

OUR TOXIC WORLD: THE CAUSES OF ALLERGY



The number of people with a skin sensitivity to substances ranging from cosmetics to household products, substances at work and in the general environment runs into the millions. One in five of the population is “atopic” – with a tendency to develop eczema, hay fever or asthma – and is liable to develop rashes, weals and other skin reactions from contact with products including perfumes, hair dyes and costume jewellery.

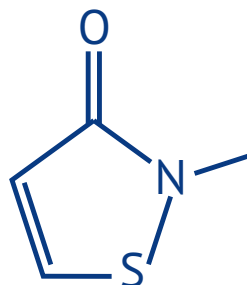
In these circumstances, the most effective intervention may not be that delivered in the clinic but that secured in Whitehall and Westminster. Changes to public health policy have spared many more people from the pain and discomfort of skin allergy than the treatments and medicaments prescribed by doctors and nurses.

St John's has been in the forefront of campaigns to secure these changes and has been instrumental in protecting populations across Europe from exposure to substances liable to inflame and irritate the skin.

In December 2013, *Cosmetics Europe*, the European Cosmetics Trade Association, called on its members to stop using the chemical methylisothiazolinone (MI) in certain products after a review committee of the European Commission, chaired by a St John's dermatologist, **Ian White**, urged it be banned.

The move followed an explosion of allergic reactions among users since the chemical, a preservative to extend shelf life, was added to cosmetics from 2005.

Dr White, head of the department of Cutaneous Allergy at St John's, said: “The frequency of reactions to MI is unprecedented in my experience.



Methylisothiazolinone, a preservative used in cosmetics to extend shelf life since 2005

Contact allergy to this permitted preservative is of epidemic proportions. We have never seen anything quite like it.”

The victory is the latest in the constant struggle to keep consumers safe from new substances – and sometimes old ones – to which they may have allergic reactions. Products from hair dyes to perfumes have been re-formulated, against intense opposition from the industries involved, to make them less harmful for customers to use.



The introduction of methylisothiazolinone into cosmetics, perfumes and hair dyes led to an explosion in allergic reactions

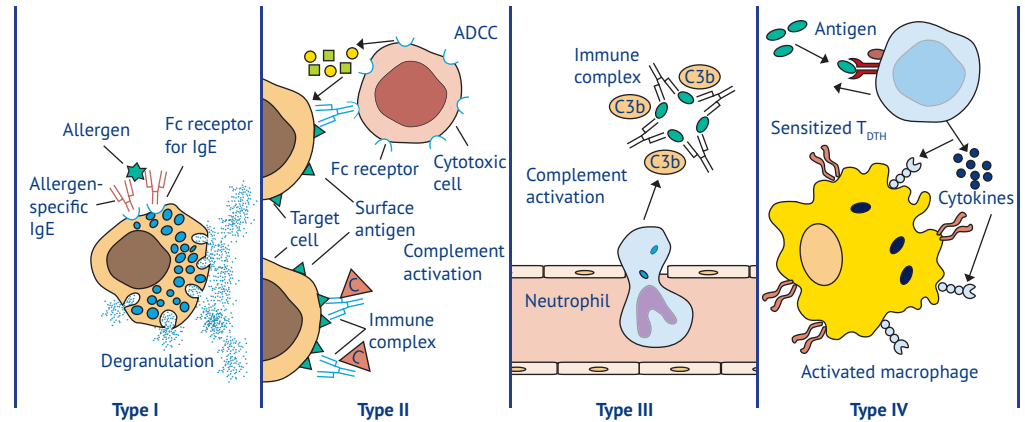


In December 2013, Cosmetics Europe called on its members to stop using methylisothiazolinone, a victory for a St John's-led campaign

Types of allergy

When a patient arrives at the St John's Cutaneous Allergy department for investigation of their eczema, they will be tested for their sensitivity to a range of contact allergens. The key to effective management of allergic diseases is making an accurate diagnosis and identifying the substance(s) responsible. Allergy testing is a crucial part of this.

Once the cause is identified, counselling and advice on how to avoid the offending substance will help reduce or eliminate symptoms and use of medication, and improve quality of life.



