

ORIGINAL RESEARCH

Frequency of positive patch test reactions to preservatives: The Australian experience

Elizabeth T Chow,^{1,2} Andrea M Avolio,⁵ Adriene Lee^{4,5} and Rosemary Nixon⁴

¹*Department of Dermatology, Liverpool Hospital, Liverpool,* ²*Skin & Cancer Foundation Australia, Westmead,*

³*Skin & Cancer Foundation Australia, Darlinghurst, New South Wales,* ⁴*Occupational Dermatology Research and Education Centre, Skin & Cancer Foundation Victoria, and* ⁵*Skin & Cancer Foundation Victoria, Carlton, Victoria, Australia*

ABSTRACT

Background/Objectives: Preservatives are important causes of allergic contact dermatitis. The frequency of allergy to preservatives in Australia has been unknown to date. Our objectives are to report the frequency of positive preservative patch test reactions in Australia, comparing them to the published international data, as well as exploring the current regulations in place for preservative use in Australia.

Methods: This was the first retrospective study of patch testing results, aggregated from four patch test clinics in three centres in Melbourne and Sydney.

Results: In all, 6845 patients were patch-tested during 1993–2006 and in this period the five most frequent preservative allergens were formaldehyde (4.6%), Euxyl K400 (containing methyl-dibromo glutaronitrile and phenoxyethanol) (3.3%), quaternium-15 (2.9%), diazolidinyl urea (2.4%), and methylchloroisothiazolinone/methylisothiazolinone (2.3%). These were followed by dimethylol dimethyl DMDM hydantoin (2.1%), chloroacetamide (2.1%) and imidazolidinyl urea (1.9%). The least frequent sensitizers were parabens (1.1%), 2-bromo-2-nitropropane-1, 3-diol (0.9%) and benzyl alcohol (0.4%).

Conclusions: Formaldehyde was the most prevalent preservative allergen. Chloroacetamide allergy was more commonly seen in Australia. Parabens, 2-bromo-2-nitropropane-1,3-diol and benzyl alcohol were the least frequent sensitizers. Household

products in Australia are not required to list all ingredients preventing sensitized individuals from properly assessing their exposure.

Key words: allergic contact dermatitis, chloroacetamide, diazolidinyl urea, DMDM hydantoin, formaldehyde, methylchloroisothiazolinone/methylisothiazolinone, methyl-dibromo glutaronitrile, quaternium-15.

INTRODUCTION

Preservatives are important causes of allergic contact dermatitis. Cosmetics and skin care products, as well as products used at home and work, are important sources of preservative allergy. The frequency of allergy to preservatives in Australia is unknown. We were interested in documenting the frequency of allergy to preservatives in Australia, comparing our data to the reported rates in Europe and North America,^{1–9} and exploring the current regulations in place for using preservative in Australia.

The Australian cosmetics and toiletries market in 2003 was valued at USD\$770 million and exceeded just over USD\$1 billion in 2008. During this time, imports increased from 35% to almost half the market, with the USA as the single largest source of products followed by France and the UK. The remaining sector of the market is made up by our local cosmetics industry.^{10,11}

METHODS

We performed a retrospective review of patch test data from 6845 patients across four clinics situated in three centres:

Abbreviations:

DMDM	dimethylol dimethyl
DMDMH	DMDM hydantoin
MDGBN	methyl-dibromo glutaronitrile
MCI	methylchloroisothiazolinone
MI	methylisothiazolinone

Correspondence: Dr Elizabeth T Chow, Department of Dermatology, Liverpool Health Service, Locked Bag 7103, Liverpool, NSW 2170, Australia. Email: dretchow@optusnet.com.au
Elizabeth T Chow, FACD. Andrea M Avolio, MBBS. Adriene Lee, FACD. Rosemary Nixon, FACD.

