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Title:
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Date:
2021-08-01

Citation:
Dear, K., Palmer, A. & Nixon, R. (2021). Contact allergy and allergic contact dermatitis from benzalkonium chloride in a tertiary dermatology center in Melbourne, Australia. Contact Dermatitis, 85 (2), pp.146-153. https://doi.org/10.1111/cod.13826.

Dear Kate (Orcid ID: 0000-0002-0302-8848)

Contact allergy and allergic contact dermatitis to benzalkonium chloride in a tertiary dermatology centre in Melbourne, Australia

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Conflicts of interest: None

Acknowledgments: None

Key words: Benzalkonium chloride, allergic contact dermatitis,

Abstract:

Background:

Benzalkonium chloride (BAK) is a quaternary ammonium compound widely used as an antiseptic and preservative. It is a strong irritant and considered a weak sensitiser.

Objective:

To analyse the temporal trend of BAK sensitisation and the demographics of sensitised patients.

Methods:

We conducted a single centre retrospective study of 7390 patients patch tested with BAK between 1 January 2003 and 31 December 2019.

Results:

Of 7390 patients patch tested to BAK, 108 (1.5%) had a positive reaction, with 21 reactions deemed clinically relevant (0.3% of total patch tested) and a further 5 doubtful reactions

deemed clinically relevant resulting in a total of 26 relevant reactions (0.4% of total patch tested). Common sources of exposure were ophthalmic drops (30.8%), topical antiseptic preparations (26.9%), cosmetics (15.4%), disinfectant solutions (11.5%), hand sanitisers (11.5%), and hand washes (7.7%). One fifth of patients with relevant reactions were healthcare workers. There has been a dramatic increase in the number of positive reactions since 2017, for reasons not totally clear.

Conclusion:

Contact allergy (CA) and allergic contact dermatitis (ACD) to BAK are now increasing at our centre. Awareness of this trend is important, given that the COVID-19 pandemic is likely to further expose people to BAK.

Main text:

Background:

Benzalkonium chloride (BAK) is a cationic quaternary ammonium compound widely used as a preservative and antiseptic. It is commonly found in personal care products (PCP) such as deodorants, cosmetics, mouthwashes, ophthalmic solutions and nasal sprays.[1] Furthermore it has important uses in the healthcare industry in antibacterial sanitisers, hand cleansers and in cleaning solutions for surfaces and surgical instruments.[2] Since the methylisothiazolinone (MI) epidemic and its subsequent removal from many products, we have observed BAK to be more commonly found in wet wipes.

BAK is well recognised as an irritant[3,4] but it also has sensitising properties however, it is a rare contact allergen.[5] Care must be taken when interpreting patch tests that appear positive to BAK, and interpretation should be verified with both an indicative morphology (erythema, papulation and vesicles, in patients with high chances of exposure) and appropriate validation tests.[4] Regardless, there have been reports of allergic contact dermatitis (ACD) to BAK from ophthalmic solutions,[6] antiseptics and disinfectant solutions,[7] topical medicaments such as in timodine cream,[8] bath emollients,[9] antibacterial wound dressings and bandages,[1] and plaster of Paris.[10,11] Recent evidence suggests that it may induce contact allergy (CA) at a higher rate than previously anticipated.[12]

The aim of this study was to analyse the temporal trend of BAK sensitisation and ACD at our institution, and to identify the demographics of sensitised individuals and the likely sources of exposure to this allergen.

Methods:

Patients

This single centre retrospective study included all patients on our electronic database who underwent patch testing with BAK 0.1% aq. from 1 January 2003 to 31 December 2019 in our Occupational Dermatology and Contact Dermatitis clinics. These are tertiary referral clinics for the investigation of patients with suspected contact dermatitis. Data were extracted from electronic medical records.