Four types of allergic reaction



Asthma



Hay fever



Skin prick test - application



Skin prick test - reaction



Dust mites



Urticaria

There are four types of allergic reaction, two of which are particularly important for the skin. Type 1 (immediate) sensitivity is evaluated by skin prick testing and involves making a series of tiny punctures into the skin through which suspected allergens are introduced such as pollen, grass, house dust mite proteins, peanut extract and so on. If the person is allergic a visible inflammatory reaction, like a mosquito bite, will appear in 10-20 minutes.

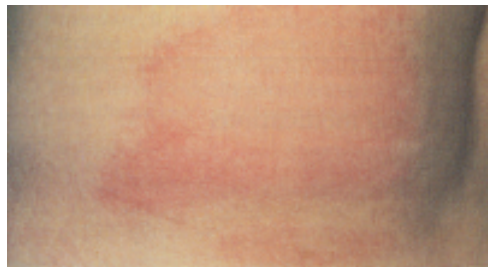
This technique is used for identifying allergens that may cause *asthma* or *hayfever* as well as skin reactions such as *urticaria*. The **Type 1 reaction** is IgE-mediated and involves the stimulation of mast cells to release histamine causing the weals which characteristically appear on the skin. This will be dealt with more fully in Chapter Six: Inflammatory Skin Disease.

The Type 2 Cytotoxic Antibody Reaction is the blood group incompatibility that causes transfusion reactions - it does not involve the skin.

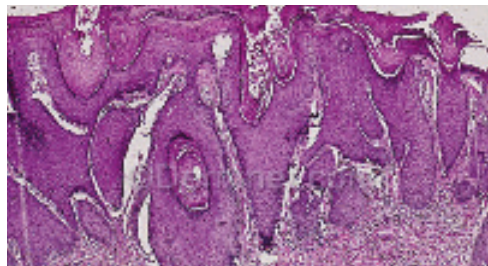
The Type 3 Immune Complex Reaction is seen in reactions to certain drugs, and may cause vasculitis with inflammation of small blood vessels in the skin.

The key allergy involving the skin, which will be discussed here, is **Type 4 cell-mediated delayed hypersensitivity**, which involves T-lymphocytes.

This is what lies behind common allergies such as that to chemicals in perfume, hair dyes, preservatives, resins, rubber and metals – in costume jewellery and coins – also known as *allergic contact dermatitis*.



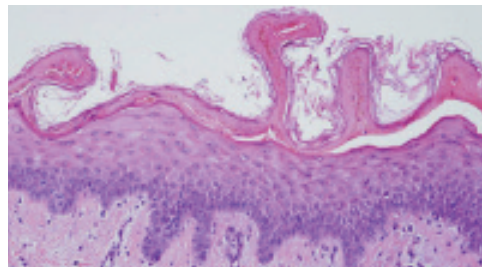
Weal - urticaria



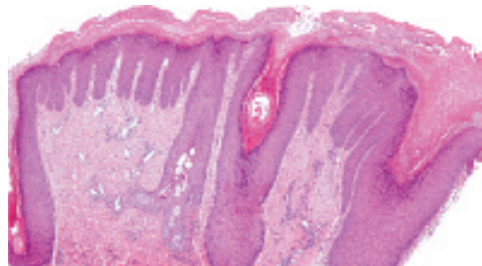
Eczema - histology



Patch testing – the Finn Chamber technique



Irritant contact dermatitis



Hyperkeratosis

Patch testing

The fundamental method for identifying Type 4 allergy is patch testing. This is designed to reveal whether the patient has a specific allergy to a substance that comes into contact with their skin and may be the cause of their skin inflammation

Common allergens such as sunscreens, hair dyes and medicaments, together with other relevant chemical substances, are applied to small aluminium discs the size of a five pence piece and applied in rows to the skin, usually on the upper back, for 48 hours.

Known as the Finn Chamber technique, it tells the dermatologist whether the individual has a contact allergy to the substances being tested.

Dr White, consultant dermatologist and head of the cutaneous allergy clinic, said:

“Patch testing is one of the few ways of objectively investigating eczema. You can demonstrate the presence or absence of an allergic factor relevant to their condition. Fundamentally you are exposing individuals under standardised conditions to the suspected allergen. Then it is up to the clinician to interpret the significance of the finding.”