Submitted 18 July 2012; accepted 21 August 2012

the Contact and Occupational Dermatitis Clinic, Skin and Cancer Foundation (SCF-NSW) comprising clinics at Westmead and Darlinghurst, Sydney, NSW; the Contact Dermatitis Clinic, (SCF-VIC) and the Occupational Dermatology Clinic (OCC) all located at the Skin and Cancer Foundation, Melbourne Victoria. Data were collected for a minimum of 5 years from each centre (SCF-NSW: 2002–2006; SCF-VIC: 2000–2006; OCC: 1993–2006). This study was classified as clinical audit and as such, ethics approval was not required. These are tertiary referral clinics where patients are referred for patch testing, predominantly by dermatologists.

Patch testing was performed with allergens purchased from Chemotechnique Diagnostics (Malmo, Sweden) or Trolab (Hermal, Germany); applied with Finn Chambers on Scanpor tape (Epitest, Oy, Finland) to the upper back and evaluated on day 2 and day 4 according to the International Contact Dermatitis Research Group scoring system. Formaldehyde, quaternium-15, imidazolidinyl urea and parabens mix were tested for in consecutive patients in all centres over the entire period of study but the other preservatives were not tested for in all patients. At the time of this study, testing for methyl dibromo glutaronitrile (MDBGN) was predominantly performed by testing with Euxyl K400 (Schülke & Mayr, Norderstedt, Germany), although subsequently MDBGN has been used. Euxyl K400 was also used in North America during this period.

Table 1 Patients' characteristics and MOAHLF index across the test centres

	SCF-NSW (%)	SCF-Victoria (%)	OCC (%)
Patients % (total)	27.2 (1 863)	35.1 (2 400)	37.7 (2 582)
Male	35.0	30.5	57.0
Occupational	16.7	3.7	62.0
Atopy	37.2	24.1	39.9
Hand	27.7	27.3	69.8
Leg	9.0	8.5	7.1
Face	19.8	31.1	18.4

OCC, Occupational Dermatology Clinic; NSW, New South Wales; SCF, Skin and Cancer Foundation.

A search of the literature was performed using the Medline search engine to find data from Europe and North America for comparison.^{1–9}

RESULTS

The characteristics of our study population are presented in Table 1.

In Table 2, our Australian data are compared with the European and North American data. As some preservatives were not tested in all 6845 patients, the rate of allergy calculated for these allergens may be an underestimation.

Our rate of chloroacetamide allergy (2.1%) was higher than that reported in European countries (a highest reported rate of 1.5%). North American figures were not available because it is not in the North American Contact Dermatitis Group patch test series.

Data from the OCC clinic from 2000–2008 revealed an allergy rate of 1.6% to Euxyl K400 compared with 0.9% to MDBGN (Table 3).

DISCUSSION

Our three most frequent preservative allergens were formaldehyde, MDBGN and quaternium-15. The three most frequent preservative allergens in Europe have been MDBGN, methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) and formaldehyde.¹ The three most frequent preservative allergens in North America were quaternium-15, formaldehyde and MDBGN.²

The frequencies of positive reactions to formaldehyde and quaternium-15 in our study population are 4.6 and 2.9%, respectively. These are between those reported from North America and Europe. The figures from North America are significantly higher than those from Europe. It is unclear whether the difference reflects an increased exposure of the North American population to formaldehyde and formaldehyde-releasers or to differences in the protocol used in testing quaternium-15 (2% petrolatum in North America and 1% petrolatum in Europe).¹² De Groot has written comprehensive and authoritative reviews on

Table 2 Comparison of frequencies (%) of positive patch test results to common preservatives