Patch testing

Patients were patch tested with allergens from Chemotechnique Diagnostics (Vellinge, Sweden) or Allergeaze (SmartPractice, Tuscon, Arizona) by use of either Finn Chambers or Allergeaze test chambers (SmartPractice). BAK was tested at 0.1% aq and obtained from Chemotechnique Diagnostics (Vellinge, Sweden). The patches were removed on day (D) 2 and read on D2 and D4. Reactions were graded according to the International Contact Dermatitis Group (ICDRG) with +/- (doubtful reactions) defined as macular erythema only, + reactions as papules and erythema, ++ reactions as oedematous papules and/or vesicles within the disc site, and +++ reactions as coalescing vesicles, bullous or extreme reactions spreading beyond the disc site. Patients were instructed to bring PCPs and medicaments to all clinic visits to enable clinicians to determine the presence of BAK in any products and thus determine the relevance of reactions.

Statistical analysis was carried out using SPSS Statistics version 26 (IBM Corp, Armonk, N.Y., USA). Univariate analysis was performed to determine statistical differences between patients who were sensitised to BAK and those who were not. Categorical variables were assessed using the Chi-squared test. Continuous data was tested for normal distribution using the Shapiro-Wilk test and analysed using either a 2-sided t-test or a Mann-Whitney U test. Significance was established at $p<0.05$.

Results:

The number of patients tested and the positive results are summarised in Table 1. A total of 7390 patients were patch tested with BAK from 1 January 2003 to 31 Dec 2019 and 1.5% (108 patients) had a positive result. Of the positive reactions, 21 (0.3% of total tested, 19% of positive reactions) were assessed by the dermatologist to be of current clinical relevance, where patients had definite exposure to a product containing BAK and a positive patch test result at D4. Doubtful reactions at day 4 were generally not deemed positive, however, in 5 cases, clinical relevance was found and these 5 patients have been grouped within the relevant positive reactions.

The number of positive reactions increased substantially from 2017. During the 14-year period between 2003 and 2016 inclusive, there were a total of 23 positive reactions of old or uncertain relevance (0.4% of total tested), and 8 relevant reactions (0.1% of total tested) amounting to a mean of 1.6 positive reactions of unknown relevance annually and 0.6 relevant reactions annually. However, most of these reactions occurred between 2003 and 2006 before decreasing to almost zero in the subsequent 10 years. In the 3 years 2017, 2018 and 2019, there were 64 positive reactions of old or uncertain relevance (6.4% of total tested) and 18 relevant reactions (1.8% of total tested), amounting to a mean of 21 positive reactions of unknown relevance annually, and 6 relevant reactions annually. The number of mean annual positive reactions of unknown relevance between 2017-2019 was over 10 times the mean annual positive reactions of unknown relevance between 2003 and 2016. The number of mean annual relevant reactions between 2017-2019 was 10 times greater than the mean number of relevant reactions between 2003-2016. Positive reactions were significantly more likely to occur between 2017 and 2019 than in the preceding 14 years ($p<0.001$).

Both irritant and doubtful reactions also increased dramatically from 2017. It is well-recognised that it is often quite difficult to distinguish irritant from doubtful reactions.[4] We notified the supplier of the BAK used for testing, Chemotechnique Diagnostics (Vellinge, Sweden), of this surprising finding. They tested the raw material and found no abnormalities (Bo Niklasson, personal communication)

Characteristics of the population studied are described in Table 2, comparing BAK sensitised patients with non-sensitised patients. There was no significant difference in age, sex, or occupational relationship between the two groups. Sensitised patients were less likely to be atopic compared with non-sensitised patients (21.2% versus 32.1%, $p = 0.02$). There was no

difference in location of dermatitis between the groups. The median age was 44 years (range 10-78) for sensitised patients, and 42 years (range 3-92) for non-sensitised patients.