Patch testing was introduced to St John's in the 1950s by **Charles Calnan**, then a registrar at the hospital who later rose to head the Institute as the University of London's first Professor of Dermatology.

He specialised in *contact dermatitis* and was appointed consultant in 1956 before being promoted to professor in 1961. He started keeping photographic records of all skin conditions treated at St John's and built up the world class skin allergy testing unit that exists today. He was the first editor

Patch testing was introduced at St John's in the 1950s. It is still one of the few ways of investigating potential causes of eczema



of the international journal *Contact Dermatitis*.

The basic methodology of patch testing that he introduced is largely unchanged, although the quality and range of the allergens has improved and standardised chambers are now used. Calnan was joined in the mid-1960s by **Etain Cronin**, an internationally recognised expert at patch testing who published a highly regarded book, *Contact Dermatitis*, in 1980.



Etain Cronin



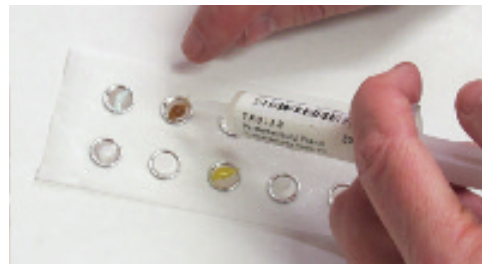
Commercially available allergens prepared in syringes



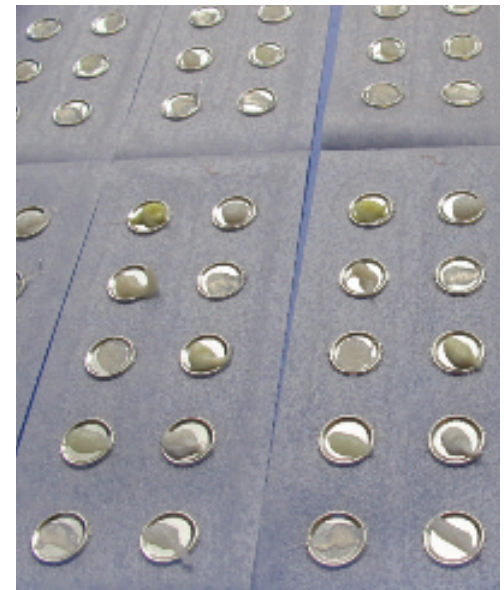
Allergens are stored refrigerated



Patch test results are recorded in a standard format



Finn Chambers being filled. Proper dosing of the chambers is important



Filled Finn Chambers

Types of eczema



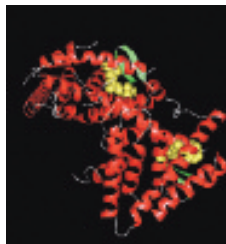
Atopic eczema, the most common form of eczema, mostly affects children



Allergic contact dermatitis caused by nickel in jewellery



Irritant contact dermatitis



Alitretinoin

There are three main types of dermatitis (or eczema):

1 Endogenous eczema – caused by genetic predisposition which results in the skin condition emerging regardless of the environment to which the individual is exposed. “Even if someone is confined to the stocks on an iceberg in the middle of the ocean the eczema will still develop,” said Dr White.

2 Allergic contact dermatitis – an allergic reaction to a specific substance such as nickel in earrings – the typical Type 4 hypersensitivity reaction

3 Irritant contact dermatitis – caused by exposure to one or more substances with irritant potential and which produce inflammation by direct chemical or physical damage to the skin. Often there are repeated exposures, each causing minor changes to the skin until a threshold is breached and clinical signs of inflammation appear.

Often cases involve a combination of two or all three of the above types.

In the past, important causes of contact dermatitis seen in the clinic were occupational – the result of exposure to chemicals and substances used in industry. In the early 1970s, **Richard Rycroft**, joined St John's. He was employed by the Employment Medical Advisory Service of the Health and Safety Executive, and he developed the internationally recognised occupational dermatology service.

In the ensuing decades, as safety standards in industry rose and factories in London and across the country closed, the patients seen at St John's changed. The number of patients with problems caused by occupational exposure declined while the number with reactions to consumer products rose.

