Activities of Butyrylcholinesterase." <u>Bioorg</u>	Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) from vertebrates, other than their predominant acylcholine hydrolase (esterase) activity, display a genuine aryl acylamidase activity (AAA) capable of hydrolyzing the synthetic substrate o-nitroacetanilide to o-nitroaniline. This AAA activity is strongly inhibited by classical cholinesterase (ChE) inhibitors. In the present study, benzalkonium chloride (BAC), a cationic detergent widely used as a preservative in pharmaceutical preparations, has been shown to distinctly modulate the esterase and AAA activities of BChEs. The detergent BAC was able to inhibit the esterase activity of human serum and horse serum BChEs and	MOA ChE inhibition and AAA activation

CITATION	ABSTRACT/NOTES	KEY WORDS
<u>Chem</u> 28 (4): 242-251.	AChEs from electric eel and human erythrocyte. The remarkable property of BAC was its ability to profoundly activate the AAA activity of human serum and horse serum BChEs but not the AAA activity of AChEs. Thus BAC seem to preferentially activate the AAA activity of BChEs alone. Results of the study using the ChE active site-specific inhibitor diisopropyl phosphorofluoridate indicated that BAC binds to the active site of ChEs. Furthermore, studies using a structural homolog of BAC indicated that the alkyl group of BAC is essential not only for its interaction with ChEs but also for its distinct effect on the esterase and AAA activities of BChEs. This is the first report of a compound that inhibits the esterase activity, while simultaneously activating the AAA activity, of BChEs. Copyright 2000 Academic Press.	
Kibble, A. H. (2009). Benzalkonium chloride. <u>Handbook of Pharmaceutical Excipients</u> (6th edition). R. C. Rowe, P. J. Sheskey and M. E. Quinn. London, Pharmaceutical Press: 56-58.		Review BAC
Kilic, E., et al. (2011). "Accidental benzalkonium chloride (zephiran) injection." <u>Oral Surg Oral Med Oral Pathol Oral Radiol Endod</u> 112 (6): e103-105.	We report a case of an accidental injection of benzalkonium chloride (zephiran) instead of a local anesthetic agent during a tooth extraction. The sudden development of chin and neck swelling led to dyspnea and the patient lost consciousness. She was sent to an emergency clinic by her dentist immediately. After medical treatment for 20 days, the necrotic tissue was debrided and a gingival sulcoplasty was performed. Healing was uneventful.	Toxicity BAC human injection
Kim, S. H. and Y. Ahn (2004). "Anaphylaxis caused by benzalkonium in a nebulizer solution." <u>J Korean Med Sci</u> 19 (2): 289-290.	Benzalkonium chloride (BAC) is commonly used as a bactericidal preservative in nebulizer solutions, and can cause paradoxical onchoconstriction following nebulizing therapy in some asthmatics. We describe a case of anaphylactic shock in a 23-yr-old asthmatic woman following an intradermal skin test with a salbutamol solution containing BAC. Since she complained of cough and dyspnea after inhalation therapy with a nebulizer solution, we conducted an intradermal skin test using the same solution, which contained BAC. About 10 min later, the patient reported dizziness, palpitations, and dyspnea. On examination, tachycardia, tachypnea, and hypotension were found. She was resuscitated with a subcutaneous injection of epinephrine and an infusion of saline. One month later, we conducted a bronchial provocation test with BAC, and she showed a positive response.	Toxicity BAC human nebuliser
King, W. W., et al. (1999). "Quaternary Ammonium-Induced Cutaneous and Gastrointestinal Mucosal Lesions in a Dog." <u>Contemp Top Lab Anim Sci</u> 38 (2): 69-73.	A dog developed severe ulcerative dermatitis and upper gastrointestinal mucosal ulceration after accidental exposure to a concentrated quaternary ammonium disinfectant solution. Secondary problems included dyspnea and cholestasis. Prolonged intensive care was required and included gastrostomy tube placement via endoscopy, extensive wound care, and systemic antibiotics. In contrast to earlier reports and although the offending compound was in higher concentration, contact irritation was much more severe yet no overt systemic toxic effects were noted. This case illustrates the great caution that must be exercised when handling commonly employed laboratory germicides.	Toxicity QAC dog
Krefft, S. (1955). "Tödliche	It is a fatal poisoning after rectal application of C4 to a 50 -year-old man weighing about 65 kg , who suffered from a	Toxicity BAC

CITATION	ABSTRACT/NOTES	KEY WORDS
Vergiftung durch rectale C4-Applikation." <u>Arch Toxikol</u> 15 (7): 391-402.	chronic pulmonary tuberculosis waited various reports . As a result of confounding the bottle he received instead of a 3% PAS solution about 300 cm3 of concentrated C4 solution containing a small addition of Ultraphen given as enema . Death came under dizziness and burning abdominal pain after 5-6 min . The pathological- anatomical findings were nonspecific. For local mucosal irritation of the rectum a general hyperemia and cyanosis of the internal organs was observed .	human enema fatal
Kuca, K., et al. (2007). "Preparation of benzalkonium salts differing in the length of a side alkyl chain." <u>Molecules</u> 12 (10): 2341-2347.	Benzalkonium salts are widely used as disinfectants, biocides and detergents,among a variety of other applications. The cationic surface-activity of these salts determines their potential to act as a biocide on both target and non-target organisms. In this study, a quick synthesis of a complete set of the benzalkonium salts differing in the length of an alkylating chain (from C(2) to C(20)) is described. Moreover, their (1)H-NMR, HPLC-MS, TLC and HPLC analysis were recorded.	MOA BAC chain length
Labbe, A., et al. (2006). "Comparison of toxicological profiles of benzalkonium chloride and polyquaternium-1: an experimental study." <u>J Ocul Pharmacol Ther</u> 22 (4): 267-278.	PURPOSE: The aim of this study was to compare, in vivo on a rat model, two different preservatives- benzalkonium chloride (BAC) and polyquaternium-1 (PQ-1)-using new experimental approaches. METHODS: Thirty (30) eyes of 15 male Lewis rats were used in this study. Rats were randomly divided into five groups instilled twice a day for 11 days with eye drops containing different concentrations of preservatives, 0.1% BAC, 0.5% BAC, 0.1% PQ-1, 0.5% PQ-1, and balanced salt solution (BSS) as a control. The ocular surface toxicity of these two preservatives was investigated using new in vivo experimental approaches. Slit-lamp examination, the fluorescein test, the red phenol test, impression cytology, and in vivo corneal confocal microscopy were used to evaluate the rat ocular surface after preservative instillation. Histology sections and immunohistochemistry were also examined to confirm these results. RESULTS: Compared to PQ-1, BAC consistently and dramatically altered the corneoconjunctival surface as evaluated by slit-lamp examination, the fluorescein test, impression cytology, in vivo confocal microscopy, and histology. The 0.5% BAC solution also significantly decreased tear production compared to the control. Although 0.5% PQ-1 significantly decreased goblet cell density in comparison to the control, and some abnormalities were observed with in vivo confocal microscopy, no statistically significant differences were observed between these two groups using the tear production test, slit-lamp and fluorescein evaluation, or histology. CONCLUSION: Using an acute rat model of ocular toxicity by comparing preservatives at high concentrations, we demonstrated in vivo that high doses of PQ-1 were much less toxic than BAC. In vivo confocal microscopy and impression cytology are new promising experimental approaches to studying the rat corneoconjunctival surface, particularly in the field of ocular surface toxicity.	Toxicity BAC rat eye
Lee, B. H. and S. H. Kim (2007). "Benzalkonium chloride induced bronchoconstriction in patients with stable bronchial asthma." <u>Korean J Intern Med</u> 22 (4): 244-248.	BACKGROUND: Although benzalkonium chloride (BAC)-induced bronchoconstriction occurs in patients with bronchial asthma, BAC-containing nebulizer solutions are still being used in daily practice in Korea. The aim of this study was to evaluate the effects of inhaled aqueous solutions containing BAC. METHODS: Thirty subjects with bronchial asthma and 10 normal controls inhaled up to three 600 microg nebulized doses of BAC using a jet nebulizer. FEV1 (forced expiratory volume at one second) was measured 15 minutes after each dose. Inhalations were repeated every 20 minutes until FEV1 decreased by 15% or more (defined as BAC-induced bronchoconstriction) or the 3 doses were administered. RESULTS: The percent fall in FEV1 in response to BAC inhalation was significantly higher in asthmatics than in normal subjects (p < 0.05). BAC administration in subjects with asthma reached a plateau (maximal effect). BAC-induced bronchoconstriction was found in 6 asthmatics (20%), with two responders after the 2nd inhalation and	Toxicity BAC human broncho-constriction