The strength of reactions is shown in Table 3 and Table 4. At D4, 87.6% (99/113) were graded as +. 7.1% (8/113) were graded as ++, and 0.9% (1/113) were graded as +++. Five doubtful reactions were included as the reactions appeared to be clinically relevant. There were 31 irritant reactions in the same time period. Of patients with relevant reactions at D4, 5 reactions were +/-, 17 reactions were + and 4 reactions were ++. Only 10 of these patients had any reaction at D2. Based on our data, a positivity ratio (PR) of 92.0 and a reaction index (RI) of 0.2 was calculated.[13]

The most common location of ACD in relevant cases was the face (11 cases; 42.3%) followed by the hands (10 cases; 38.5%). Only 2 patients (7.70%) had leg dermatitis. The suspected sources of exposure in patients with relevant reactions is summarised in Table 5. The most common source was ophthalmic drops (30.8%, 8 cases) and topical antiseptic preparations (26.9%, 7 cases). Other sources of exposure included cosmetics (4 cases), disinfectant solutions (3 cases), hand sanitisers (3 cases), hand wash (2 cases), Plaster of Paris (1 case) and antibacterial laundry rinses (1 case). Some patients had more than one exposure. Whilst current exposure was recorded, it was not usually possible to identify the source of sensitisation. Occupations of sensitised patients is shown in Figure 1. Among relevant reactions, five (19.2%) were occupationally related, and 21 cases (80.8%) were not. Of the occupationally related relevant cases, all five patients were healthcare workers which included one surgeon and four nurses.

Discussion:

We report our rates of CA to BAK over a 17-year time period, noting a decline from 2006 followed by a dramatic increase from 2017. Rates of contact allergy to BAK worldwide range from 1.6 to 12.1%.[14–18] Prior to 2017, our rates of CA were lower than elsewhere in the world.

Our study is not the first to report increasing rates in BAK allergy. Veverka et al found BAK to be in sixth most common allergen in 2,546 patients tested to the Mayo Standard series between 2011 and 2015.[16] Data from the Mayo Clinic also found a statistically significant increase in BAK reactions from 1998 to 2000 (5.5%) compared with 2006 and 2010 (8.8%, p

= 0.005).[12] More recently, Isaac & Scheinman report increasing rates of allergy to BAK 0.1% aq, which was also supplied by Chemotechnique Diagnostics (Vellinge, Sweden), at their centre with a positive reaction rate of 32% in 615 patients between 2015 and 2016.[2]

One reason for the recent increase in BAK allergy, as observed and postulated by Veverka et al, may be a result of skin care product manufacturers seeking alternatives to preservatives, such as formaldehyde releasers and MI, following the MI epidemic, which peaked in Europe and America in 2013 and later in Australia in 2015,[19,20,21,22] prior to legislation being introduced in Europe in 2014/2015 and Australia from 2017.[21,23] Although the peak in Australia was later than Europe, and legislation occurred at a later date, it may be that manufacturers here began to change their preservatives prior to 2017.

Our doubtful and irritant reactions have also increased since 2017. The same concentration of BAK has been used throughout in our centre, and allergens have consistently been ordered from Chemotechnique Diagnostics (Vellinge, Sweden). It has been suggested that the strong irritant properties of BAK may complicate the interpretation of patch test results for this allergen.[24] Uter et al found positive reactions in 0.6-1.5% of 42, 898 patients in 42 different departments in central Europe between 1996 and 2006. They concluded that because of the poor reproducibility of positive reactions, the majority of positive reactions to BAK should be interpreted as false positives. However, they found that patients tested to the allergen as part of the disinfectant series had more than a sixfold higher proportion of strong positive (++) and very strong (+++) positive reactions, and therefore suggested that reactions to BAK, when tested following exposure to disinfectants, or as part of the disinfectant series, should be interpreted as allergic.[4] Contrary to this, a study by Dao et al found that doubtful readings or morphologically irritant readings at day 7 often occurred in relevant reactions, with half of their study group with definite or possible ACD as determined by clinical follow up, having had these reactions.[25]

