SKIN HYPERSENSITIVITY REACTIONS TO PRESERVATIVES
Thuraya Isaacs, MB ChB, MFamMed
Division of Dermatology, University of Cape Town, South Africa

ABSTRACT
Preservatives are chemicals that are added to water-based products to prevent microbiological contamination and to protect the integrity of the product. The ideal preservative should be an effective antimicrobial that is stable, non-toxic, non-irritant and non-sensitising. Unfortunately preservatives are well known causes of contact allergy. We present a case of allergic contact dermatitis to methyldibromo glutaronitrile (MDBGN) in a patient employed in an industry that manufactures polypropylene fibres from plastic polymers. The article reviews the most important classes of preservatives in the industrial and cosmetic industry, namely parabens, isothiazolines, formaldehyde and formaldehyde-releasers, Euxyl K 400 and iodopropynyl butylcarbamate. The chemical and physical characteristics, antimicrobial efficacy, exposures, cross-reactivity and reported rates of sensitisation are discussed.

INTRODUCTION
Preservatives are chemicals that are added to products that contain an aqueous phase. These include cosmetics, topical medications, household products, foods, and industrial products such as glues, paints, dyes, metalworking fluids, and spin finishes. They are biocidal or biostatic, inhibiting the overgrowth of micro-organisms and protecting and retarding the chemical degradation of the product. The ideal preservative should be an effective antimicrobial that is stable, non-toxic, non-irritant and non-sensitising. No one preservative fulfils these ideal criteria and all preservatives are known to cause contact allergy. In cosmetics, preservatives are second only to fragrances as the commonest cause of allergic contact dermatitis. We present a case of allergic contact dermatitis to methyldibromo glutaronitrile (MDBGN) in a worker employed in an industry that manufactures polypropylene fibres from plastic polymers. The article reviews the most important classes of preservatives in the industrial and cosmetic industry, namely parabens, isothiazolines, formaldehyde and formaldehyde-releasers, Euxyl K 400 and iodopropynyl butylcarbamate (IPBC). The chemical and physical characteristics, antimicrobial efficacy, exposures, cross-reactivity and reported rates of sensitisation are discussed.

CASE REPORT
A 53-year-old man presented to the Occupational Dermatology Clinic at Groote Schuur Hospital with an itchy rash involving the face and hands. It was associated with swelling of the eyes. The rash responded to treatment with topical corticosteroids but relapsed when they were stopped. He had no past medical or family history of atopy, and his hobbies were non-contributory. He had a 20-pack year history of smoking. On clinical examination, he had erythematosus patches with scale on his face with periorbital postinflammatory hyperpigmentation (Fig. 1). He also had hyperkeratotic palms, with mild erythema and scale (Fig. 2).

He was employed in the manufacture of polypropylene fibres from plastic polymers. He had previously been employed in a similar industry producing nylon fibres without any symptoms. The current fibre-manufactur-
ing process involved melting plastic polymers and pigments or dyes at high temperatures, then extruding them under high pressure through extruders to produce filaments. The filaments were then cooled through an air-quenching chamber after which spin finish was applied to the product to facilitate the filaments being spun into a single tow of yarn.

The patient was assessed as having a combination of allergic and irritant contact dermatitis caused by exposures at work. He was treated with an ultrapotent topical corticosteroid for his hands, and weak-potency topical corticosteroid for his face. We advised his employer to decrease his exposure to potential allergens and irritants while investigating the problem.

Investigations included an initial patch test to 45 commercial allergens commonly implicated in allergic contact dermatitis which showed a 2+ reaction to MDBGN. Potential exposures identified from history included spin finish, dyes and pigments, polymers, yarn, hand wash and silicon lubricant spray. The spin finish was considered the most likely source of preservative despite MDBGN not being listed on the material safety and data (MSD) sheet for the product. A specific patch test to these identified hazards was performed but was negative. A workplace visit was conducted to try to identify further relevant exposures, but no additional hazards were identified.

He was assessed as having allergic contact dermatitis to MDBGN on a background of irritant contact dermatitis. The source of exposure was most likely the spin finish. Despite the construction and implementation of protective screens in front of the areas of maximum exposure, the spin finish was present as a fine mist in the whole work environment so ongoing exposure was unavoidable. The use of personal protective equipment when handling the moistened filaments and yarn was not an option because of fast-moving machinery. We advised that he be removed from the environment and be given alternative employment within the factory.