CITATION	ABSTRACT/NOTES	KEY WORDS
	4 after the 3rd inhalation. The percent fall in FEV1 in response to the 1st inhalation of BAC was significantly higher in asthmatics with higher bronchial hyperresponsiveness (BHR) than in those with lower BHR. CONCLUSIONS: This study suggests that the available multi-dose nebulized solution is generally safe. However, significant bronchoconstriction can occur at a relatively low BAC dose in asthmatics with severe airway responsiveness.	
Lee, C. S., et al. (2008). "Hospital-acquired Burkholderia cepacia infection related to contaminated benzalkonium chloride." <u>J Hosp Infect</u> 68 (3): 280-282.		Contamination microbial BAC
Liang, H., et al. (2008). "Conjunctival and corneal reactions in rabbits following short- and repeated exposure to preservative-free tafluprost, commercially available latanoprost and 0.02% benzalkonium chloride." <u>Br J Ophthalmol</u> 92 (9): 1275-1282.	AIM: To compare the conjunctival and corneal reactions of commercially available solution of latanoprost (Xalatan) and preservative-free (PF) tafluprost in rabbits. METHODS: The rabbits received 50 microl of phosphate-buffered saline (PBS), PF-tafluprost 0.0015%, latanoprost 0.005% or benzalkonium chloride (BAK) 0.02%; all solutions were applied at 5 min intervals for a total of 15 times. The ocular surface toxicity was investigated using slit-lamp biomicroscopy examination, flow cytometry (FCM) and on imprints for CD45 and tumour necrosis factor-receptor 1 (TNFR1) conjunctival impression cytology (CIC) and corneal in vivo confocal microscopy (IVCM). Standard immunohistology also assessed inflammatory/apoptotic cells. RESULTS: Clinical observation and IVCM images showed the highest ocular surface toxicity with latanoprost and BAK, while PF-tafluprost and PBS eyes presented almost normal corneal aspects. FCM showed a higher expression of CD45+ and TNFR1+ in latanoprost- or BAK-instilled groups, compared with PF-tafluprost and PBS groups. Latanoprost induced fewer positive cells for inflammatory marker expressions in CIC specimens compared with BAK-alone, both of which were higher than with PF-tafluprost or PBS. Immunohistology showed the same tendency of toxic ranking. CONCLUSION: The authors confirm that rabbit corneal surfaces presented a better tolerance when treated with PF-tafluprost compared with commercially available latanoprost or BAK solution.	Toxicity BAC rabbit eye
Liang, H., et al. (2011). "Toxicological evaluation of preservative-containing and preservative-free topical prostaglandin analogues on a three-dimensional-reconstituted corneal epithelium system." <u>Br J Ophthalmol</u> 95 (6): 869-875.	AIMS: Using an established three-dimensional (3D) toxicological model based on reconstituted human corneal epithelium (HCE), this study investigated the tolerability of four topical intraocular-pressure-lowering agents: the commercial solutions of benzalkonium chloride (BAC)-containing 0.005% latanoprost, 0.004% travoprost, 0.03% bimatoprost containing 0.02%, 0.015% and 0.005% BAC, respectively, and the preservative-free (PF) tafluprost. Solutions of 0.01% and 0.02% BAC alone were also evaluated for comparison. METHODS: The 3D-HCEs were treated with solutions for 24 h followed or not by a 24 h recovery period. We used a modified MTT (3(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) procedure to assess cell viability in the HCE. Frozen sections of HCE were analysed using fluorescence microscopy for the evaluation of apoptosis (terminal deoxynucleotidyl transferase mediated dUTP nick end labelling), inflammation (ICAM-1) and proliferation (Ki67). Corneal epithelial tight junctions (occludin and tight junction protein 1 (zona occludens 1)) were also assessed by en face confocal microscopy in response to the different eye-drops. RESULTS: The MTT test revealed that the cytotoxicity of antiglaucoma eye-drops was primarily related to the concentration of their common BAC preservative (0.02%	Toxicity BAC human corneal epithelium

CITATION	ABSTRACT/NOTES	KEY WORDS
	BAC-latanoprost>0.015% BAC-travoprost>0.005% BAC-bimatoprost). PF-tafluprost did not induce any obvious cytotoxicity, showed the least expression of inflammatory or apoptotic markers and revealed preservation of membrane immunostaining of tight junction proteins in comparison with BAC-containing solutions. CONCLUSION: The toxicological model of the 3D reconstructed corneal epithelia model confirmed the ocular surface cytotoxicity of BAC-containing antiglaucomatous solutions. Compared with the formulations containing the toxic preservative BAC, PF-tafluprost was well tolerated without inducing significant corneal epithelium deterioration.	
Ling, T. C. and A. S. Highet (2000). "Irritant reactions to an antiseptic bath emollient." <u>Journal of Dermatological Treatment</u> 11 (4): 263-267.	BACKGROUND: Antiseptic bath emollients are important in the management of atopic eczema, helping to reduce the Staphylococcus aureus load and the frequency and severity of infective relapse. METHODS: We report seven cases who developed an irritant reaction to Oilatum Plus® (OP), an antiseptic bath emollient containing benzalkonium chloride (6%) and triclosan (2%). RESULTS: A typical feature is the lack of itch and patients often report only slight discomfort, in contrast with atopic eczema. Clinically, there is erythema, sometimes surmounted or surrounded by desquamation, often of an unusual brown colour. The most frequently involved areas are skin flexures and otherwise occluded skin, which may be explained by an increased penetration of the offending agent into the skin. In three cases, the reaction followed excessive or inappropriate use of OP bath emollient, but in other cases the reaction occurred even with apparently correct use of OP. CONCLUSION: Individual susceptibility to an irritant reaction from benzalkonium chloride and/or triclosan seems likely. The clinician should be aware of the potential for irritation from OP, and should advise patients on its correct use. (J Dermatol Treat (2000) 11: 263-267)	Toxicity BAC human bath
Liu, H., et al. (2001). "Toxic endothelial cell destruction from intraocular benzalkonium chloride." <u>J Cataract Refract Surg</u> 27 (11): 1746-1750.	PURPOSE: To present a cluster of cases of corneal edema occurring after phacoemulsification. SETTING: Regional hospital in rural Australia. METHODS: This retrospective case series comprised 12 patients from a single surgical list comprising 19 cases who developed persistent corneal edema after having phacoemulsification. RESULTS: After 6 months, the edema improved in 1 patient. Inadvertent intraocular use of balanced salt solution (BSS) preserved with benzalkonium chloride was found to be the cause of this serious complication. CONCLUSIONS: Benzalkonium chloride in concentrations commonly used extraocularly is highly toxic to the corneal endothelium. Every possible safeguard should be taken to prevent inadvertent intraocular use of such preserved solutions.	Toxicity BAC human eye
Lorenz, M. D., et al. (2011). Chapter 8 - Ataxia of the Head and the Limbs. <u>Handbook of Veterinary Neurology (Fifth Edition)</u> . M. D. L. R. C. Kent. Saint Louis, W.B. Saunders: 250-281.		Toxicity ototoxicity
Lovell, D. L. (1946). "Zephiran chloride for the preoperative preparation of the hands." <u>Archives of Surgery</u> 53 (3): 304-311.		Use BAC preoperative
Magee, P. (2005). Antiseptic	Publisher Summary This chapter discusses antiseptic drugs and disinfectants. Benzalkonium chloride is widely used as	Toxicity QAC

CITATION	ABSTRACT/NOTES	KEY WORDS
drugs and disinfectants. <u>Side Effects of Drugs Annual</u> . J. K. Aronson, Elsevier. Volume 28: 261-264.	a preservative in pharmaceutical formulations for the eyes, ears, and nose. Its adverse effects as a preservative have been observed recently. Bronchiolitis obliterans organizing pneumonia has also been observed. Chemical cystitis due to intravesical installation of gentian violet is rare. Cases have occurred in adult women when an undiluted solution was used. Cystitis has now been observed in a child after bladder instillation of diluted gentian violet. Ethylene oxide is a direct alkylating agent that causes increased chromosomal aberrations and sister-chromatid exchange. It is considered to be a human carcinogen, with an excess of hemopoietic cancers reported in cohorts of occupationally exposed sterilization workers. Seizures, which can occur with iodinated contrast media, have only rarely been associated with the use of povidone iodine. Partial complex seizures with secondary generalization occurred after intrapleural povidone iodine irrigation. Contact dermatitis from povidone iodine is not rare, and the responsible antigens are iodine and polyoxyethylene nonylphenyl ether. However, immediate-type allergy is uncommon.	human
Magee, P. (2010). 24 - Antiseptic drugs and disinfectants. <u>Side Effects of Drugs Annual</u> . J. K. Aronson, Elsevier. Volume 32: 437-443.	Publisher Summary This chapter discusses the effects of antiseptic drugs and disinfectants on human physiology. It is suggested at low concentrations formaldehyde irritates the respiratory tract by a chemosensory effect—that is, an interaction with local nerve endings. High occupational concentrations of inhaled formaldehyde increase the risks of impaired lung function and asthma. At low concentrations formaldehyde irritates the eyes by a chemosensory effect—that is, an interaction with local nerve endings. In a case-control study of excess nasopharyngeal cancer mortality among formaldehyde-exposed workers in Wallingford, Connecticut, the results suggested that the mortality excess may not have been because of formaldehyde exposure, but rather reflected the effect of external employment in the ferrous and non-ferrous metal industries in the local area. Chlorhexidine , a bisbiguanides, has been associated with occasional reports of ulcerative keratitis, cataract, and iris atrophy when it is used in the treatment of Acanthameba keratitis. Although chlorhexidine-induced anaphylaxis is rare, Cationic surfactants such as benzalkonium compounds has been related to ulcer in high concentration.	Toxicity QAC human
Magee, P. (2012). 24 - Antiseptic drugs and disinfectants. <u>Side Effects of Drugs Annual</u> . J. K. Aronson, Elsevier. Volume 34: 377-383.	Abstract This review of the 2010 publications on adverse reactions to antiseptic drugs and disinfectants covers aldehydes (formaldehyde and glutaral), the bisbiguanide chlorhexidine, cationic surfactants (benzalkonium, ethylene oxide, and triclosan), halogens (sodium hypochlorite and tosylchloramide), iodophors (iodine, polyvinylpyrrolidone, and povidone-iodine, and phenol. Antiseptic drugs and disinfectants continue to be used in a variety of medical and occupational settings. The respiratory effects and carcinogenicity of the sterilizing agent formaldehyde are still a subject of discussion, as is the mutagenicity of ethylene oxide in manufacturing workers and hospital sterilant workers. Adverse reactions to chlorhexidine have led to a search for alternative antiseptics for many of its clinical uses. Iodine and povidone-iodine are also well-established topical antiseptics, but they continue to cause adverse reactions, including allergic reactions and effects on thyroid function. Antiseptics and disinfectants are also used as preservatives and antimicrobials in numerous pharmaceutical formulations and personal care products, and their safety continues to be evaluated. Benzalkonium chloride as a preservative in eye drops can cause allergic reactions and dry eyes. While the safety of triclosan in antibacterial personal care products and cosmetics has been evaluated in clinical trials and human volunteers, long-term studies of its safety and possible effects on drug metabolism are still required.	Toxicity QAC human
Mandal, P. K., et al. (2004).	Four groups comprising 16 broiler birds each were given benzalkonium chloride (BC) at 100, 300, 500 and 700 ppm in	Toxicity BAC