In our study, all 87 patients with reactions which were not clinically relevant, reacted at day 4. Reactions that were deemed to be irritant by the dermatologist, and 'decrescendo' reactions (doubtful early reactions subsequently lost at day 4) were not included in this group. Out of the 108 patients who had a positive reaction at D4, 91.7% were deemed positive (+), 7.4% were deemed strongly positive (++) and one patient had an extreme positive reaction (+++). Five patients with doubtful reactions appeared to have relevant reactions, despite not

fulfilling the criteria for a positive patch test reaction. There was predominantly an increase in positive reactions (+) over time. Strongly positive (++) reactions only occurred in 8 cases, with 5 of these cases occurring after 2017. There was only one extreme positive reaction (+++) which occurred in 2006.

BAK has been labelled a 'problematic' allergen in the past, based on a PR greater than 55% and an RI less than or equal to 0.46.[26] 'Problematic' allergens tend to produce many doubtful reactions and potentially false positive reactions. In our study, we obtained a PR of 92.0 and a RI of 0.2, falling within the 'problematic' range. There is a chance that some of our reactions may have been interpreted as false positives caused by irritation, however the rate of false positives is likely to have been stable over time, and this would not explain the dramatic increase in reactions seen since 2017.

The most common source of BAK exposure in patients with relevant reactions was from ophthalmic solutions, which were responsible for one third of cases over the entire duration of the study. Allergy to BAK in eye drops has been well documented with some of the oldest reports dating back to a case described by Fisher & Stillman in 1972.[27] Following this, Afzelius & Thulin in Denmark described a case series of six patients with ACD to BAK in eyedrops with patients patch tested to numerous dilutions of 0.05, 0.025, 0.01 and 0.005%.[27] More recently, in a retrospective study of 105 patient with eyelid dermatitis, Amin et al found BAK to be the fifth most common allergen responsible for ACD, in 8.7% of patients.[18]

Topical antiseptics and anaesthetic formulations were the next most common source of BAK exposure, accounting for 26.9% of cases. It is a common ingredient in topical antiseptic creams as well as antiseptic dressings and ACD to BAK in these products has been reported.[1] CA to BAK has also been found to be particularly prevalent in patients with chronic leg ulcers. A recent study by Raudonis et al found BAK to be the most common sensitiser in patients with chronic leg ulcers, with 18.6% of 145 patients sensitised to the allergen, which is not surprising given it is likely to be found in many topical medicaments and dressings used for ulcers.[28] Other studies report a prevalence of between 6.1-13% in patients with chronic leg ulcers.[29–31]

We found PCPs to be a source of exposure to BAK in four patients, from the use of bath oils, topical emollients and makeup remover. ACD secondary to BAK in Oilatum Plus® (Stiefel,

High Wycombe, U.K.) has been described in a case series of six patients with flexural eczema and positive patch test reactions to BAK.[9] The product contains a relatively high concentration of BAK (6%) and in all cases, the flexural eczema resolved on avoidance of the product. Furthermore, there have been several reports of severe irritant contact dermatitis attributed to BAK in bath oils and emollients.[32–34] Granular parakeratosis, or more suitably named 'hyperkeratotic flexural erythema' recently by Kumarasinge et al, is another condition which presents with a non-pruritic, desquamating brown erythematous rash thought to be a reaction pattern.[35,36] BAK in laundry rinse aids has been reported as the cause in some cases,[37,38] although this condition is not due to a delayed allergic reaction.

One patient was exposed to BAK through plaster of Paris, causing a pruritic rash two days after the cast was applied to his finger. This was further aggravated by the application of a topical local anaesthetic cream (Paxyl), which also contained BAK. There have been several reports of ACD following the application of Plaster of Paris, from BAK added to improve the handling properties of the plaster.[10,11,39,40]

We found that one fifth (5 cases) of patients with relevant BAK allergies were healthcare workers, which included four nurses and one surgeon. These patients all presented with hand dermatitis, and in three cases the source of exposure was through hand sanitiser and in two cases it was through disinfectant wipes. Suneja and Belsito found an incidence of ACD to BAK in 7.5% of healthcare workers, which was statistically higher than the incidence of 2.3% in non-healthcare workers ($p < 0.025$).[41] Other studies have reported similar rates of CA to BAK in healthcare workers with 9.7% out of 72 healthcare personnel with occupational ACD in a study by Nettis et al,[42] and 7.1% of 42 healthcare workers in a study by Shaffer et al.[43] Both these studies also found healthcare workers to have a higher prevalence of CA to BAK compared to non-healthcare workers.