“We used to see a lot of occupational skin disease.

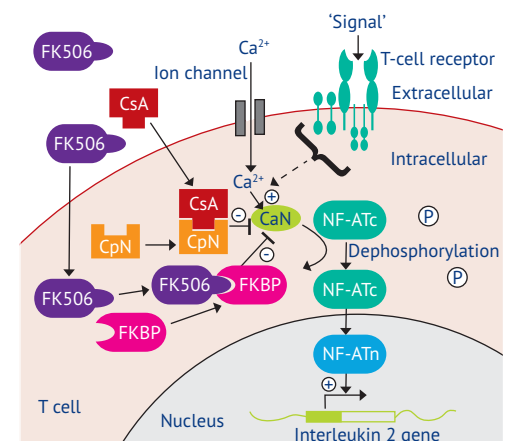
But the way people work has changed, thanks to Health and Safety regulations brought in during the 1970s and 1980s. They have transformed working practices and the exposures have changed enormously,” said Dr White.



Richard Rycroft

Prevention is the goal but once the *dermatitis* is established, treatment is required. Treatments for *eczema* are based, as they long have been, around moisturisers and topical steroids for symptomatic relief. In severe cases of *eczema*, when there is a strong endogenous component, systemic immunosuppressive agents such as ciclosporin and azathioprine are used. More recently alitretinoin, a vitamin A derivative, has become available for the treatment of *hyperkeratotic hand and foot eczema*, where the skin becomes thick and fissured.

Mechanism of action of ciclosporin



Mechanism of action of ciclosporin – a treatment for severe cases of eczema which suppresses the immune system

Occupational allergies

Today, a significant proportion of the patients seen at St John's who are suffering from occupational contact dermatitis work in the health service. That may sound odd as hospitals and clinics are among the cleanest environments. But repeated hand washing and wearing gloves, now required of all health workers in the battle against hospital infections, is an issue for people with an atopic tendency. Modern hand cleansers are milder than traditional tablet soap, but while they minimise the problem they cannot remove it.

In the past latex gloves were a particular problem for health workers. When universal precautions were introduced over contact with patients in the 1980s in the wake of the HIV/Aids epidemic, hospitals began using cheap latex gloves from Asia and the Far East. These had not been properly treated to remove the proteins in the rubber which eluted out during wear causing allergic contact *urticaria* (Type 1 allergy) in large numbers of people.

The problem was solved when manufacturing standards were raised or gloves were sourced elsewhere and synthetic rubber gloves were introduced. Dr White said: "The problem has disappeared. I have not seen a genuine new case of latex protein allergy for several years."

Caterers also suffer with *contact dermatitis* as a result of exposure to fruit and vegetable juices. Chefs cutting up potatoes and peeling vegetables are often seen as patients of St John's.

Bricklayers, whose hands are frequently coated with wet cement, used to beat a constant path to the Institute complaining of rashes, rough skin and



Ian White



John McFadden



Jonathan White



Piu Banerjee

soreness. Cement is alkaline and thus an irritant, but in addition it contains a chemical, hexavalent chromium, which is a known allergen. Since 2005 the addition of ferrous sulfate to cement has eliminated exposure to hexavalent chromium in cement. Thanks in part to awareness of the problems it caused raised by St John's, the next generation of builders are protected from this devastating disease.

But management can be tricky. A worker laying floor tiles using epoxy resin-based cement complained of an allergic reaction on his hands despite wearing gloves. Doctors at St John's pointed out that if he was wearing gloves all day there would be more epoxy resin inside the gloves than out.

Dr White said: "The aim is to keep people at work and the treatment often consists of identifying the cause of their allergy and advising them on how to avoid exposure. In that way we cure people. That is rare in medicine."



Bricklayers suffered frequent rashes and sore skin until the composition of cement was changed in 2005

The clinic's global reputation means its dermatologists – there are currently four consultants in the department: **Ian White, John McFadden, Jonathan White** and **Piu Banerjee** – are in demand to give lectures in the UK and overseas and help promote cutaneous allergy and occupational dermatology services in developing countries. "In many countries where there is a wide manufacturing base and high prevalence of *occupational dermatitis* the patch testing service is still underdeveloped" said Dr McFadden.