CITATION	ABSTRACT/NOTES	KEY WORDS
"Pathology of benzalkonium chloride toxicity and its effect on body weight gain in broiler birds." <u>Indian J Exp Biol</u> 42(11): 1107-1111.	drinking water for 40 days and one group of 16 birds (control) was kept on plain water. Clinical signs in higher dose groups were respiratory distress, drooling of saliva, difficulty in deglutition, inappetence, apathy, lethargy and loss of body weight. Better body weight gain was recorded in 100 ppm dose rate. At 300 ppm, no significant body weight variation was recorded, whereas, at 500 and 700 ppm dose rates, significantly poor body weight gain was recorded. Major pathological changes were seen in 500 and 700 ppm groups, which exhibited formation of yellow diphtheritic plaques in the buccal cavity, swollen and pale commissures of beak and shortening of tongue. Minute necrotic and ulcerative foci were seen in oesophagus and crop. Hyperplastic and hypertrophic alterations were seen in mucosa of the upper digestive tract. Crop of 300 ppm group revealed formation of well developed epithelial nest with pseudoepitheliomatous hyperplasia at the margin of the lesion. Serum alanine transaminase, urea and uric acid in 500 and 700 ppm groups were elevated whereas no significant variations were observed in the 100 and 300 ppm groups. BC could enhance performance of broiler birds at 100 ppm dose rate. It should not be used beyond 300 ppm.	broiler
Marple, B., et al. (2004). "Safety review of benzalkonium chloride used as a preservative in intranasal solutions: an overview of conflicting data and opinions." <u>Otolaryngol Head Neck Surg</u> 130(1): 131-141.	BACKGROUND: For most multiuse aqueous nasal, ophthalmic, and otic products, benzalkonium chloride (BKC) is the preservative of choice. The American College of Toxicology has concluded that BKC can be safely used as an antimicrobial agent at concentrations up to 0.1%. BKC has been in clinical use since 1935 and is contained in a wide variety of prescription and over-the-counter products. However, over the past several years there have been conflicting reports of damage to human nasal epithelia and/or exacerbation of rhinitis medicamentosa associated with intranasal products containing BKC. OBJECTIVE: We sought to review the published literature and determine whether there is sufficient, clinically significant data that would confirm that intranasal products containing BKC are likely to damage human nasal epithelia or exacerbate rhinitis medicamentosa. METHODS: A literature search was conducted for in vivo and in vitro studies that evaluated the effects of BKC on human nasal epithelia. RESULTS: A total of 18 studies (14 in vivo, 4 in vitro) were identified that evaluated short- and long-term exposure of concentrations of BKC in concentrations ranging from 0.00045% to 0.1%. Eight studies, including a 6-month and 1-year long-term treatment study, demonstrated no toxic effects associated with BKC, indicating that BKC was neither harmful to nasal tissue nor prone to exacerbate rhinitis medicamentosa. Furthermore, of the 10 studies that concluded that BKC resulted in degenerative changes in human nasal epithelia (eg, ciliary beat frequency, ciliary morphology, mucociliary clearance, epithelial thinning and/or destruction) or that BKC exacerbates rhinitis medicamentosa, only 2 (it was 2 according to the Results section) of these studies were supported by statistically significant differences between BKC and placebo or active control groups were compared. It is important to note that in both of these studies, the protocol incorporated the use of oxymetazoline in some or all of the subjects. Oxymetazoline is associated with rhinitis medicamentosa. CONCLUSION: Intranasal products containing the preservative BKC appear to be safe and well tolerated for both long- and short-term clinical use.	Review BAC
Merola, V. M. and E. K. Dunayer (2006). "The 10 most common toxicoses in cats." <u>Veterinary Medicine</u> 101: 339-342.		Toxicity BAC cat
Meyer, R. J. (2001). "Comment		Toxicity BAC

CITATION	ABSTRACT/NOTES	KEY WORDS
on call for worldwide withdrawal of BAC from nebulizer solutions." <u>J Allergy Clin Immunol</u> 108 (3): 469-470.		human nebuliser
Mezger, E., et al. (2012). "Anaphylactic reaction following administration of nose drops containing benzalkonium chloride." <u>Head Face Med</u> 8 : 29.	We describe a case of anaphylactic reaction in a 46-year-old female post application of decongestant nose drops containing benzalkonium chloride (BAC). With some latency, the patient complained of cough, dyspnea, sensation of heat, croakiness and pruritus. Since she showed all of these symptoms, typical of an anaphylactic reaction, we proceeded some weeks later with a prick test with solutions containing BAC, a cationic surfactant commonly used as an antibacterial preservative in many medical solutions. The prick test was positive, confirming the assumption of a hypersensitive reaction to BAC.	Toxicity BAC human anaphylaxis
Michopoulou, A., et al. (2009). "Early intestinal morphological changes following benzalkonium chloride treatment in a rat model of short bowel syndrome." <u>Ann Ital Chir</u> 80 (2): 135-139.	BACKGROUND: The aim of this study was to assess early morphological changes of the residual small intestine 30 days after application of Benzalkonium Chloride (BAC) in a rat model of short bowel syndrome (SBS). MATERIALS AND METHODS: Twenty nine Wistar rats (260 +/- 20 g) underwent 80% midsmall bowel resection with end to end anastomosis. In group 1 (n=14) BAC solution 0.1% was applied to a 2 cm segment of jejunum, and in group 2 (n=15) normal saline was applied in a similar manner and the rats were sacrificed 30 days after operation. Specimens for histological examination were obtained initially and at sacrifice. RESULTS: In the BAC treated jejunal segment (group 1), a statistically significant increase (p< 0.05) was noted in villous height by 33.2%, in crypt depth by 26.4%, in muscle thickness by 26%, 109.6% in intestinal diameter, and 20% in total intestinal length, compared to group 2. CONCLUSIONS: BAC application to the serosal surface of rat's jejunum in SBS is a simple method that within only 4 weeks can topically augment the natural adaptation process noticed following intestinal resection. Further research with a tapering technique performed in sequence is suggested, to prevent possible problems associated with pseudoobstruction in the long term.	Toxicity BAC rat
Miszkil, K. A., et al. (1988). "The contribution of histamine release to bronchoconstriction provoked by inhaled benzalkonium chloride in asthma." <u>Br J Clin Pharmacol</u> 25 (2): 157-163.	1. To investigate the possibility that benzalkonium chloride-induced bronchoconstriction results from the endogenous release of histamine, we examined the effect of the selective histamine antagonists terfenadine and astemizole, on the airways response to inhaled benzalkonium chloride and histamine in 12 asthmatic subjects. 2. Double-blind concentration- and time-course studies were undertaken, 3 h after treatment with terfenadine or matched placebo. 3. Benzalkonium chloride and histamine caused concentration-related falls in FEV1 in all subjects with benzalkonium chloride being 7.4 times less potent as a bronchoconstrictor agonist than histamine. Terfenadine displaced to the right the benzalkonium chloride and histamine concentration-response curves by 3.7 and 111 fold respectively. Terfenadine attenuated the initial (5 min) bronchoconstrictor response to benzalkonium chloride by 40%. However, over the whole 45 min period, the response was reduced by only 13% compared with 86% inhibition of the response to histamine. 4. In an open study, eight of the 12 subjects undertook a time course study with inhaled benzalkonium chloride after pretreatment with the chemically unrelated histamine antagonist astemizole. Astemizole inhibited benzalkonium chloride-induced bronchoconstriction to an almost identical degree as that achieved with terfenadine. 5. We conclude that the initial bronchoconstrictor effect of benzalkonium chloride is due, in part, to histamine release. However, the majority of the adverse effect relates to other, as yet unrecognised effects of this bacteriocidal	MOA broncho constriction histamine release

CITATION	ABSTRACT/NOTES	KEY WORDS
	substance.	
Miszkiel, K. A., et al. (1988). "The influence of ipratropium bromide and sodium cromoglycate on benzalkonium chloride-induced bronchoconstriction in asthma." <u>Br J Clin Pharmacol</u> 26(3): 295-301.	1. Benzalkonium chloride, an antibacterial preservative that is added to nebuliser solutions, has been shown to cause bronchoconstriction when inhaled by asthmatic subjects. 2. To investigate the potential role of reflex and mast cell-dependent mechanisms in the pathogenesis of bronchoconstriction produced by benzalkonium chloride we examined the effects of ipratropium bromide and sodium cromoglycate on this response in both concentration-response and time-course studies in nine asthmatic subjects. 3. Pretreatment with inhaled ipratropium bromide (1 mg) and sodium cromoglycate (40 mg) displaced the benzalkonium chloride concentration-response curves to the right by a mean 2.2 fold and 3.1 fold respectively. 4. Ipratropium bromide and sodium cromoglycate markedly attenuated the airway response to benzalkonium chloride throughout the 45 min time course period, inhibiting the overall response by 56% and 78% respectively. 5. We conclude that benzalkonium chloride provokes bronchoconstriction in asthmatic subjects through a combination of mast cell activation and stimulation of peripheral and central neural pathways.	MOA bronchoconstriction histamine release
Moen, B., et al. (2012). "Subminimal inhibitory concentrations of the disinfectant benzalkonium chloride select for a tolerant subpopulation of Escherichia coli with inheritable characteristics." <u>Int J Mol Sci</u> 13(4): 4101-4123.	Exposure of Escherichia coli to a subminimal inhibitory concentration (25% below MIC) of benzalkonium chloride (BC), an antimicrobial membrane-active agent commonly used in medical and food-processing environments, resulted in cell death and changes in cell morphology (filamentation). A small subpopulation (1-5% of the initial population) survived and regained similar morphology and growth rate as non-exposed cells. This subpopulation maintained tolerance to BC after serial transfers in medium without BC. To withstand BC during regrowth the cells up regulated a drug efflux associated gene (the acrB gene, member of the AcrAB-TolC efflux system) and changed expression of outer membrane porin genes (ompFW) and several genes involved in protecting the cell from the osmotic- and oxidative stress. Cells pre-exposed to osmotic- and oxidative stress (sodium chloride, salicylic acid and methyl viologen) showed higher tolerance to BC. A control and two selected isolates showing increased BC-tolerance after regrowth in BC was genome sequenced. No common point mutations were found in the BC- isolates but one point mutation in gene rpsA (Ribosomal protein S1) was observed in one of the isolates. The observed tolerance can therefore not solely be explained by the observed point mutation. The results indicate that there are several different mechanisms responsible for the regrowth of a tolerant subpopulation in BC, both BC-specific and general stress responses, and that sub-MIC of BC may select for phenotypic variants in a sensitive E. coli culture.	Resistance QAC
Nagamune, H., et al. (2000). "Evaluation of the cytotoxic effects of bis-quaternary ammonium antimicrobial reagents on human cells." <u>Toxicol In Vitro</u> 14(2): 139-147.	The cytotoxic effects of newly synthesized bis-quaternary ammonium compounds (bis-QACs) and benzalkonium chloride were investigated on skin and blood cells, namely normal human epidermal keratinocytes of neonatal foreskin, a normal human skin fibroblast cell line NB1RGB, erythrocytes and a lymphoma cell line JM. The bis-QACs tested were 4, 4'-(1,6-hexamethylenedithio)bis(1-octylpyridinium iodide) (4DTBP-6, 8), N,N'-tetramethylenebis(1-dodecyl-4-carbamoylpyridinium iodide) (4BCAP-4,12), N,N'-hexamethylenebis(1-decyl-4-carbamoylpyridinium iodide) (4BCAP-6,10), 4,4'-(1,4-tetramethylenedicarbonyldiamine) bis (1-decylpyridinium iodide) (4DCABP-4,10), 4,4'-(1,4-tetramethylenedicarbonyldiamine) bis (1-dodecylpyridinium iodide) (4DCABP-4,12), 4,4'-(1,4-phenyldicarbonyldiamine)bis(1-dodecylpyridinium iodide) (4DCABP-P, 12), and 4,4'-(1,6-hexamethylenedioxycarbonyl)bis(1-dodecylpyridinium iodide) (4DOCBP-6,12). All bis-QACs consisted of two	Toxicity QAC cytotoxicity