Healthcare workers are likely to be exposed to BAK through use of hand cleansers, the use of hand sanitisers, and the use of disinfectant wipes and sprays containing BAK. A recent study by Rodriguez-Homs et al found that almost 20% of hand cleansers in healthcare settings in the United States contained BAK.[44] Similarly, Voller et al investigated allergenic ingredients in hand sanitizers used in healthcare. Out of 80 hand sanitisers included, BAK was found in 8.8% of products.[45] Whilst hand sanitisers have been available commercially for some years, their use is likely to have increased in recent months secondary to the COVID-19 pandemic.

With increasing awareness of their importance in hand hygiene, the use by healthcare professions, as well the general public is likely to increase further. BAK also appears to have replaced MI in many brands of wet wipes. Increased exposure to BAK through disinfectant solutions and cleaning wipes is likely to occur with the increased need for cleaning and hygiene practices within healthcare settings and businesses in the wake of this unprecedented pandemic.

Despite previously being ranked as the 89th most common relevant allergen in the our population, BAK was added to the first Australian Baseline Series proposed by our group in 2014.[46] This decision was made based on its inclusion in several popular topical medicaments in Australia, and thus its potential relevance for our population. Of 21 other national series, BAK only features in the American Core Series of 80 allergens, recommended by the American Contact Dermatitis Society and the Mayo Clinic. Having previously been included in the NACDG series, it was removed because of low rates of CA in the past and concerns about its potential for irritancy.[26] Could it be that increasing CA to BAK is not being picked up worldwide, as so few baseline series include this allergen?

Limitations to this study include that it was a single centre study, which may be associated with a regional bias. In addition, data from our tertiary centre may include patients with more severe contact dermatitis as well as more occupational cases, so perhaps are less applicable to the broader dermatology population. Furthermore, patients did not always bring all their products for inspection, which may have led to an underestimate of true exposures to BAK and hence the number of relevant reactions. Patch testing to BAK was only performed at 0.1% aq. rather than the higher concentration of 0.15% in petroleum and aqueous as suggested by Dao et al, who reported that approximately 58% of patients with definite or possible ACD to BAK would not have been identified if only 0.1% aq was tested. This may have led to an underestimation of the number of cases of true BAK allergy.[25] However, the study strengths include standardised patch test methods and patch test reading techniques for reactions throughout the entire study period, as well as a comprehensive database.

While there may be some scepticism regarding the number of positive reactions to BAK because of the irritant nature of the allergen, there should be an increasing awareness of the allergenicity of BAK, and further studies regarding the trends in rates of CA and ACD to

BAK worldwide. This is particularly important given the increasing its use in disinfectants, wipes and sanitisers related to hygiene practices in the prevention of COVID-19.

Conclusion

We have evaluated the demographics of subjects sensitised to BAK, common exposure sources and sensitisation trends, and found an increasing trend in CA and ACD to BAK particularly in the last three years. Healthcare workers appear to be especially at risk, relating to their increased exposure through disinfectant wipes, sprays, and hand hygiene products. With the current COVID-19 pandemic, CA and ACD to BAK may also impact the general public.