Cosmetics



Repeated handwashing (above) and use of detergents (below) are now required of health workers to prevent hospital infections and can cause problems in people with sensitive skin



When ingredient labelling of cosmetics was introduced in 1993, fragrances were omitted – yet they are second only to nickel as a cause of allergic reactions

The ingredients of all cosmetics are listed on the label. That may seem a small matter to shout about – but it took a 15 year campaign to achieve and was only introduced in 2005. Even then fragrances were exempted.

“It transformed the outlook for allergy sufferers. Now they can look at the label and if they are allergic to, say, a formaldehyde releasing preservative, they can avoid it. It has revolutionised our ability to investigate and treat allergy,” said Dr White.

The campaign began in the late 1980s and St John’s played a prominent role from the start. Representatives of the industry claimed listing ingredients would confuse consumers. “‘They don’t need to know’, was their view,” said Dr White.

There were meetings with the Departments of Health and Trade and Industry and the EU Commission. Gradually opposition to labelling was

beaten down. “I am not a laboratory-based researcher, I am someone who bangs on people’s doors. If you bang on them long enough eventually they will open up and let you in,” said Dr White.

That is what happened. Ingredient labelling of cosmetics was finally introduced following an EU ruling in 1993. But fragrances – the substances that give the products their smell – were exempted, because, it was claimed, they were too complicated to list. Confidentiality of formulations was also an issue. The fragrance manufacturers were a powerful lobby.

When the EU Directive requiring cosmetics to list their ingredients on the label came in, fragrances were excluded.

In 1999, the issue was re-examined by the *Scientific Committee on Cosmetics and Non-food products*. It said there were 26 important fragrance chemicals which consumers needed to be aware of and labelling was



mandated by another EU ruling from March 2005.

Given there were around 3,000 fragrance substances in use, this should not have been a great problem for the cosmetics industry. But manufacturers protested. They demanded a review claiming some of the 26 named chemicals were not important as the level of exposure in the population was low.

In response the EU commissioned Dr White to conduct the review. The outcome was not what the industry had hoped. After a three year study, including public hearings, the review committee published an exhaustive 334 page report which was adopted in June 2012. It confirmed that the original 26 chemicals named in the first report remained suspect. In addition it identified further suspect chemicals it said should be listed, bringing the total to 83.

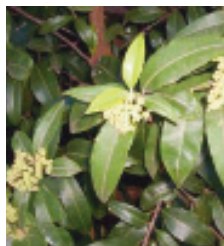
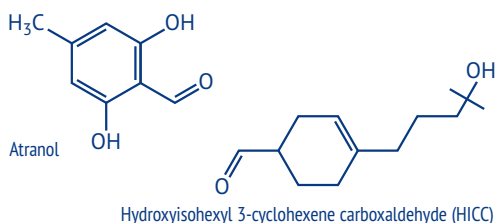
Three substances should be banned, it said: atranol and chloratranol, constituents of tree and oak moss, used in perfumes to provide “woody notes” but which are “extreme allergens”; and hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC), a synthetic substance widely used in skin care products to provide a floral aroma for more than a decade. An estimated 1.5 per cent of the population of Europe has become allergic to HICC as a result of this exposure.

A further 13 chemicals should be restricted including citral, found in lemon and tangerine oil, coumarin, found in spicy tonka beans, and isoeugenol, a component of rose oil.

The report, which estimated 16 per cent of patients with *eczema* were “sensitised to fragrance ingredients”, triggered a war of words between the



Oak moss (above) and Tree moss (below): used in perfumes to provide woody notes but both are extreme allergens



Lemon Myrtle



Tangerine Oil

perfume houses behind some of the biggest cosmetics and the dermatologists committed to protecting their patients. News reports appeared warning that consumers could be left without their favourite scent because of meddling EU bureaucrats. “It would be the end of beautiful perfumes if we could not use these ingredients,” Françoise Montenay, the non-executive chairman of Chanel, told Reuters.

The protests highlighted oak moss, which manufacturers pointed out had been used as a constituent of perfume brands such as Chanel for more than 90 years.

Dr White responded: “This is not a trivial problem. After nickel, fragrances are the most important cause of contact allergy. Most things applied to the skin contain fragrances of one sort or another: deodorants, hand creams, body sprays. When susceptible people put these things on their skin they get *eczema*.”