CITATION	ABSTRACT/NOTES	KEY WORDS
	identical alkylpyridinium rings and bridge structure linking rings to each other have a methylene bridge but only 4DCABP-P,12 has a phenyl ring as a bridge. Most of the LD(50) values in acute cytotoxic assays of these bis-QACs tended to be lower than those of benzalkonium chloride. However, the comparison of the antibacterial activity against cytotoxic effects on several human cells revealed that bis-QACs, especially 4DTBP-6,8, have wide concentration ranges showing sufficient antibacterial activity and lower cytotoxic effect on human cells (except for 4DOCBP-6,12), although benzalkonium chloride caused significant human cell damage at the concentrations necessary for antibacterial activity. Moreover, judging from the LD(50) value of 4DTBP-6,8 [67 microM, a 6.7-fold higher concentration than the upper value of MIC] obtained in an artificial human skin model TESTSKIN, 4DTBP-6,8 is thought to be a more effective and safer antiseptic reagent for application to the skin surface than benzalkonium chloride. Taken together, bis-QACs are expected to be a promising new generation of antimicrobial QACs.	
NICNAS (2005). Final Report on Hazard Classification of Common Skin Sensitisers. Sydney, NSW, National Industrial Chemicals Notification and Assessment Scheme.		Review BAC
Norsworthy, G. D. (1977). "Localized disinfectant toxicity." <u>Feline Practice</u> 7(5): 48, 50.		Toxicity BAC cat
Oie, S. and A. Kamiya (1998). "Microbial contamination of benzalkonium chloride products." <u>Am J Health Syst Pharm</u> 55(23): 2534, 2537.		Contamination microbial BAC
Okan, F., et al. (2007). "A rare and preventable cause of respiratory insufficiency: ingestion of benzalkonium chloride." <u>Pediatr Emerg Care</u> 23(6): 404-406.	Caustic agents stored in ordinary containers can be ingested by children. These materials should be stored in soft distinctive bottles and in safe places. The probability of ingestion of a caustic agent is low in the newborn period, and caustic burns have been reported infrequently. In this case study, a newborn baby with severe respiratory insufficiency after ingestion of benzalkonium chloride is reported.	Toxicity BAC human ingestion
Park, H. J., et al. (2000). "Allergic contact dermatitis from benzalkonium chloride in an antifungal solution." <u>Contact Dermatitis</u> 42(5): 306-307.		Toxicity BAC human dermatitis
Preller, L., et al. (1995). "Lung	OBJECTIVES: The prevalence of chronic respiratory symptoms among pig farmers is known to be high, but the	Toxicity OHS

CITATION	ABSTRACT/NOTES	KEY WORDS
function and chronic respiratory symptoms of pig farmers: focus on exposure to endotoxins and ammonia and use of disinfectants." <u>Occup Environ Med</u> 52(10): 654-660.	aetiology of these symptoms is not yet unravelled. Long term average exposure to dust was evaluated, endotoxins and ammonia and use of disinfectants were compared with chronic respiratory symptoms and depressed base line lung function. METHODS: A cross sectional study was performed among 194 Dutch pig farmers, of whom 100 had not and 94 had chronic respiratory symptoms. Exposure-response relations were evaluated with multiple logistic and linear regression analysis. Estimates of long term average exposure were based on two personal exposure measurements, taken on one day in summer and one day in winter. Information on use of disinfectants and disinfection procedures was assessed by a walk through survey and interview by telephone. RESULTS: Exposure to dust, endotoxins, and ammonia were not related to chronic respiratory symptoms. Duration of the disinfection procedure and pressure used at disinfection were strongly and positively related to chronic respiratory symptoms. A significant inverse association between base line lung function and endotoxin exposure was found only among asymptomatic farmers. Ammonia exposure and duration of the disinfection procedure were significantly associated with base line lung function in the entire population. CONCLUSION: Results suggest that use of disinfectants is an important aetiological factor in chronic respiratory health effects of pig farmers. This factor has not been studied before. Results also suggest an aetiological role for exposure to endotoxins and ammonia in development of chronic respiratory health effects, but longitudinal studies with detailed exposure assessment strategies are required to assess their roles.	
Preller, L., et al. (1996). "Disinfectant use as a risk factor for atopic sensitization and symptoms consistent with asthma: an epidemiological study." <u>Eur Respir J</u> 9(7): 1407-1413.	Exposure to some nonallergenic compounds has been shown to increase the risk of atopic sensitization and asthmatic symptoms. In order to gain more insight into the largely unknown aetiology of respiratory symptoms in pig farmers, we studied the role of nonallergic exposure. We evaluated associations between chronic respiratory symptoms, specific and total serum immunoglobulin E (IgE) levels, use of disinfectants, and endotoxin exposure levels in a population of 194 Dutch pig farmers. Atopic sensitization (defined as increased production of IgE to common allergens) was found to occur more frequently in farmers who used disinfectants containing quaternary ammonium compounds (QACs) (odds ratio (OR) 7.4; 95% confidence interval (95% CI) 1.3-43.1). ORs for other disinfectants ranged 2.3-4.1 (NS). Atopic sensitization was not found to occur more frequently in farmers with a high endotoxin exposure. The use of disinfectants was only related to respiratory symptoms consistent with asthma in atopics. This is illustrated by the significantly elevated ORs for farmers with IgE to common allergens (house dust mite, grass pollen, birch pollen), and who used disinfectants containing QACs, in the total population and in a subgroup of the total population restricted according to bronchial hyperresponsiveness to histamine (symptomatics with a provocation dose of histamine producing a $\geq 10\%$ decrease in forced expiratory volume in one second (PC10) < 16 mg.mL⁻¹, compared with asymptomatics with a PC10 > 16 mg.mL⁻¹) (OR 4.4, 95% CI 1.3-14.6; and OR 8.2, 95% CI 1.6-42.6, respectively). Atopy and use of QACs and endotoxin exposure level taken individually were not associated with respiratory symptoms. A combination of atopic sensitization and high endotoxin exposure (> 101 ng.m⁻³) was strongly associated with respiratory symptoms in the restricted population (OR 6.1; 95% CI 1.0-36.2). Our results suggest that occupational exposure to nonallergenic agents (disinfectants) may induce immunoglobulin E sensitization to common aeroallergens, and that the combination of atopy and exposure to nonallergenic agents (disinfectants and endotoxin) is an important risk factor for development of symptoms consistent with asthma.	Toxicity OHS

CITATION	ABSTRACT/NOTES	KEY WORDS
Price, P. B. (1950). "Benzalkonium chloride (zephiran chloride) as a skin disinfectant." <u>Archives of Surgery</u> 61 (1): 23-33.		Use BAC skin disinfectant
Purohit, A., et al. (2000). "Quaternary ammonium compounds and occupational asthma." <u>Int Arch Occup Environ Health</u> 73 (6): 423-427.	OBJECTIVE: Quaternary ammonium compounds, among which benzalkonium chloride is one of the best-known, are commonly used as antiseptics, disinfectants, detergents and preservatives. They can cause occupational asthma, which however, has been rarely reported so far, despite wide use of these products. We report three such cases. Possible mechanisms causing asthma are discussed, taking into account their characteristics. METHODS AND RESULTS: Our patients, all female nurses, manifested asthma symptoms upon handling disinfectant solutions containing benzalkonium chloride. Work-related fall in PEFR was observed in all of them. The diagnosis was confirmed by challenge tests where the patients were exposed, in a closed chamber, to suspected disinfectant contained in a tray. All of the women developed early or delayed symptoms upon exposure. Similar challenge tests to placebo or other disinfectants devoid of quaternary ammonium compound were negative. CONCLUSION: These three cases, in addition to others reported in the literature, point out an as yet poorly known etiology of occupational asthma to quaternary ammonium compounds in hospital employees. The exact mechanism of the action remains unexplained.	Toxicity OHS
Quirce, S. and P. Barranco (2010). "Cleaning agents and asthma." <u>J Investig Allergol Clin Immunol</u> 20 (7): 542-550; quiz 542p following 550.	Although cleaners represent a significant part of the working population worldwide, they remain a relatively understudied occupational group. Epidemiological studies have shown an association between cleaning work and asthma, but the risk factors are uncertain. Cleaning workers are exposed to a large variety of cleaning products containing both irritants and sensitizers, as well as to common indoor allergens and pollutants. Thus, the onset or aggravation of asthma in this group could be related to an irritant-induced mechanism or to specific sensitization. The main sensitizers contained in cleaning products are disinfectants, quaternary ammonium compounds (such as benzalkonium chloride), amine compounds, and fragrances. The strongest airway irritants in cleaning products are bleach (sodium hypochlorite), hydrochloric acid, and alkaline agents (ammonia and sodium hydroxide), which are commonly mixed together. Exposure to the ingredients of cleaning products may give rise to both new-onset asthma, with or without a latency period, and work-exacerbated asthma. High-level exposure to irritants may induce reactive airways dysfunction syndrome. Cleaning workers may also have a greater relative risk of developing asthma due to prolonged low-to-moderate exposure to respiratory irritants. In addition, asthma-like symptoms without confirmed asthma are also common after exposure to cleaning agents. In many cleaners, airway symptoms induced by chemicals and odors cannot be explained by allergic or asthmatic reactions. These patients may have increased sensitivity to inhaled capsaicin, which is known to reflect sensory reactivity, and this condition is termed airway sensory hyperreactivity.	Toxicity OHS
Rahn, O. and W. P. Vaneseltine (1947). "Quaternary ammonium compounds." <u>Annual Review of Microbiology</u> 1 : 173-192.		Review QAC