Preservative	Australia <i>n</i> /% relevance	Australia (%)	Europe (%)	NA (%)
Formaldehyde 1% aq	6845/42.4	4.6	2.2	8.4
MDBGN 0.5% pet	5628/19.7	3.5 [†]	3.5 [‡]	5.8 [‡]
Quaternium-15 1% pet	6845/48.7	2.9	1.2	9.3 (2% pet)
Diazolidinyl urea 2% pet	5215/54.8	2.4	1	3.1 (1% pet)
MCI/MI 0.01% aq	5927/38.2	2.3	2.3	2.3
DMDM hydantoin 2% aq	3709/51.9	2.1	0.5 (3,4)	2.8 (1% pet)
Chloroacetamide 0.2% pet	4451/32.6	2.1	0.23–1.5 (4–8)	NT
Imidazolidinyl urea 2% pet	6845/45.9	1.9	1	3
Paraben mix 16% pet	6845/20.8	1.1	0.5–1%	0.6
2-bromo-2-nitropropane-1,3-diol 0.25% pet	4756/26.2	0.9	0.8–1.25% (0.5% pet) (4,9)	3.3 (0.5%pet)
Benzyl alcohol 1% pet	4552/29.4	0.4	0.28 (4)	NT

[†]MDBGN (methyl dibromo glutaronitrile) tested as Euxyl K400 1.5% pet. [‡]Europe tested as MDBGN 0.1–0.3% pet or Euxyl K400 0.5–1% pet. USA uses Euxyl K400 2.5% pet. % relevance, percentage of current relevance; aq, aqueous; DMDM, dimethylol dimethyl; MCI/MI, methylchloroisothiazolinone/methylisothiazolinone; NA, North America; NT, not tested; pet, petrolatum.

Table 3 Frequency of Euxyl K400 reactions compared to methyl-dibromo glutaronitrile in the Occupational Dermatology Clinic 2000–2008

	Number tested	Positive reactions (%)	Relevance (%)
Euxyl K400 1.5% pet.	5208	1.6	34.1
MDBGN 0.5% pet.	4551	0.9	42.4

MDBGN methyl-dibromo glutaronitrile; pet, petrolatum.

formaldehyde and formaldehyde-releasers. Those allergic to formaldehyde should avoid formaldehyde-releasers such as quaternium-15, diazolidinyl urea, imidazolidinyl urea, DMDM hydantoin and 2-bromo-2-nitropropane-1,3-diol.^{12–14}

In Australia the National Industrial Chemical Notification and Assessment Scheme (NICNAS) regulates all industrial chemicals imported or manufactured locally. Their official database, the Australian Inventory of Chemical Substances, contains a list of chemicals already in use in Australia. If a chemical is not in this inventory it is classed as a new chemical and must be scientifically assessed and approved by NICNAS before being used.¹⁵

The way medicine and chemicals are available to the consumers in Australia is controlled through a system of scheduling classifications and these chemicals are then listed in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP).¹⁶ This is governed by the Therapeutics Goods Administration (TGA) and the classification is available in their website¹⁷ and SUSMP.¹⁶

All cosmetics sold in Australia are required to list all ingredients used.¹⁸ Therapeutic goods are required to list the active ingredients and preservative used.¹⁹ Household products in Australia are not required to list all ingredients, thus preventing sensitised individuals from properly assessing their exposure.

Formaldehyde is classified as a poison (Schedule 6 and Appendix C) with the exception that it can be used to a maximum concentration of 0.2% for cosmetics, 0.1% for oral hygiene products, 5% for nail hardeners and 0.005% in aerosols sprays. Cosmetics containing free formaldehyde of 0.05 to 0.2% are required to be labelled 'contains formaldehyde' on the container in addition to listing the preservative in the ingredients section.¹⁶ In the EU all cosmetic and household products containing more than 500 ppm (0.05%) of formaldehyde are required to be specifically labelled 'contains formaldehyde'.¹⁵ De Groot argues that the threshold concentration required for labelling may not be strict enough and should be lowered, as it has been shown that cosmetic products containing 200–300 ppm free formaldehyde can induce dermatitis from short-term use on normal skin and many formaldehyde-sensitive individuals have reacted to lower concentrations, especially when the products are used on compromised skin.¹⁵

Formaldehyde is also a Schedule 2 pharmacy medicine where there is no restriction in the concentration used.¹⁶ This allows pathologists and embalming industries to use formaldehyde to preserve tissue. Medical practitioners in

Australia still occasionally use formaldehyde as a topical treatment of verruca vulgaris in concentrations up to 35%. Using such high concentrations repeatedly on inflamed skin could cause formaldehyde sensitisation and such a practice is to be discouraged.