The industry claimed the report was an attack on some of Europe’s most famous fashion houses. But Dr White pointed out that it was possible to extract the harmful chemicals without affecting the smell of the perfume. “Oak moss contains chemicals which are extreme allergens. The manufacturers know this perfectly well. They have funded research to reduce them – they can extract these ingredients so the other constituents of the moss can still be used,” he said.

Since 2005, the 26 chemicals named in the first review have been listed on labels. EU member states are expected to ratify a new regulation banning the three named substances and extending the labelling requirement to the chemicals named in the second review.

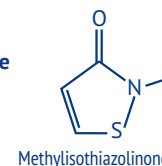
“It has been a 25 year battle but we are nearly there,” said Dr White.

Cosmetics again



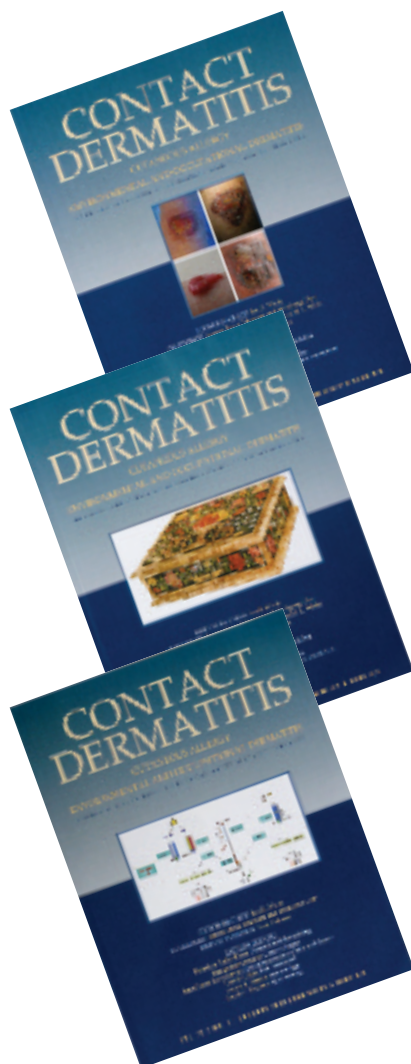
One in ten patients tested at St John's is allergic to the preservative methylisothiazolinone used in cosmetics.

As one problem is resolved, another raises its head. Methylisothiazolinone (MI) is a preservative that has increasingly been used in cosmetics over the last decade. A risk assessment in 2003 concluded it was safe in both leave-on and rinse-off products.



However, in 2011, dermatologists at St John's started seeing patients who were allergic to MI and by 2013 it had become an epidemic, according to Dr White. "One in ten of our patch tested patients are now allergic to it," he said.

The EU were, once again, slow to act. Despite being alerted to the problem by St John's in early 2012, the EU authorities at first ignored it and then dismissed it as of low priority. When reports started appearing in the media they asked the *Scientific Committee on Consumer Safety*, chaired by Dr White, to review it.



The journal *Contact Dermatitis* started in 1975 by Charles Calnan remains the most important publication relevant to the specialty. It is now also the official publication of the European Society of Contact Dermatitis

1. Nickel sulfate	5%
2. Disperse Yellow 3	1%
3. Colophonium	20%
4. 2-Bromo-2-nitropropane-1,3-diol	0.5%
5. p-Phenylenediamine	1%
6. MBT	2%
7. Formaldehyde	2%
8. Potassium dichromate	0.5%
9. Lanolin alcohol	30%
10. Fragrance Mix II	14%
11. Paraben mix	1%
12. Neomycin	20%
13. Cobalt chloride	1%
14. Quaternium - 15	1%
15. p-Chloro-m-cresol	1%
16. Thiuram mix	1%
17. Mercapto mix	1%
18. Fragrance mix I	8%
19. IPPD	0.1%
20. Sesquiterpene lactone mix	0.1%
21. Clioquinol	5%
22. PTBP resin	1%
23. MCI/MI	0.02%
24. Calne mix	10.0%
25. Myroxylon pereirae (balsam of Peru)	25%
26. Imidazolidinyl urea	2%
27. Tixocortol pivalate	0.1%
28. Cetearyl alcohol	20%
29. Phenoxyethanol	1%
30. Dermovate cream	
31. Betnovate cream	
32. Budesonide	0.1%
33. Diazolidinyl urea	2%
34. Methylidibromo glutaronitrile	0.3%
35. Epoxy Resin	1%
36. Sodium Metabisulfite	1%
37. Methylisothiazolinone	0.2%
38. Sorbic acid	2%
39. Octylisothiazolinone	0.1%
40. Benzisothiazolinone	0.05%
41.	
42.	
43.	
44.	