CITATION	ABSTRACT/NOTES	KEY WORDS
Read, G. W. and E. F. Kiefer (1979). "Benzalkonium chloride: selective inhibitor of histamine release induced by compound 48/80 and other polyamines." <u>J Pharmacol Exp Ther</u> 211(3): 711-715.	Benzalkonium chloride (BAC) is a mixture of quaternary benzyldimethylalkylammonium chlorides which was found to inhibit histamine release induced by polyamines (48/80, ATP, bradykinin, curare, guanethidine, polylysine, polymyxin B, poly-THIQ, protamine, stilbamidine or substance P), but not that caused by antigens, concanavalin A, dextran, ionophores (A23187 or X-537A), enzymes (chymotrypsin or phospholipase C), monoamines (dextromethorphan, meperidine or chlorpromazine) or detergents (decylamine, Triton X-100 or a fire ant venom alkylpiperidine). Inhibition by 1.5 and 3 microgram of BAC per ml caused parallel shifts of the 48/80 dose-response curves to the right with no loss of efficacy, indicating that the antagonism was surmountable. Phospholipase C was partially inhibited by BAC, but Triton X-100 also inhibited phospholipase C (but not 48/80), indicating that the inhibition of phospholipase C by BAC was probably a nonspecific, detergent effect. BAC caused histamine release by itself at concentrations over 5 microgram/ml. Heat inactivation (50 degrees C for 15 min) of the mast cells did not prevent this release, suggesting a lytic mechanism for this action. Structure-activity relations studies on various members of the BAC family for their ability to inhibit 48/80-induced histamine release indicated that benzyldimethyltridecylammonium chloride was the most potent.	MOA mast cell lysis
Richardson, J. A. (1999). "Potpourri hazards in cats." <u>Veterinary Medicine</u> 94(12): 1010-1012.	Liquid potpourris are popular household fragrances, especially during the holiday season. But many people don't know that these products can be hazardous. Cats exposed to liquid potpourris can develop severe oral, dermal and ocular damage. Since 1995, veterinarians at the ASPCA Animal Poison Control Center (APCC) have consulted on more than 125 cases of cat exposure to liquid potpourri products (ASPCA APCC Database: Unpublished data, 1999). Exposed cats exhibited hypersalivation (51%), hyperthermia (42%), vomiting or retching (40%), depression (38%), dyspnea and abnormal respiratory sounds (37%), and oral ulcers (35%). Fortunately, with prompt, aggressive treatment and good supportive care, most cats will recover completely. Dogs also are affected by liquid potpourri, but the signs seen in dogs don't seem as severe. Cats may be at greater risk of exposure since liquid potpourri containers and simmer pots are usually kept on countertops or other areas where cats have easy access. Cationic Detergents. The severe clinical signs of mucosal ulceration seen with liquid potpourri ingestion appear to be due to cationic detergents. These detergents are quaternary ammonium compounds commonly used as fabric softeners, germicides, and sanitizers.¹ Cationic detergents are generally more toxic than anionic or nonionic detergents, which are commonly found in hand soaps and shampoos.² Dermal exposure to cationic detergents can result in erythema, edema, intense pain, and ulceration. Depending on the concentration of cationic detergent, ocular exposure could result in mild irritation to severe corneal injury.² Ingesting cationic detergents can lead to tissue necrosis and inflammation of the mouth, tongue, pharynx, and esophagus. Vomiting, pulmonary edema, hypotension, metabolic acidosis, and central nervous system depression have also been reported.¹ Signs of increased salivation, depression, and dyspnea could easily be confused with a cholinesterase inhibiting agent and may mislead the clinician. The severity of injury depends on the concentration of the cationic detergent and the duration of contact. The concentration of cationic detergents in liquid potpourri varies with the brand. concentrations between 1% and 7.5% have been reported to damage mucous membranes, while concentrations greater than 7.5% are considered corrosive to mucous membranes and the underlying tissue.² In the experience of the APCC, oral ulcers, stomatitis, and pharyngitis can be seen in cats exposed to concentrations of 2% or less. Mucosal ulceration could take several hours	Toxicity BAC cat

CITATION	ABSTRACT/NOTES	KEY WORDS
	to appear. Ulcerated mucous membranes appear gray-white or red and inflamed. With time, the tissue may turn black and become wrinkled. ² Lesions may be limited to the mucosal layer. Animals with mild mucosal damage after ingesting liquid potpourri may appear asymptomatic or may only exhibit hypersalivation and inappetence. Mucosal damage can extend into deeper tissues with possible perforation. Signs suggestive of mucosal ulceration include lethargy or weakness, persistent vomiting, dysphagia, excessive salivation, severe hyperthermia (> 104 F [40C]), or inappetence. The animal may also vocalize, shiver, or pant in response to pain. Complications can include aspiration pneumonia, esophageal perforation, and secondary bacterial infection. ³	
Riechelmann, H., et al. (2004). "Nasal toxicity of benzalkonium chloride." <u>Am J Rhinol</u> 18 (5): 291-299.	BACKGROUND: Benzalkonium chloride (BAC) is added to nasal preparations to prevent microbial contamination. Adverse effects of BAC on human nasal mucosa should be evaluated. METHODS: The ciliotoxicity of BAC was assessed in isolated human nasal epithelia from 15 donors. The effects of nasal BAC 0.05% (4 x 200 microL/day for 8 days) on nasal saccharin transport time, inflammatory cells and cytokine levels in nasal secretions, and nasal symptom scores were assessed in a randomized, double-blind crossover trial in 16 healthy volunteers. RESULTS: In vitro, BAC was ciliotoxic (p < 0.0001). In vivo, BAC did not alter saccharin transport time in healthy individuals (p > 0.8). No BAC-associated proinflammatory effects were observed. The staining index for myeloperoxidase was 4.8% in the placebo period and 6.3% (p = 0.42) in the BAC period. Also, nasal secretion levels of cytokines and the neuropeptide substance P revealed no BAC-associated differences. Concentrations for interleukin (IL)-6 in the placebo period were 41.5 pg/mL (0.9-91.7 pg/mL) and in the BAC period were 17.6 pg/mL (3.2-65.9 pg/mL; p = 0.46), and concentrations for substance P were 119 pg/mL (58-293 pg/mL) and 131 pg/mL (80-330 pg/mL; p = 0.31), respectively. Immediately after application, BAC caused nasal irritation (p = 0.001), a burning sensation (p = 0.0003), and hypersecretion (p = 0.006). Moreover, BAC caused a persistent sensation of nasal irritation (p < 0.01). CONCLUSION: BAC in concentrations used in nasal preparations is ciliotoxic. In healthy individuals, the ciliotoxic effect of BAC is neutralized, probably by components of nasal secretions. No BAC-related proinflammatory effects have been observed. At higher doses than normally used therapeutically, BAC caused significant nasal irritation.	Toxicity BAC human nasal
Serrano, L. J. (1972). "Dermatitis and death in mice accidentally exposed to quaternary ammonium disinfectant." <u>J Am Vet Med Assoc</u> 161 (6): 652-655.		Toxicity QAC mouse
Shapiro, S., et al. (1966). "The use of benzalkonium chloride in root canal therapy." <u>J Oral Med</u> 21 (3): 123-126.		Use QAC dental
Shumacker, H. B. and W. R. Bethea (1943). "Some studies with zephiran - With particular reference to its use in time or		Use QAC wounds

CITATION	ABSTRACT/NOTES	KEY WORDS
war." <u>Surgery</u> 14 : 931-945.		
Slifierz, M. J., et al. (2015). "Methicillin-resistant Staphylococcus aureus in commercial swine herds is associated with disinfectant and zinc usage." <u>Appl Environ Microbiol</u> .	Methicillin-resistant Staphylococcus aureus (MRSA) originating from swine is concerning for public health but an understanding of the emergence and persistence of MRSA in nursery herds is lacking. The aim of this study was to determine whether MRSA in nursery pigs is associated with particular herd-level parameters, including the use of antimicrobials, disinfectants, and heavy metals, which may be driving the selection and persistence of antimicrobial-resistance. Nasal cultures for MRSA were completed for 390 pigs from 26 farms at the end of the suckling phase and again at 3-weeks post-weaning. Herd-level information was collected and a random subset of MRSA isolates were screened for resistance to zinc and quaternary ammonium compounds (QACs). Multivariate analysis revealed that in-feed concentrations of zinc ($P<0.001$) and frequent disinfection of nursery pens ($P<0.001$) are associated with MRSA shedding in nursery pigs. Furthermore, 62.5% (25/40) of MRSA isolates carried the zinc-resistance gene <i>czrC</i> and demonstrated decreased susceptibility to zinc. All MRSA isolates carried at least 1 QAC-resistance gene. The most common genotype was <i>qacG-qacH-smr</i> which occurred in 32.5% (13/40) of isolates. Seven isolates (17.5%) demonstrated a significant tolerance to benzalkonium chloride, indicating a potential to survive commercial QAC exposure in the presence of organic matter. Overall, these findings indicate that high levels of in-feed zinc and QAC-based disinfectants may be important drivers in the selection and persistence of MRSA in commercial swine herds and these agents may potentially be co-selecting for other antimicrobial-resistance genes.	Resistance QAC
Spann, W. (1955). "Über die toxische Wirkung von Zephirol auf den menschlichen Organismus." <u>Arch Toxikol</u> 15 (4-5): 196-201.	In a 50-year old patient a greater amount Zephirol stock solution was injected into the left side of the neck by mistake instead of novocaine solution. The clinical course was noticeable that completely stayed away despite the parenteral administration of relatively large amounts of the agent curare -like effects . The consequences were injection survived 15 days clinically led to the occurrence of heart attacks and finally to uremia. At autopsy there are extensive local necrosis and thrombosis of the left side of the neck and toxic damage of the myocardium , liver and kidney , but no emboli of large or small circuit found despite extensive mural thrombi in the left and right ventricle.	Toxicity BAC human intramuscular injection
Spiller, H. A. (2014). "A Case of Fatal Ingestion of a 10% Benzalkonium Chloride Solution." <u>Forensic Toxicology & Pharmacology</u> 3 (1).	Benzalkonium chloride (BAC) is a mixture of quaternary ammonium compounds of alkyl-dimethylbenzylammonium chlorides. It has wide ranging use as a disinfectant, germicidal cleaner, algaecide, cationic detergent and topical dermal antiseptic. Ingestion of BAC can cause local caustic effects and systemic effects. The present report involved a 78 year old male with a history of severe dementia who ingested up to 240ml of a germicidal disinfectant containing 10% benzalkonium chloride. Shortly after, he complained of oral pain and nausea, and experienced one episode of vomiting. Upon arrival to the emergency department approximately 45 minutes post-ingestion the patient's complaints included oral pain, sialorrhea, drooling, spitting, nausea, and coughing, but no increase in work of breathing. Initial evaluation of the oral cavity and oropharynx showed mild erythema and swelling, but without lesions or erosions. A chest x-ray showed no acute abnormalities. Over the next three hours, the patient developed rhonchi and increasing respiratory distress. Approximately 12 hours post-ingestion, an esophagogastroduodenoscopy (EGD) and bronchoscopy were performed revealing: sloughing of the mucosa in the posterior oropharynx, and throughout the length of the esophagus, multiple gastric ulcers with bleeding, severe laryngeal edema, tracheobronchial mucosal edema, sloughing of mucosa of the larynx, severe tracheobronchomalacia with 75-90% collapse of distal trachea and possible aspiration. The patient was extubated, provided palliative care and expired 24 hours after arrival at the	Toxicity BAC human ingestion