Euxyl K400 1.5% contains MDBGN and phenoxyethanol in a ratio of 1:4. Reactions to Euxyl K400 in most cases indicates an allergy to MDBGN. Allergies to phenoxyethanol are rare, with reported rates of 0.2, 0.24 and 0.06%.^{2,4,19} The Australian MDBGN allergy frequency of 3.3% is comparable with the European figure of 3.5%. The multicentric European study reported MDBGN allergy levels by testing with MDBGN 0.1–0.3% or with Euxyl K400 0.5–1% pet.¹ The higher North American figure of 5.8% for MDBGN allergies is based on testing with Euxyl K400 2.5% pet.² While it has been suggested that Euxyl K400 is a more sensitive detector of MDBGN allergy than MDBGN on its own,²⁰ most centres now test with MDBGN alone at a slightly higher concentration (0.5%). Our results show that this is associated with increased clinical relevance (Table 3). The use of MDBGN in leave-on and rinse-off products has been prohibited in Europe since 2005 and 2007, respectively. Since then, contact allergies due to MDBGN have significantly decreased.²¹ In Australia, MDBGN (Schedule 6 and Appendix C) is also prohibited for use in cosmetics and products intended to be in contact with the skin.¹⁶

The Australian rate of MCI/MI allergy is 2.3%. This is the same across the continents. When MI is combined with MCI, its maximum permitted concentration in cosmetics is 3.75 ppm. Since 2005 MI alone has been permitted in cosmetics in the EU at a maximum concentration of 100 ppm. This is more than 26-fold the previous limit.²¹ The current reported allergy rate of MI is around 1.5% and its prevalence trend is being monitored closely, as increasing number of cases of MI allergy have been reported from Europe.^{22,25} This has also been observed recently in Australia (Nixon, pers. comm.). The use of MCI/MI is not regulated in Australia and is not listed in the SUSMP.

The Australian allergy prevalence rate for chloroacetamide of 2.1% is higher than the reported rates of 0.79, 0.23, 0.83, 1 and 1.5%, respectively, from a number of European countries.^{4–8} The recent Scientific Committee on Consumer Safety (SCCS) of the EU compiled all reported cases of chloroacetamide allergy, including data from Australia, and reported an allergy frequency rate of approximately 1%.²⁴ Reported cases in the literature were linked to sorbolene lotion,²⁵ roll-on deodorant,²⁶ wall paint,²⁷ leather shoes²⁸ and anti-wrinkle serum.²⁹ Chloroacetamide is also used as a biocide in soluble cutting oils and in the leather, paper, textile and plastic industries.²⁴

In cosmetics chloroacetamide is often used as a mixture of chloroacetamide and sodium benzoate in a 70:30% mixture called CA24. Chloroacetamide is thought to be the allergen. Some of the reported cases have confirmed this by having their patients patch tested and demonstrating a negative reaction to sodium benzoate.²⁵

In America (2003) the expert panel of the Cosmetic Ingredient Review reported that chloroacetamide is a human

sensitiser at 0.5 and 1.25%, respectively, and concluded that it is unsafe for use as an ingredient in cosmetics.⁵⁰ In Europe, it is currently used at less than 0.3% in cosmetics. The recent report by the SCCS from the EU concluded that chloroacetamide is not safe when used under the current conditions of 0.3% in cosmetic products because human data have demonstrated that allergic reactions can be elicited at concentrations lower than 0.3% and, additionally, there are systemic toxicity issues.²⁴ In Australia chloroacetamide is used in a popular brand of moisturiser (Redwin sorbolene lotion with vitamin E manufactured by PharmCare laboratories in Australia) marketed for use in sensitive skin. Medical practitioners in Australia commonly recommend sorbolene products to patients with eczema. Although the chloroacetamide concentration used is low (0.07%), it may be sufficient to cause sensitisation in compromised skin, especially when used repeatedly. A number of chloroacetamide reactions have been traced to that specific brand of sorbolene lotion with the use of repeat open application tests. Importantly, chloroacetamide is not present in TRUE test, (SmartPractice, Hillerød, Denmark) which is widely used as the only screening test by dermatologists, allergists and immunologists in Australia and thus many cases of chloroacetamide allergy may be missed outside the major patch testing centres. The use of chloroacetamide is not regulated in Australia and the substance is not listed in the SUSMP.