The baseline series of contact allergens used at St John's is regularly updated

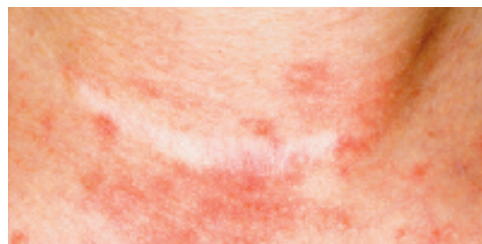
In December 2013, the committee concluded that MI should be prohibited in leave-on cosmetic products, including wet wipes, and restricted to 15 parts per million (ppm) in rinse-off products.

At the same time, the industry trade association called on manufacturers to cease using MI in leave-on products, including wet wipes. But it made no recommendation about rinse-off products.

Dr White said: "The MI problem will, belatedly, be resolved in Europe. But will the lessons be learned? In a few years, no doubt, we will experience another catastrophe. The cosmetics industry must have faith in the clinical data generated and given freely by the dermatological community. Safety cannot continue to be a competition."



Millions of people are sensitive to chemicals in cosmetics and household products and are liable to develop rashes, weals or other skin reactions from contact with them



A case of nickel allergy (above) and (below) 5p nickel coins introduced in 2013. Studies have shown the nickel released from the coins is seven times higher than the legal limit



5p Nickel coins



Nickel

Nickel is a common cause of allergy affecting around one in ten people. It is acquired from exposure to the metal, often as a result of contact with nickel-containing jewellery, such as ear studs. It is therefore more common in women, affecting around 17 per cent.

Denmark was the first country to restrict exposure to nickel in the 1980s. A decade later in 1994, the restriction was extended across Europe by the *EU Nickel Directive*. This set a limit on the amount that could be released onto the skin of 0.5 micrograms per sq cm, per week.

However, the nickel in coins remains an uncontrolled risk, according to experts at St John's who have campaigned to have it removed. In April 2013, the UK Government introduced new 5p and 10p coins made of nickel-plated steel which it claimed would save the Treasury £7 million a year.

Studies in Sweden have shown that nickel released from the new UK coins was seven times higher than the legal limit for other nickel-containing products. The Swedes carried out a risk assessment and concluded the coins were not safe for consumers because of the risk they might cause *contact dermatitis*. Nickel coins were rejected in Sweden.

In the UK, a risk assessment concluded the coins had no effect on health. But enquiries by St John's revealed that this was based on the observation that the coins were marketed in other countries and there had been no complaints. The Royal Mint had not undertaken any formal risk assessment.

In an editorial in *Contact Dermatitis* in 2012, Dr White and colleagues wrote: "Nickel exposure from coins could be the straw that broke the camel's back in many nickel-allergic individuals with hand eczema. It is time to rethink the use of nickel in coins."

Hair dye

After nickel, hair dye is one of the most common and potent allergens – with widespread population exposure. Reactions range from mild irritation of the scalp to severe dermatitis, redness, swelling and a weeping scalp.

In the worst cases the face may swell causing difficulty breathing. In May 2000, a 38 year old mother of three, **Narinder Devi**, collapsed and died after using hair dye at her home in Edgbaston, Birmingham.

A year later scientists at the University of California published research suggesting women who dyed their hair for more than 15 years doubled their risk of *bladder cancer*.

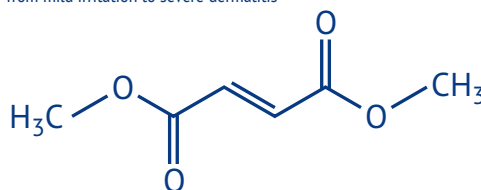
The European Commission set up a working party in response to growing concerns about hair dyes. It critically reviewed the safety of more than 100 hair dyeing chemicals used by industry. But it warned that individuals were still at risk of an allergic reaction to many of the dyes.