**DISCUSSION**

Since the mid-twentieth century, three contact allergy epidemics to preservatives have been observed: increased prevalence of formaldehyde contact allergy in the 1950s and 1960s due to exposure to textile finishes and cosmetics; methyl chloroisothiazolinone/methylisothiazolinone (MCI/MI) attributed mainly to cosmetic leave-on products in the 1970s and 1980s; and finally in the 1990s and 2000s MDBGN found in industrial and cosmetic products.²

We focus on the most important classes of preservatives used in the industrial and cosmetic industry, namely parabens, isothiazolinones, formaldehyde and formaldehyde-releasers, as well as Euxyl K 400 and IPBC.

**Parabens**

Parabens are alkyl esters of parahydroxy benzoic acid and include methyl, ethyl, propyl and butyl paraben. Exposures include predominantly cosmetics, foods, and topical and systemic medication. They are commonly combined relative to their different solubilities and spectrum of activity, and methyl and ethyl parabens are frequently combined. Parabens are more effective against fungi than bacteria, and antibacterial activity is most effective against Gram-positive organisms. For effective *Pseudomonas* coverage, parabens are combined with other preservatives such as formaldehyde releasers, isothiazolinones and phenoxethanol. Parabens are the most commonly used preservatives in cosmetics, their usual concentrations ranging between 0.1 and 0.3%.³

Several cases of allergic contact dermatitis and a few cases of contact urticaria have been reported.⁴ Angioedema and bronchospasm to intravenous medication containing parabens have been reported.⁵ Systemic contact dermatitis has been reported after parenteral administration of systemic medication preserved with parabens.⁴

Patch testing is usually conducted with commercial paraben mix which contains methyl, ethyl, propyl and butyl paraben in petrolatum. Each type of paraben is included at a concentration of 4%, giving a final paraben concentration of 16%. This high concentration is necessary to overcome the epidermal barrier and avoid false-negatives. However, weak positives should be interpreted with caution as this high concentration is near the irritancy threshold.¹ Patch testing with cosmetics or

<table>
<thead>
<tr>
<th>Preservative</th>
<th>Industrial</th>
<th>Other</th>
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</thead>
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<tr>
<td>Parabens</td>
<td>Industrial oils, glues, textiles, foods</td>
<td>Cosmetics, food, topical and systemic medication</td>
</tr>
<tr>
<td>MCI/MI</td>
<td>Metal-working fluids, latex paints, lacquers, cleaning products, printing inks, glues, slime control products</td>
<td>Cosmetics</td>
</tr>
<tr>
<td>MI</td>
<td>Paint, glues</td>
<td>Cosmetics</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>Disinfectant in fumigations, renal dialysis, tissue fixation, embalming fluid, resins in paper sizing, permanent press clothing, leather glues, contact cement, neoprene</td>
<td>Nail varnish, shampoos, Brazilian blow-dry</td>
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<tr>
<td>Q-15</td>
<td>Latex paints, metal-working fluids and glues</td>
<td>Shampoos, conditioners, bath and shower gels, liquid soap, shaving products, make-up, moisturising lotions and creams</td>
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<tr>
<td>MDBGN</td>
<td>Latex paint, metal-working oils, adhesives, dishwashing fluids, fabric softeners, liquid detergents, industrial cleaners and barrier creams</td>
<td>Leave-on and rinse-off cosmetics</td>
</tr>
<tr>
<td>IPBC</td>
<td>Wood and paint preservative, metal-working fluids, adhesives, textiles, plastics, inks and paper</td>
<td>Make-up, creams, moisturising lotions, contact lenses, baby products, shampoos and moist toilet paper</td>
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**Table I. Preservatives and possible sources of exposure adapted from Sasseville¹**
Sensitisation rates range between 2% and 3% in Europe. Most recent sensitisation rates for MCI are reported at 2.3%. In the early 2000s MI was introduced alone into industrial products, and in 2005 permitted for use in cosmetics. Shortly thereafter the first case of industrial allergic contact dermatitis was published and in 2010, the first cases of cosmetic-related contact allergy were published. The prevalence of MI allergy is around 1.5% and exposures include occupational, cosmetic and industrial products. Most of the reported cases are due to paint, either from occupational exposure or allergic airborne contact allergy to MI in consumers from the painted product or carpet glue.