The limitations of this retrospective multi-centre study on 6845 patients include the pooling of data from different centres and collected over different time frames, and, more importantly, the difficulty of standardising reading of patch test reactions within and between centres. As not all preservatives were tested in the entire study population, some of the rates of preservative allergy may have been underestimated. While we were able to assess the percentage relevance of the positive patch test reactions to the clinical presentation, it was difficult to determine the precise source of the preservative allergy.

Finally, tracking allergies to preservatives is a dynamic process with the prevalence rate generally reflecting the trend of preservative usage at the time. This is the first attempt at amalgamating data from four clinics in three Australian centres. As has occurred in Europe, ongoing studies of the local prevalence rate of allergies is important, as this provides essential information enabling our regulators to take decisive action based on patch test data.

CONCLUSION

Amalgamated Australian data from 1993 to 2006 indicate that formaldehyde is our most common preservative allergen. We endorse the recommendation of the NICNAS to limit its topical use to a concentration of less than 0.2%. Chloroacetamide allergy is higher in Australia than in Europe. Parabens, 2-bromo-2-nitropropane-1,3-diol and benzyl alcohol were the least frequent sensitisers in Australia. The ingredient labelling of household products in Australia is inadequate, making it difficult for sensitised

individuals to properly assess and avoid their exposure to allergens.

REFERENCES

1. Wilkinson JD, Shaw S, Andersen KE *et al.* Monitoring levels of preservative sensitivity in Europe, a 10-year overview (1991–2000). *Contact Dermat.* 2002; **46**: 207–10.
2. Pratt MD, Belsito DV, DeLeo VA *et al.* North America Contact Dermatitis Group patch-test results, 2001–2002 study period. *Dermatitis* 2004; **15**: 176–85.
3. Uter W, Frosch PJ. Contact allergy from DMDM hydantoin, 1994–2000. *Contact Dermat.* 2002; **47**: 57–8.
4. Schnuch A, Lessmann H, Geier J *et al.* Contact allergy to preservatives. Analysis of IVDK data 1996–2009. *Br. J. Dermatol.* 2011; **164**: 1516–25.
5. Perrenoud D, Bircher A, Hunziker T *et al.* Frequency of sensitisation to 13 common preservatives in Switzerland. Swiss Contact Dermatitis Research Group. *Contact Dermat.* 1994; **30**: 276–9.
6. Schnuch A, Geier J. Formaldehydeallergie: Aktuelle trends im internationalen vergleich. Auswertungen der IVDK- Daten der Jahre 1992–1995. *Allergologie* 1997; **20**: 205–14.
7. Brasch J, Uter W. Characteristics of patch test reactions to common preservatives incorporated in petrolatum and water, respectively. *Contact Dermat.* 2011; **64**: 43–8.
8. Goossens A, Claes L, Drieghe J *et al.* Antimicrobials: preservatives, antiseptics and disinfectants. *Contact Dermat.* 1998; **39**: 135–4.
9. Britton JER, Wilkinson SM, English JSC *et al.* The British standard series of contact dermatitis allergens: validation in clinical practice and value for clinical governance. *Br. J. Dermatol.* 2005; **148**: 259–64.
10. Ahern A. Australian cosmetics and toiletries market 2005. (Data compiled from Australian Bureau of Statistics). Available from URL: <http://strategies.ic.gc.ca/epic/site/imr-ri.nsf/en/gr117981e.html>. (Accessed 1 May 2007; no longer available at this URL).
11. Ahern A. Australian cosmetics and toiletries market 2008. (Data compiled from Australian Bureau of Statistics). Available from URL: http://www.docstoc.com/docs/36812970/Aus_cosmetics_08. (Accessed 15 September 2012.)
12. De Groot AC, White IR, Flyvholm M *et al.* Formaldehyde-releasers in cosmetics: relationship to formaldehyde contact allergy. *Contact Dermat.* 2010; **62**: 2–17.
13. de Groot AC, Flyvholm M, Lensen G *et al.* Formaldehyde-releaser: relationship to formaldehyde and inventory of formaldehyde-releasers. *Contact Dermat.* 2009; **61**: 63–85.
14. de Groot AC, White IR, Flyvholm M *et al.* Formaldehyde-releasers in cosmetics: relationship to formaldehyde contact allergy. *Contact Dermat.* 2010; **62**: 18–31.
15. Australian Inventory of Chemical Substances. AICS. Available from URL: <http://www.nicnas.gov.au/industry/aics.asp>. (Accessed 10 Sept 2012.)
16. Australian Government. Poisons Standard. 2011 Available from URL: <http://www.comlaw.gov.au/Details/F2011L01612>. (Accessed 10 September 2012.)
17. Australian Government. Scheduling basics. (updated Apr 2011). Available from URL: <http://www.tga.gov.au/industry/scheduling-basics.htm>. (Accessed 10 Sept 2012.)
18. Australian Government. Cosmetics – your online guide. (Updated Sept 2012). Available from URL: http://www.nicnas.gov.au/Current_Issues/Cosmetics/Labeling_Of_Cosmetics.asp. (Accessed 10 Sept 2012.)
19. Australian Government. Therapeutics Goods Order No. 69 – General requirements for labels for medicines. Clause 3(9) Preparations for use on skin or mucous membranes. 2009.