Dr White said: “The problem is that many hair dyes are extreme or potent allergens. You cannot ban them because of the social need that has developed. The industry is trying to develop alternatives and one new one is already on the market. Those that come up with safer alternatives will have a competitive advantage.”

Dr McFadden, author of a doctoral thesis and a number of papers on hair dye allergy, said: “One of the difficult aspects has been understanding the nature and mechanisms of sensitisation. Now that these aspects are beginning to be better understood, there is a real prospect of reducing hair dye allergy rates.”



Hair dyes are potent allergens and can cause reactions ranging from mild irritation to severe dermatitis



Dimethyl fumarate



A toxic fungicide used in leather sofas caused an outbreak of “furniture-related dermatitis” in 2006-8

Sofas

From 2006-8, there was an outbreak of furniture-related dermatitis in the UK and in some neighbouring countries including France and Finland. People began turning up at St John's with severe, red, swollen rashes on their back, buttocks and the backs of their legs. In some cases the rash went septic and the patient had to be hospitalised. Over 5,000 people were affected.

Investigation revealed that all patients had recently bought leather couches which were imported from China. The condition came to be known as *toxic sofa dermatitis*.

The cause was a fungicide – dimethyl fumarate – which was used to prevent the growth of mould. It was packaged in small sachets, similar to silica gel sachets used to remove moisture, which were stapled to the wooden frame or directly under the leather covering.

Transporting sofas across the world and through different climates leads to moisture build up and the growth of mould and the use of dimethyl fumarate was a way of counteracting this problem.

What the manufacturers had not realised is that the chemical is a potent allergen which permeates the leather goods as it evaporates. Allergic individuals who sat on the sofas developed reactions, even when they were clothed. Many filed lawsuits.

Dimethyl fumarate has since been banned in Europe, and the problem has disappeared. “We now see only the occasional case,” said Dr White. But for a few years sofa dermatitis added an extra dimension to warnings about the health hazards of spending too much time on the couch.

CASE STUDY

A 34-year old non-atopic physiotherapist presented with a 6-month history of hand eczema, which developed several weeks after the birth of her first child. Examination showed diffuse eczematous changes over the palmar aspect of her hands; her skin elsewhere was not affected.

Diagnostic patch test investigations revealed contact allergy to the preservatives methylisothiazolinone, octylisothiazolinone and also to the fragrance substances citral, oxidised limonene and hydroxyisohexyl 3-cyclohexene carboxaldehyde. As in Europe there is now ingredient labelling of cosmetic (skincare) products and household detergents, it was possible to identify her current exposure to methylisothiazolinone in wet wipes she was using on her new baby. Additionally, she had current exposures to citral and limonene in several of the cleaning products she was using at home. Avoidance of these allergens resulted in resolution of her *hand eczema*.

Three months after returning to work, she attended with an *acute facial eczema* that occurred the day after returning home from a short break out of the country. Whilst away, her husband had painted the living room and bedroom of their flat. He had used a well-known brand of paint; there was no declaration of content on the paint container, no warnings or other relevant information.

Paints may contain isothiazolinone preservatives although manufactures are not obliged to reveal this as methylisothiazolinone is not classified as an



Allergic contact dermatitis caused by the preservative in a wet wipe product for babies

allergen under existing legislation (Classification for Labelling and Packaging) covering such products and, therefore, may not appear on product safety data sheets. We were able to advise that any isothiazolinones would dissipate over a week if the rooms were well-ventilated. Subsequent chemical analysis confirmed the presence of both methylisothiazolinone and octylisothiazolinone in the paint.

Ingredient labelling of cosmetic and household products has transformed the management of patients with *contact allergy*. Quality of life has

dramatically improved for such patients, a fact that is often not appreciated for such a simple intervention. The goal now is to achieve full ingredient listing for all types of products that may be encountered at home and at work.



“The cosmetics industry must have faith in the clinical data generated and given freely by the dermatological community. Safety cannot continue to be a competition.”