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Tables

Table 1: Number of patients patch tested with benzalkonium chloride and positive and relevant reactions between 1 January 2003 and 31 December 2019

* **Includes a total of 5 doubtful reactions which were deemed relevant**

Year	No. tested	Doubtful reactions by year (% tested)	Positive reactions to benzalkonium chloride (%)	Relevant reactions to benzalkonium chloride (% of positive reactions)	Old/unknown reactions to benzalkonium chloride (% of positive reactions)	Irritant reactions to benzalkonium chloride
2003	424	2 (0.5)	6 (1.4)	3 (50.0)	3 (50.0)	0
2004	499	1 (0.2)	2 (0.4)	1 (50.0)	1 (50.0)	0
2005	522	0 (0.0)	9 (1.7)	1 (11.1)	8 (88.9)	0
2006	600	1 (0.2)	6 (1.0)	1 (16.7)	6 (100.0)	0
2007	492	0 (0.0)	3 (0.6)	0 (0.0)	3 (100.0)	0
2008	457	0 (0.0)	1 (0.2)	0 (0.0)	1 (100.0)	1
2009	481	2 (0.4)	1 (0.2)*	1 (100.0)*	0 (0.0)	0
2010	487	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0
2011	432	0 (0.0)	2 (0.5)	1 (50.0)	1 (50.0)	0

2012	452	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0
2013	371	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1
2014	430	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0
2015	388	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0
2016	362	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0
2017	365	14 (3.8)	36 (9.9)*	5 (13.9)*	31 (86.1)	6
2018	324	16 (4.9)	26 (8.0)*	8 (30.8)*	18 (69.2)	9
2019	304	29 (9.5)	21 (6.9)	5 (23.8)	15 (71.4)	14
Total	**7390**	**67**	**113**	**26**	**87**	**31**

Table 2: MOAHLFA characteristics (male, occupational dermatitis, atopic dermatitis, hand, leg, face dermatitis, and age >40) for sensitised and non-sensitised patients

Index	Sensitised patients (% of total sensitised)	Non sensitised patients (% of total non-sensitised)	P value (χ^2)
Male	35 (31)	2319 (32.3)	0.84
Occupational dermatitis	21 (18.6)	1741 (24.2)	0.179
Atopic dermatitis	24 (21.2)	2304 (32.1)	**0.02**
Hand dermatitis	29 (25.7)	2317 (32.3)	0.16
Leg dermatitis	9 (8.0)	541 (7.5)	0.83
Face dermatitis	31 (27.4)	1677 (23.4)	0.27
Age above 40	64 (56.6)	3904 (54.4)	0.53

Table 3: Strength of reactions in patients with a positive reaction at Day 4 to benzalkonium chloride 0.1% aq between 1 Jan 2003 and 31 December 2019

Strength of reaction	D2 number (%)	D4 number (%)

-	60 (53.1)	0
+/-	25 (22.1)	5* (4.4)
+	21 (18.6)	99 (87.6)
++	7 (6.2)	8 (7.1)
+++	0	1 (0.9)

* Five patients with doubtful reaction at D4 were included as their reactions were felt to be relevant.

Table 4: Strength of reactions in patients tested to benzalkonium chloride 0.1% aq between 1 Jan 2017 and 31 December 2019

2017 Strength of reaction	D2	D4
-	16	0
+/-	12	2
+	7	33
++	1	1
+++	0	0
2018 Strength of reaction	D2	D4
-	11	0
+/-	4	2
+	8	22
++	3	2
+++	0	0
2019 Strength of reaction	D2	D4
-	16	0
+/-	3	0
+	1	19
++	1	2
+++	0	0