- Available from URL: <http://www.comlaw.gov.au/Details/F2009C00264>. (Accessed 10 Sept 2012).
20. Tosti A, Vincenzi C, Trevisi P *et al*. Euxyl K400: incidence of sensitisation, patch test concentration and vehicle. *Contact Dermat*. 1995; **33**: 193–5.
 21. Johansen JD, Veien N, Laurberg G *et al*. Decreasing trends in methyldibromo glutaronitrile contact allergy – following regulatory intervention. *Contact Dermat*. 2008; **59**: 48–51.
 22. Lundov MD, Zachariae C, Johansen JD. Methylisothiazolinone contact allergy and dose-response relationships. *Contact Dermat*. 2011; **64**: 330–6.
 23. Lundov MD, Krongaard T, Menne TL *et al*. Methylisothiazolinone contact allergy: a review. *Br J Dermatol*. 2011; **165**: 178–82.
 24. Scientific Committee on Consumer Safety (SCCS). Opinion on chloroacetamide. 22 March 2011. Available from URL: http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_053.pdf. (Accessed 10 Sept 2012).
 25. Sutton T, Nixon R. Allergic contact dermatitis to sodium benzoate chloroacetamide in a sorbolene lotion. *Australas J Dermatol*. 2006; **47**: 209–10.
 26. Taran J, Delaney T. Contact allergy to chloroacetamide. *Australas J Dermatol*. 1997; **38**: 95–6.
 27. Bogebrieder T, Landthaler M, Stolz W. Airborne contact dermatitis due to chloroacetamide in wall paint. *Contact Dermat*. 2001; **45**: 55.
 28. Jelen G, Cavelier C, Protois P *et al*. A new allergen responsible for shoe allergy: chloroacetamide. *Contact Dermat*. 1989; **21**: 110–1.
 29. de Groot AC, Weyland JW. Contact allergy to chloroacetamide in an anti-wrinkle serum. *Contact Dermat*. 1986; **15**: 97–8.
 30. Cosmetic Ingredient Review. *Cosmetic Ingredient Review Compendium*. Washington, DC: Cosmetic Ingredient Review, 2003.