**Formaldehyde and formaldehyde releasers**

Formaldehyde, methanal, is a gas with a pungent odour, and is ubiquitous in the environment. It has been used in numerous industrial and household settings as a disinfectant in fumigations, renal dialysis and dairy equipment and in cleaning products such as household detergents. It is also used as a histological fixative and embalming fluid. Formaldehyde is combined with other compounds to form resins such as aminoplast and phenolic resins, used in paper sizing and permanent press clothing. Other formaldehyde resins, such as tosylamide formaldehyde resin, are found in nail varnish, contact cement and neoprene. These resins are also used in plywood adhesives, fibre boards and plastics.

In cosmetics, the use of formaldehyde has decreased, and when used the level of free formaldehyde should not exceed 0.2%. Products containing formaldehyde are frequently not directly labelled. Hair-straightening products such as the Brazilian blow-out have been found to contain formaldehyde. A Swedish study found that 10% of moisturisers sampled contained formaldehyde.

Formaldehyde may also be present from occult sources such as release from plastic containers or impurities from raw materials, or released by other formaldehyde donor preservatives during storage and use.

Formaldehyde is a moderate to strong sensitisier, with sensitisation rates ranging between 1% and 9%. Most recent sensitisation rates reported by Schnuch et al. at 1.54% for formaldehyde. The threshold for elicitation varies widely. Jordan et al. have demonstrated that the threshold concentration required to cause dermatitis in formaldehyde-sensitive subjects was as low as 30 ppm (0.003%), whereas Flyvholm and Menné found that the threshold concentration was 250 ppm (0.025%). The United States Cosmetic Ingredient Review Expert Panel of the Cosmetic, Fragrance and Foliery Association recommends that the concentration not exceed 0.2% free formaldehyde in cosmetics. This has also been endorsed by the European Economic Council, which has also regulated that products containing more than 0.05% free formaldehyde be labelled as formaldehyde sensitisers. With the decline in the use of formaldehyde in cosmetics, there has been an increase in the use and thus sensitivity to formaldehyde-releasing preservatives. These include quaternium 15 (Q-15), dimethylidimethyl (DMDM) hydantoin, imidazolidinyl urea, diazolidinyl urea, 2-bromo-2-nitropropane-1,3-diol (Bronopol). They all have formaldehyde-releasing action because of their easily detachable formaldehyde moiety. Although the concentration of free formaldehyde released is low, it may produce sensitisation if applied to damaged skin, and in those already sensitised to formaldehyde.
Q-15 is a colourless and odourless biocide, which is water soluble, and effective against yeasts, moulds and bacteria especially *Pseudomonas aeruginosa*. It is found in personal and cosmetic products such as shampoos, conditioners, bath and shower gels, liquid soap, shaving products, make-up, moisturising lotions and creams, and in the industrial industry in latex paints, metal-working fluids and glues. Q-15 is a potent formaldehyde releaser, and 0.1% concentration of Q-15 releases 100 ppm of free formaldehyde.\(^3\)

Imidazolidinyl urea is the second most frequently used preservative in cosmetics after parabens. It is a water-soluble biocide, marketed as Germall 115, and is effective mostly against bacteria. It is often used in combination with parabens for increased coverage against yeasts and fungi. It is an infrequent sensitiser, and releases approximately one-eighth less formaldehyde than Q-15, and less than 50% of those allergic to imidazolidinyl urea show an allergic reaction to formaldehyde.\(^14\) Cross-reactions with diazolidinyl urea may be observed.

Diazolidinyl urea was introduced in 1982 as a preservative under the trade name Germall II. It is biocidal against Gram-positive and Gram-negative bacteria and is often combined with parabens for increased coverage against fungi. It is currently believed to be a more potent sensitizer than imidazolidinyl urea, and co-sensitisation with formaldehyde and other formaldehyde releasers may be found.\(^15\)

2-bromo-2-nitropropane-1,3-diol (Bronopol) is a water-soluble diol and broad-spectrum biocide. It is used in cosmetics and topical medications at concentrations ranging between 0.001% and 1%. It is irritant above 1%. Personal products, such as shampoos, may release more than 30 ppm of free formaldehyde, which is considered to be the elicitation threshold in formaldehyde-sensitive individuals. Numerous cases of allergic contact dermatitis to Bronopol have been reported, with and without cosensitisation to formaldehyde. Schnuch et al.\(^6\) reported sensitisation frequencies of 1.25%.