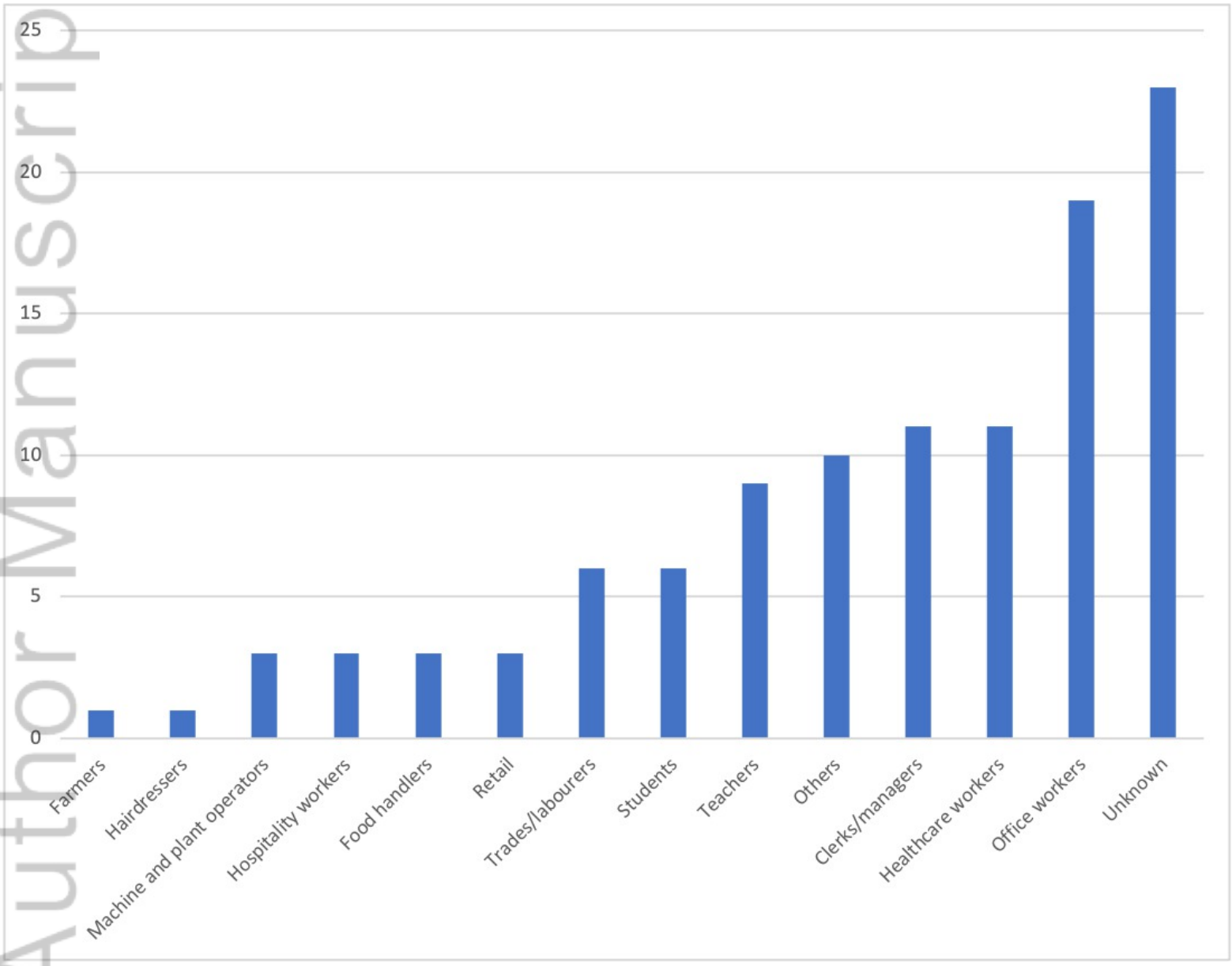
Table 5: Suspected sources of exposure to benzalkonium chloride in patients with relevant reactions*

Source of exposure	Number of patients (%)
Ophthalmic drops	8 (30.8)
Topical antiseptics/anaesthetics	7 (26.9)
Cosmetics	4 (15.4)
Disinfectant solutions	3 (11.5)
Hand sanitisers	3 (11.5)
Hand wash	2 (7.7)
Plaster of Paris	1 (4.8)
Antibacterial laundry rinses	1 (4.8)

*Some patients had more than one source of exposure

Figure legends

Figure 1: Occupations of subjects sensitised to benzalkonium chloride between 1 January 2003 and 31 December 2019



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