CITATION	ABSTRACT/NOTES	KEY WORDS
	hospital. The risks after ingestion of BAC appear to be related to caustic injury, airway impairment and respiratory compromise if aspirated. In cases with a fatal outcome the terminal event appears to be airway compromise. In summary a case is reported of a fatal ingestion of a 10% BAC solution producing severe oral tracheal, esophageal, and stomach injury.	
Staniforth, P. (1980). "Allergy to benzalkonium chloride in plaster of Paris after sensitisation to cetrimide. A case report." <u>J Bone Joint Surg Br</u> 62-b (4): 500-501.		Hypersensitivity BAC plaster of Paris
Sullivan Jr, J. B., et al. (2013). Chapter 14 - Indoor Environmental Quality and Health. <u>Small Animal Toxicology (Third Edition)</u> . M. E. P. A. Talcott. Saint Louis, W.B. Saunders: 139-158.		Toxicity BAC dog cat
Swiercz, R., et al. (2007). "[Toxic effect of benzalkonium chloride on animals and humans]." <u>Med Pr</u> 58 (2): 139-142.	Benzalkonium chloride (BAC) exerts toxic effects on microorganisms. This property has been utilized in the cosmetic industry and medicine, where it is used as effective germicide and preservative agents. Various BAC-containing preparations used by people may induce a number of adverse effects on the human body. Bearing in mind that BAC is widely used in different branches of the national economy, its toxic effect may cause a health problem of significant importance to humans. The authors describe BAC toxic effects exerted on humans and laboratory animals as well as relevant hazards resulting from the use of BAC-contained preparations.	Toxicity BAC human
Swiercz, R., et al. (2008). "Pulmonary irritation after inhalation exposure to benzalkonium chloride in rats." <u>Int J Occup Med Environ Health</u> 21 (2): 157-163.	BACKGROUND: Benzalkonium chloride (BAC) is a quaternary ammonium compound (QAC) with a C8 to C18 chain length of alkyl groups. Since BAC exerts toxic effects on microorganisms, it has been used as an effective germicide and preservative, mostly in cosmetic industry and medicine. However, the toxic potential of BAC may be hazardous to humans, due to the common use of preparations containing BAC as a preservative. MATERIAL AND METHODS: To assess the possible toxic effects of BAC, two-stage experiments were performed on female Wistar rats. At first, LC50 after a single exposure to BAC aerosol was determined. Then, the animals were exposed to BAC aerosol at 30 mg/m3 for 6 h, and for 3 days (6 h/day). The controls were unexposed rats. Directly after BAC exposure and 18 h afterwards, BALF concentrations were measured of total protein, Clara cell protein, matrix metalloproteinase-9 (MMP-9), hyaluronic acid (HA), immunoglobulin E (IgE) and cytokines (TF-alpha, IL-6 and MIP-20), lactate dehydrogenase (LDH) and GSH-S-transferase (GST). RESULTS: The LC50 value for exposed rats was ca. 53 mg BAC in m3 air for 4 h. All the rats survived single and repeated inhalation exposure to 30 mg/m3 BAC. After single and repeated exposure, lung weight, total protein, HA and LDH activity in BALF of exposed rats were higher than in controls while CC16 levels were decreased. A significantly higher BALF concentration of IL-6 and IgE was noted in animals exposed to single and repeated doses. BALF concentrations of MMP-9, TNF-alpha, and MIP-2 in exposed rats were similar to those in control	MOA BAC rat pulmonary irritation

CITATION	ABSTRACT/NOTES	KEY WORDS
	animals. CONCLUSION: BAC may be classified to class I acute inhalation toxicity. It showed a strong inflammatory and irritant activity on the lungs after 6h inhalation and stimulated dynamic patterns of IL-6 and IgE production and protein infiltration from blood vessels to BALF. Continued exposure resulted in cellular destruction, a statistically significant increase in LDH activity and a continuous decrease in CC16 concentration in BALF.	
Swiercz, R., et al. (2009). "Catecholamine levels in the brain of rats exposed by inhalation to benzalkonium chloride." <u>Int J Occup Med Environ Health</u> 22(2): 107-113.	OBJECTIVES: The aim of the study was to obtain quantitative data on the effect of inhalation exposure to benzalkonium chloride (BAC) on the concentration of catecholamines and their metabolites in selected brain structures. Additionally, concentration of corticosterone (CORT) in plasma was estimated. MATERIAL AND METHODS: Wistar rats were subjected to a single (6-hour) or repeated (3 days, 6 h/day) exposure to BAC aerosol at ca. 30 mg/m³. The Waters integrated analytical system of HPLC was used to determine the plasma corticosterone. Qualitative and quantitative determinations of catecholamines and their metabolites: 3,4-dihydroxyphenylacetic (DOPAC) and homovanillic (HVA) acids were performed with the use of the Waters integrity HPLC. RESULTS: The determinations have shown that in the BAC-exposed rats the plasma CORT concentration was several times higher than in the control rats. A significant increase of the concentration of dopamine (DA) (striatum and diencephalon) and noradrenaline (NA) (hippocampus and cerebellum) and a significant reduction of adrenaline (A) level (cortex, hippocampus, striatum and mesencephalon) was found to occur in the brain of rats exposed to BAC compared to control. In the animals exposed to BAC, the concentration of DOPAC, a DA metabolite, was significantly reduced, but the change occurred mainly in the striatum. This resulted in a significant decrease of the DOPAC/DA and HVA/DA metabolic ratio in this structure. CONCLUSION: It is assumed that the alterations in the concentration of catecholamines and their metabolites in the BAC-exposed rats were related to the unexpectedly strong and persistent activation of the hypothalamo-pituitary-adrenocortical (HPA) axis evidenced by the high plasma CORT concentration.	MOA BAC rat brain catecholamines
Swiercz, R., et al. (2013). "Toxic effect in the lungs of rats after inhalation exposure to benzalkonium chloride." <u>Int J Occup Med Environ Health</u> 26(4): 647-656.	BACKGROUND: Benzalkonium chloride (BAC) is a quaternary ammonium compound (QAC) toxic to microorganisms. Inhalation is one of the major possible routes of human exposure to BAC. MATERIALS AND METHODS: Experiments were performed on female Wistar rats. The rats were exposed to aerosol of BAC water solution at the target concentration of 0 (control group) and 35 mg/m³ for 5 days (6 h/day) and, after a 2-week interval, the animals were challenged (day 21) with BAC aerosol at the target concentration of 0 (control group) and 35 mg/m³ for 6 h. RESULTS: Compared to the controls, the animals exposed to BAC aerosol were characterized by lower food intake and their body weight was significantly smaller. As regards BAC-exposed group, a significant increase was noted in relative lung mass, total protein concentration, and MIP-2 in BALF both directly after the termination of the exposure and 18 h afterwards. Significantly higher IL-6 and IgE concentrations in BALF and a decrease in the CC16 concentration in BALF were found in the exposed group immediately after the exposure. The leukocyte count in BALF was significantly higher in the animals exposed to BAC aerosol compared to the controls. In the lungs of rats exposed to BAC the following effects were observed: minimal perivascular, interstitial edema, focal aggregates of alveolar macrophages, interstitial mononuclear cell infiltrations, thickened alveolar septa and marginal lipoproteinosis. CONCLUSION: Inhalation of BAC induced a strong inflammatory response and a damage to the blood-air barrier. Reduced concentrations of CC16, which is an immunosuppressive and anti-inflammatory protein, in combination with increased IgE concentrations in BALF may be indicative of the immuno-inflammatory response in the animals exposed	MOA BAC rat lung