DMDM hydantoin is a highly water-soluble broad-spectrum biocide and is commonly used in shampoos. DMDM hydantoin contains 2% free formaldehyde and is used in concentrations of 0.1-1% in cosmetics, yielding 20-200 ppm free formaldehyde. One study demonstrated that 57% of patients sensitive to DMDM hydantoin will cross-react to formaldehyde.\(^16\)

Patch testing to formaldehyde and formaldehyde releasers is done in aqueous vehicle, because of their relative insolubility in oils. Formaldehyde is tested at a concentration of 1%, and therefore weak reactions should be interpreted with caution as they may be irritant. Q-15 (concentration 2%) and Bronopol (0.5%) are tested in petrolatum, while imidazolidinyl urea is tested at 2% in aqueous vehicle. Diazolidinyl urea and DMDM hydantoin are tested at concentrations of 1% in water.\(^1\)

Cross-reactions are common. Comcomitant reactions to formaldehyde and formaldehyde releasers ranged from 15% to 50%.\(^6\) The strongest association is seen between Q-15 and formaldehyde. Allergic contact dermatitis and contact urticaria have been reported, as well as severe anaphylactic reactions due to systemic exposure.\(^1\)

**Methyldibromo glutaronitrile (dibromo dicyanobutane)/phenoxyethanol**

MDBGN, also known as dibromo dicyanobutane (Tektamer 38), is found in the formulation Euxyl K 400, which consists of phenoxyethanol and MDBGN in a 4:1 ratio. It has broad-spectrum biocidal activity against bacteria, fungi and yeasts. It was responsible for an epidemic of contact allergy in Europe which peaked in the late 1990s and early 2000s. In the cosmetic industry, it was used predominantly in leave-on and rinse-off products. In the industrial arena, it is found in latex paint, metal-working oils, adhesives,\(^17\) dishwashing fluids, fabric softeners, liquid detergents, industrial cleaners and barrier creams. Johansen et al.\(^18\) found that creams and lotions accounted for 31% of the products causing reactions and liquid soaps for 23%. The same study showed that occupational disease accounted for 14% of cases of MDBGN allergy, most of them among health-care workers.\(^18\)

The high rate of contact dermatitis led to the subsequent total ban of MDBGN in cosmetic products in the EU.\(^19\) The prevalence of contact allergy to MDBGN in 2008 in Denmark was 3.7%, the highest of all preservatives, but the epidemic has started to level off following the total ban in cosmetics in the EU.\(^1\) In the UK the sensitisation rate decreased from 2.4% in 2000 to 1.1% in 2004-2006.\(^19\)

Patch testing is done using petrolatum as the best vehicle. The optimal patch concentration of Euxyl K 400 is still unclear. Most authors agree that Euxyl K400 should be tested at a concentration of 2.5% which contains 0.5% MDBGN. Concentrations of MDBGN below 0.3% result in too many false-negatives. Hence testing at concentrations of 0.5% MDBGN may result in irritant reactions, but false-negatives are less likely.

**Iodopropynyl butylcarbamate**

IPBC is an organo-iodine fungicide, bactericide and pesticide. It has been used as a wood and paint preservative, but also in metal-working fluids, adhesives, textiles, plastics, inks and paper at concentrations ranging between 0.02% and 4%. It has been used in the cosmetic industry in concentrations up to 0.1% and is found in make-up, creams, moisturising lotions, contact lenses, baby products, shampoos and moist toilet paper.\(^1\)

The sensitisation rate in a Danish study for the period 1996 to 2008 was 0.4%, and in another study conducted in the EU 0.88%.\(^2,6\) Patch testing is done at a concentration of 0.1% in petrolatum.

**Clinical aspects**

Diagnosis of skin allergy to preservatives requires a thorough dermatological and occupational history, as well as examination of the skin. The MSD sheets provide a guide only to the exposures encountered at work and list only the main ingredients and hazardous substances included in a product; hence ingredients like preservatives may be excluded. In these situations, communication with manufacturers of products may be useful. Patch testing is essential in establishing a diagnosis. A factory visit may be invaluable in providing additional information when a cause cannot be established from history, or in determining the source of an allergen detected on patch testing.

Preservative hypersensitivity commonly presents as an allergic contact dermatitis, but unusual presentations such as systemic contact dermatitis, contact urticaria and anaphylaxis may also occur.\(^1\) In occupational contact dermatitis the primary site of involvement is usually the hands. As indicated by the Male, Occupation, Atopic dermatitis, Hand dermatitis, Leg dermatitis, Facial dermatitis, Age > 40 (MOAHFA) index,\(^1\) certain of the preservatives are more strongly associated with occupational dermatitis where the hands are most affected, namely MI, phenoxyethanol, MCI/MI, IPBC, formaldehyde (and certain formaldehyde releasers) and MDBGN.\(^6\) Others such as imidazolidinyl urea and...
diazolidinyl urea are more strongly associated with face dermatitis, indicating cosmetic exposure. For example, IPBC in Denmark shows a typical occupational pattern using MOAHLFA index (male 46%, occupational 31%, hands 46%) which is in keeping with its use in cutting fluids and paints. MI sensitivity has shown a significant increase in recent years and also shows a strong occupational pattern in Schnuch et al.’s study in the Danish population (male 47.9%, occupational 41% and hands 48%). MDBGN, as in our patient, also shows a more occupational pattern using the MOAHLFA index (male 41.2%, occupational 21% and hands 36%). In a study by Johansen et al., a significant association can be seen between hand eczema and MDBGN allergy (p<0.001) and between occupational skin disease and MDBGN allergy (p=0.01). In summary, we have presented a patient with an allergic contact dermatitis to MDBGN. Since the ban of MDBGN in the cosmetic industry, sources of exposure are mostly occupational, in the case of our patient, the most likely source being the spin finish. Our patient was male and presented with a hand and face dermatitis, which is consistent with MDBGN allergy in the literature. His facial dermatitis can be explained by an airborne contact dermatitis component secondary to the fine mist of spin finish present in the work environment. This case also highlights the fact that MSD sheets only provide data on hazardous substances, and do not list all ingredients such as preservatives.

Preservatives are essential chemicals added to industrial, household and cosmetic products to prevent spoilage. Allergy to preservatives is well known. Compulsory labelling of cosmetics and complete disclosure of potential sensitisers on MSD sheets should be mandatory to avoid exposure in those already sensitised and to assist in identifying the source of exposure. Doctors should be encouraged to continue to report cases of occupational preservative allergy, to regulate the concentrations of preservatives in both the industrial and cosmetic industry, and also to recommend products that are free of potential sensitisers, or choose products with less-sensitising preservatives.

Declaration of conflict of interest

The author declares no conflict of interest.

REFERENCES


Product News

AstraZeneca encourages patients to ‘stick’ with asthma compliance programmes

AstraZeneca Pharmaceuticals has unveiled a new asthma awareness campaign to educate patients on correct inhaler technique as well as boosting patient compliance with their daily asthma management.

The campaign is centred on the Turbuhaler which features an innovative design that allows for accurate dosage of asthma medications Symbicord and Pulmicort without any propellant gas or other additives. ‘The campaign has two distinct aims: to improve patient compliance by dispelling any patient uncertainty around using the inhaler through the introduction of an innovative way for patients to personalise their Turbuhalers and to help alleviate the stigma around asthma,’ says Dr Bhana, Senior Manager: Medical, Regulatory and Quality Assurance for AstraZeneca.

When the Turbuhaler was introduced in 1987, it was welcomed as a revolutionary inhaler design - the first powder inhaler synchronised to operate with the patient’s breathing, thus replacing the need for propellant gas. ‘As with any novel design, patients may be uncertain on how to use the Turbuhaler correctly. Unfortunately, this uncertainty can lead to poor administration of medication, a lack of trust in the medicine’s efficacy and poor compliance,’ says Dr Bhana.

To combat this, AstraZeneca Pharmaceuticals will be distributing step-by-step instruction stickers to doctors’ rooms and pharmacies. These stickers are to be applied to the exterior surface of the Turbuhaler and provide a quick and easy explanation of how to use the device correctly. To meet the second objective, AstraZeneca will be introducing the ‘Style My Turbuhaler’ at doctor’s rooms. ‘Style My Turbuhaler is a collection of removable themed stickers that allows patients to personalise their Turbuhaler. The concept draws on the trend of customisation by offering 25 bold designs in a variety of themes including sports, nature and the arts,’ adds Dr Bhana. The stickers are easy to apply and remove, allowing patients to swap as they please.

‘The rationale behind Style My Turbuhaler is that customisation allows patients to identify with their inhalers and therefore encourages proactive ownership of the disease,’ says Dr Bhana, ‘and destigmatisation of the disease.’

‘We know so much more about treating asthma effectively these days. The right medicines and following the correct regimen should have a positive impact on both patients’ asthma and quality of life. Using an inhaler correctly and as often as prescribed is a key part of any such regimen.’

Symbicord, Pulmicort and Turbuhaler are registered trademarks of the AstraZeneca group of companies.

For further information contact: Christo Olivier, Product Manager: Respiratory, tel 011- 797-6000, cell 083-260-0882, e-mail christo.olivier@astrazeneca.co.za