CITATION	ABSTRACT/NOTES	KEY WORDS
	to BAC aerosol by inhalation. Histopathological examinations of tissue samples from the BAC-exposed rats revealed a number of pathological changes found only in the lungs.	
Tanada, M., et al. (1991). "Adsorption removal of benzalkonium chloride by granular activated carbon for medical waste water treatment." <u>Asia Pac J Public Health</u> 5 (1): 27-31.	The adsorption removal of benzalkonium chloride disinfectant by granular activated carbon is discussed. The adsorption isotherm of benzalkonium chloride was expressed by the Freundlich equation. A significant correlation was found between the amount of benzalkonium chloride adsorbed in less than 1000 ppm of equilibrium concentration and the micropore volume of activated carbon. As for the adsorption rate, a change in intraparticle diffusiveness was found with increasing adsorption ratio. No significant correlation between the values of intraparticle diffusiveness and the properties of activated carbon was found. It was concluded that the micropore volume of activated carbon was the dominant factor in the adsorption removal of benzalkonium chloride by granular activated carbon.	Treatment BAC activated charcoal
Tarbox, B. B., et al. (1998). "Benzalkonium chloride. A potential disinfecting irrigation solution for orthopaedic wounds." <u>Clin Orthop Relat Res</u> (346): 255-261.	The efficacy of benzalkonium chloride was evaluated as an irrigating solution for the eradication of Staphylococcus aureus from a contaminated orthopaedic wound. Thirty Sprague Dawley rats were randomized into two groups. A stainless steel wire was placed in a lumbar spinous process, and the wound was inoculated with 10(7) or 10(6) colony forming units of Staphylococcus aureus. The wound was irrigated with 1 L of normal saline or 0.1% benzalkonium chloride solution. The animals were sacrificed, and cultures were obtained. Rats inoculated with 10(7) colony forming units of Staphylococcus aureus and irrigated with benzalkonium chloride had a significant decrease in the total number of positive cultures, deep wound cultures, and stainless steel wire cultures. Rats inoculated with 10(6) colony forming units of Staphylococcus aureus and irrigated with benzalkonium chloride also had a significant decrease in the total number of positive cultures, deep wound cultures, and stainless steel wire cultures. In a parallel noninoculation study, histologic evaluation of tissues did not show toxicity in the rats irrigated with benzalkonium chloride. This study shows that benzalkonium chloride is more effective than normal saline as an irrigating agent for eradicating Staphylococcus aureus from a contaminated orthopaedic wound.	Use BAC rat irrigation solution wounds
Trapani, M., et al. (1982). "Quaternary ammonium toxicosis in cats." <u>Lab Anim Sci</u> 32 (5): 520-522.		Toxicity QAC cat
Traverse, M. and H. Aceto (2015). "Environmental Cleaning and Disinfection." <u>Veterinary Clinics of North America: Small Animal Practice</u> AIP .		Use QAC disinfectant veterinary
Turan, C., et al. (2000). "Corrosive injuries of the esophagus in newborns." <u>Pediatr Surg Int</u> 16 (7): 483-484.	To evaluate the morbidity and mortality of corrosive esophageal injuries (CEI) in the neonatal period, the records of 184 children hospitalized following caustic ingestion over a 10-year period from January 1987 to November 1997 were reviewed. Eight (4.3%) were newborns (5 boys and 3 girls). The mean age of the newborns was 12 days (range 1-28). The ingested caustic materials were benzalkonium chloride in six patients and trichloroacetic acid in two. Oropharyngeal examination and esophagoscopy were performed for diagnosis. Hyperemia and fibrin plaques were	Toxicity BAC human oesophagus

CITATION	ABSTRACT/NOTES	KEY WORDS
	present in the oropharynx in all patients. The management consisted of endotracheal intubation, antibiotics, corticosteroids, and total parenteral nutrition. Pneumonia and sepsis developed in three patients and one died of sepsis. Stenosis developed in two patients, who were treated three times with antegrade dilatations. The morbidity was 62.5% (five patients) and the mortality was 12.5% (one) in newborns with CEI. These results indicate that ingestion of a caustic substance results in high morbidity and mortality in newborns. Parents and nurses should be warned about this risk.	
Uematsu, M., et al. (2010). "Influence of alkyl chain length of benzalkonium chloride on acute corneal epithelial toxicity." <u>Cornea</u> 29 (11): 1296-1301.	PURPOSE: To evaluate acute corneal epithelial toxicity induced by benzalkonium chloride (BAC) homologs with different alkyl chain lengths using an in vivo electrophysiological method. METHODS: BAC homologs with C12, C14, and C16 alkyl chain lengths were used at concentrations of 0.0025%, 0.005%, and 0.01%, respectively. Cytotoxicity of BAC homologs on the normal rabbit corneal epithelial cells was examined by using a WST-1 assay. Corneal transepithelial electrical resistance (TER) was measured in living Japanese white rabbits by 2 Ag/AgCl electrodes placed in the anterior aqueous chamber and on the cornea. TER changes were then evaluated after a 60-second exposure to these BAC homologs. Morphological changes in corneal epithelium after exposure to the BAC homologs were examined using scanning electron microscopy. The antimicrobial activity of BAC homologs against Escherichia coli was also assessed. RESULTS: All BAC homologs caused cytotoxicity and corneal barrier dysfunction in a concentration-dependent manner. However, the degree of corneal toxicity differed among the BAC homologs. Based on cytotoxicity and TER measurement, C14-BAC caused the greatest corneal impairment followed in order of severity by mixed BAC/C16-BAC and C12-BAC. Scanning electron microscopy images indicated an intact corneal epithelium after exposure to 0.005% C12-BAC, whereas 0.005% C14-BAC damaged the epithelium. There were no remarkable differences noted in the antimicrobial activity among the BAC homologs. CONCLUSIONS: Acute corneal epithelial toxicity induced by BAC homologs depends on the alkyl chain length. Thus, the use of C12-BAC instead of commercially available BAC is potentially safer for patients undergoing ophthalmological pharmacotherapy.	MOA BAC chain length
US EPA (2006). Reregistration Eligibility Decision for Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC). Washington DC, US EPA.		Review BAC
US FDA (2013). Benzalkonium chloride as a component of Free N Clear. GRAS Notification. College Park, Maryland, Center for Food Safety and Applied Nutrition, Food and Drug Administration.		Review BAC
Uter, W., et al. (2008). "Is the irritant benzalkonium chloride a	BACKGROUND: Benzalkonium chloride (BAC) is a well-recognized irritant. However, doubts exist that it is also a contact allergen. OBJECTIVE: Analysis of clinical patch test data addressing the reaction profile and synchronous	Toxicity BAC human skin

CITATION	ABSTRACT/NOTES	KEY WORDS
contact allergen? A contribution to the ongoing debate from a clinical perspective." <u>Contact Dermatitis</u> 58 (6): 359-363.	reproducibility of BAC 0.1% in petrolatum (pet.) and possible increases in risk of BAC contact allergy in certain (occupationally exposed) subgroups. PATIENTS /METHODS: Data of 42 898 patients tested with BAC 0.1% in pet. in 3 different series (topical drugs, ophthalmics, and disinfectants) in the departments of the Information Network of Departments of Dermatology (http://www.ivdk.org) between 1996 and 2006 was analysed. RESULTS: Overall, morphologically 'positive' reactions were rare, 0.6-1.5%, with a total of 41 stronger positive reactions. Concordance, assessed in 3322 patients tested in duplicate, was low (kappa coefficient 0.15, 95% CI: 0-0.31). Positive test reactions were observed significantly more often in the disinfectants series compared with the 2 other series, indicating that suspected exposure to disinfectants may be associated with sensitization. However, variation of stronger BAC test positivity across potentially relevant (occupational) groups was non-significant. CONCLUSION: This analysis of routine clinical data and a number of previous reports add further, if weak, evidence to the notion that BAC is a contact allergen, albeit a very rare one.	
Valsecchi, R., et al. (2003). "Occupational contact dermatitis and contact urticaria in veterinarians." <u>Contact Dermatitis</u> 49 (3): 167-168.		Toxicity OHS
van Berkel, M. and F. A. de Wolff (1988). "Survival after acute benzalkonium chloride poisoning." <u>Hum Toxicol</u> 7 (2): 191-193.	Quaternary ammonium compounds have curare-like depolarising properties [quoted by Inchem]	Toxicity BAC human
Varani, J., et al. (2007). "Human skin in organ culture and human skin cells (keratinocytes and fibroblasts) in monolayer culture for assessment of chemically induced skin damage." <u>Toxicol Pathol</u> 35 (5): 693-701.	Human skin cells (epidermal keratinocytes and dermal fibroblasts) in monolayer culture and human skin in organ culture were exposed to agents that are known to produce irritation (redness, dryness, edema and scaly crusts) when applied topically to skin. Among the agents used were three well accepted contact irritants (i.e., all-trans retinoic acid [RA], sodium lauryl sulfate [SLS] and benzalkonium chloride) as well as the corrosive organic mercury compound, aminophenyl mercuric acetate (APMA), and 5 contact sensitizers (oxazolone, nickel sulfate, eugenol, isoeugenol and ethylene glycol dimethacrylate [EGDM]). As a group, the contact irritants (including the corrosive mercuric compound) were cytotoxic for keratinocytes and fibroblasts and suppressed growth at lower concentrations than the contact sensitizers. The contact irritants also produced histological changes (hyperplasia, incomplete keratinization, loss of the granular layer, acantholysis and necrosis) in organ-cultured skin at dose levels at which the contact sensitizers appeared to be inert. Finally, the profile of secreted molecules from organ-cultured skin was different in the presence of contact irritants versus contact sensitizers. Taken together, these data suggest that the use of organ-cultured skin in conjunction with cells derived from the skin in monolayer culture may provide an initial approach to screening agents for deleterious changes in skin.	Toxicity BAC human skin (in vitro)
Vogelzang, P. F., et al. (1997). "Bronchial hyperresponsiveness	OBJECTIVE: To study the effect of exposure on bronchial responsiveness in pig farmers. METHOD: A group of 196 pig farmers were tested for lung function and bronchial responsiveness to histamine in the summer of 1992. To achieve	Toxicity OHS

CITATION	ABSTRACT/NOTES	KEY WORDS
and exposure in pig farmers." <u>Int Arch Occup Environ Health</u> 70 (5): 327-333.	sufficient contrast in respiratory morbidity and exposure, 96 of the farmers were selected because they had chronic respiratory symptoms and the remaining 100 because they were free from any respiratory symptoms. Personal exposure to dust, endotoxins and ammonia was measured during 1 working day in the summer of 1991 and 1 day in the winter of 1992. Data on farm characteristics were gathered in the same period. RESULTS: After adjusting for age and smoking behaviour, mild bronchial responsiveness, defined as PC10 < or = 16 mg/ml, was associated with the use of quaternary ammonium compounds as disinfectant [prevalence odds ratio (POR) 6.7, 95% confidence interval (CI) 1.4-32.8], use of wood-shavings as bedding (POR 13.3, CI 1.3-136.7), use of automated dry feeding (POR 2.8, CI 1.0-7.8), use of pellets as feeding material (POR 4.8, CI 1.1-21.1) and location of air exhaust via pit or roof in the confinement units (POR 2.7, CI 1.2-6.3). The association with the use of disinfectants other than quaternary ammonium compounds was not significant (POR 2.4, CI 0.7-8.4). No associations between bronchial responsiveness and measured exposure to dust, endotoxins or ammonia were discernible. CONCLUSION: Protective measures, designed to prevent airway disease in confinement farming, should be based on information about the operational and other characteristics of farms that are related to high exposure and health effects. Specifically, the use of quaternary ammonium compounds as disinfectant, the use of wood-shavings as bedding and the use of automated dry feeding should be discouraged.	
Wagner, H.-J. (1965). "3 Todesfälle durch Intoxikation (Invertseife) oder durch anaphylaktischen Schock (Roskastanienextrakt)?" <u>Arch Toxikol</u> 21 (2): 83-88.	Three fatal cases are described with intermediate survival time of 21-46 h after an intravenous injection of 1.8 mg allegedly Strophanthin, 2 ml of vitamin B complex and an extract of horse chestnut (2.5 ml). However, the investigation results, the clinical picture, the autopsy findings and histological studies provide an invert soap solution intoxication appear likely. This may thus come about, instead of this the horse chestnut extract obtained an appropriate amount Zephiriol was drawn into the syringes and intravenous route. In the absence of positive toxicology findings, however, mute the possibility of anaphylactic reaction by the horse chestnut extract may be discussed in conjunction with vitamin B1.	Toxicity BAC human intravenous
Warren, M. R., et al. (1942). "Pharmacological and toxicological studies on cetylpyridinium chloride, a new germicide." <u>Journal of Pharmacology and Experimental Therapeutics</u> 74 (4): 401-408.	The acute as well as the chronic toxicity of cetylpyridinium chloride has been determined. The MLD in rabbits following intravenous administration was 20 mgm. per kgm. Following oral administration this compound in an amount of 400 mgm. per kgm. killed one out of six rabbits. It was found that cetylpyridinium chloride was most toxic following intraperitoneal administration. In many cases death was delayed for from three to six days. The results of the chronic toxicity tests indicate that cetylpyridinium chloride in the amounts administered for a period of four weeks has no significant harmful effects. The irritant action on intact skin and mucous membranes was determined. Cetylpyridinium chloride exerted a "curare-like" action. It produced a central stimulation and a peripheral paralysis.	Toxicity QAC curare like
Wilson, J. T. and I. M. Burr (1975). "Benzalkonium chloride poisoning in infant twins." <u>Am J Dis Child</u> 129 (10): 1208-1209.	Infant twins sustained severe circumoral and pharyngeal burns from a concentrated solution of benzalkonium (Zephiran) chloride prescribed for treatment of candidiasis. This report emphasizes the unnecessary hazard accompanying use of a potentially toxic drug-especially when prepared in error by the pharmacist-when a safer drug (nystatin) is available for treatment of oral candidiasis. Risks from use of a prescription drug for other than the intended patient are also highlighted by this episode of poisoning.	Toxicity BAC human oral
Wolff, F. (1961). "Tödliche Vergiftung durch Trinken des	First observation of a fatal poisoning by drinking commercially available concentrated C4 solution in a 2-year small child. Death after 10-15 minutes with the clinical signs of suffocation due curare-like effect. Pathological- anatomical	Toxicity BAC human oral

CITATION	ABSTRACT/NOTES	KEY WORDS
Desinfektionsmittels „C4“. <u>Arch Toxikol</u> 19 (1): 8-14.	findings nonspecific.	
Wong, D. A. and A. B. Watson (2001). "Allergic contact dermatitis due to benzalkonium chloride in plaster of Paris." <u>Australas J Dermatol</u> 42 (1): 33-35.	Plaster of Paris (POP) bandages are extensively used for splinting and casting injured or surgically repaired body parts. Allergic contact dermatitis caused by POP has been reported only rarely in the medical literature. An 81-year-old woman developed multiple large, tense, haemorrhagic bullae on the palm, and an acute vesicular eczematous eruption on the forearm, after the application of a POP splint. Subsequent patch testing revealed positive reactions to both the POP bandage used and to benzalkonium chloride, a component of the POP formulation. Patch tests to two other POP products without benzalkonium chloride were negative. These results confirm those of previous studies which have implicated the quaternary ammonium compound benzalkonium chloride as the allergen responsible for POP-induced allergic contact dermatitis.	Hypersensitivity BAC plaster of Paris
Wood, C. L., et al. (2014). "Effectiveness of a steam cleaning unit for disinfection in a veterinary hospital." <u>Am J Vet Res</u> 75 (12): 1083-1088.	OBJECTIVE: To evaluate whether the application of steam to a variety of surface types in a veterinary hospital would effectively reduce the number of bacteria. SAMPLE: 5 surface types. PROCEDURES: Steam was applied as a surface treatment for disinfection to 18 test sites of 5 surface types in a veterinary hospital. A pretreatment sample was obtained by collection of a swab specimen from the left side of each defined test surface. Steam disinfection was performed on the right side of each test surface, and a posttreatment sample was then collected in the same manner from the treated (right) side of each test surface. Total bacteria for pretreatment and posttreatment samples were quantified by heterotrophic plate counts and for <i>Staphylococcus aureus</i> , <i>Pseudomonas</i> spp, and total coliforms by counts on selective media. RESULTS: Significant reductions were observed in heterotrophic plate counts after steam application to dog runs and dog kennel floors. A significant reduction in counts of <i>Pseudomonas</i> spp was observed after steam application to tub sinks. Bacterial counts were reduced, but not significantly, on most other test surfaces that had adequate pretreatment counts for quantification. CONCLUSIONS AND CLINICAL RELEVANCE: Development of health-care-associated infections is of increasing concern in human and veterinary medicine. The application of steam significantly reduced bacterial numbers on a variety of surfaces within a veterinary facility. Steam disinfection may prove to be an alternative or adjunct to chemical disinfection within veterinary practices.	Disinfection alternative
Xue, Y., et al. (2004). "Distribution and disposition of benzalkonium chloride following various routes of administration in rats." <u>Toxicol Lett</u> 148 (1-2): 113-123.	Benzalkonium chloride (BZK) is a cationic surfactant used widely as a disinfectant, preservative and sanitizer in hospitals, at home and many public places. The toxicity of BZK is not well established although several human fatalities have been reported over the years. In this study, distribution and disposition of BZK following oral administration (PO) and intravascular (jugular vein (JV), femoral artery (FA), femoral vein (FV) and jugular artery (JA)) administration in rats were investigated along with pathological examinations. Toxic doses of 250 and 15 mg/kg of BZK were used for PO and intravascular administration, respectively. The fatal effects of BZK appeared soon in JV-, FV- or JA-rats, but took hours in PO or FA-rats. No rat receiving BZK via FA survived longer than 1 day. The PO-rats that aspirated BZK into their lungs had some systemic symptoms and higher blood and tissue concentrations of BZK. The blood BZK levels and kinetics were similar among the different routes of intravascular administration, but the lung and kidney levels were higher in JV-rats. Pathological examinations confirmed severe congestion and edema in the lungs and kidneys. These results suggest that (1) the toxic effects of BZK varied depending on the route of administration, (2) the degree of toxicity correlated with peak blood and tissue concentrations in orally dosed rats, (3) different	PK BAC rat

CITATION	ABSTRACT/NOTES	KEY WORDS
	toxicological progressions and manifestations were observed in FA- and JV-dosed rats even though these groups had similar blood concentration profiles, and (4) lung and kidney are reservoirs for BZK and considered to be the target organs of BZK.	
Xue, Y., et al. (2004). "Kinetic characteristics and toxic effects of benzalkonium chloride following intravascular and oral administration in rats." <u>J Chromatogr B Analyt Technol Biomed Life Sci</u> 811 (1): 53-58.	Kinetic characteristics and toxic effects of benzalkonium chloride (BZK) following injection via jugular vein (JV), femoral artery (FA) and oral administration (PO) were experimentally investigated using rats. The BZK concentrations in blood and tissues (lung, liver and kidney) were determined by high-performance liquid chromatography with solid phase extraction. Toxic doses of 15 and 250 mg/kg of BZK were used for intravascular (JV and FA) and PO administration, respectively. The fatal effects appeared soon after the dose in JV-rats, while delayed in FA- or PO-rats. The blood BZK concentrations and the elimination half-lives were similar between JV- and FA-rats, while the distribution of BZK in tissues was slightly different. In PO administration, the rats that aspirated BZK into their lungs had some symptoms, while the rats that did not aspirate BZK appeared to be normal. The BZK concentrations in blood and tissues were significantly higher in the aspirated PO-rats. The toxic degree of BZK was correlated with the BZK concentration in orally dosed rats. Lung and kidney had higher BZK concentrations compared to blood or liver, and they could be the target organs of BZK. Keyword: Benzalkonium chloride	PK BAC rat oral intravascular
Xue, Y., et al. (2012). "Comparative study on toxic effects induced by oral or intravascular administration of commonly used disinfectants and surfactants in rats." <u>J Appl Toxicol</u> 32 (7): 480-487.	Accidental ingestion or injection of household products sometimes occurs due to their accessibility, but the toxic manifestations have not been well characterized when they are internally administered. The aim of this study was to investigate the toxic effects induced by ingestion or injection of different ionic surfactants and disinfectants in rats. The test drugs involved benzalkonium and benzethonium (BZK and BZT, both cationic surfactants used as disinfectants), alkyldiaminoethylglycine (AEG, an amphoteric surfactant used as a disinfectant), linear alkylbenzenesulfonate (LAS, an anionic surfactant), polyoxyethylene cetyether (PEC, a nonionic surfactant), chlorhexidine (CHX, not a surfactant but a disinfectant) and saline (control). Male Sprague-Dawley rats were administered one of the test drugs orally (p.o.), intravenously (i.v.) or intraarterially (i.a.). The fatal effects appeared rapidly (<30 min) in i.v.-administered rats, while taking hours (>5 h) in i.a./p.o.-administered rats after a dose of around LD(50) , although the progress and degree of toxic effects varied among the drugs tested. In intravascular administration, BZK and BZT were fatal at doses of 15-20 mg kg ⁻¹ . Higher concentrations in lung and kidney than in blood were determined. CHX showed a high toxic effect compared with cationic surfactants. The rats administered anionic (LAS) or amphoteric (AEG) surfactant died in less than 24 h at doses over 100 mg kg ⁻¹ . In p.o. administration, the toxic effects were concentration/dose-dependent, and all rats administered high doses of surfactants except for PEC died at 5-20 h. The overall toxic ranks could be: cationic surfactant/CHX> anionic/amphoteric surfactant > nonionic surfactant.	Toxicity BAC rat oral intravascular